BOSTON PEPPER CENTER
Claude D. Pepper Older Americans Independence Center

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Program Administrator

CENTER DESCRIPTION

The Boston OAIC is unique in its thematic focus on Function Promoting Therapies (FPTs) and its positioning across the entire spectrum of translational science from mechanism elucidation, preclinical proof-of-concept studies, biomarker validation, epidemiologic investigation to randomized trials of FPTs. The Boston OAIC integrates 19 NIH-funded studies of function promoting therapies, 3 Research Education Component projects, 3 pilot projects, and 3 developmental projects into an interdisciplinary program that is supported by a Leadership and Administrative Core, a Research Education Component (REC), a Pilot and Exploratory Studies Core (PESC), and 3 resource cores (Function Assessment Core, Preclinical Discovery Core, Biostatistical and Data Analysis Core). Our REC and PESC candidates include several rising stars in Geriatrics and Gerontology, including 3 Beeson and K grant awardees. The REC will recruit the most promising stars from a vast reservoir of talent at Harvard, Tufts and BU, and train them through a didactic education and mentored research program. Integration will be achieved by the PROMOTE Program that includes a research concierge service, research meetings, annual retreats, a website and a newsletter. The Boston OAIC is well integrated with the the Harvard Geriatrics and Gerontology research community and programs, including its T32 training grant, Harvard Clinical Translational Science Institute, the Roybal Center, The New England Geriatrics Research Clinical Education Center, and the Glenn Foundation Center for Biology of Aging.

Boston OAIC's unique strengths include its focus on Function Promoting Therapies, emphasis on translation and commercialization, access to a large pool of talented young investigators, its extension across the entire spectrum of translational research, and its infrastructure for developing intellectual property and companies, and supporting several seminal randomized trials of FPTs.

CORES

Leadership and Administrative Core (LAC)

Leader 1:   Shalender Bhasin, MD   sbhasin@bwh.harvard.edu

Leader 2:   Roger Fielding, PhD

Leader 3:   Lewis A. Lipsitz, MD   lipsitz@hsl.harvard.edu

The LAC is responsible for stimulating, sustaining, evaluating, and reporting OAIC's progress towards its goals and enabling integration of OAIC activities. In addition to providing administrative support, the LAC coordinates the activities of Boston OAIC's investigators, resource cores, its conferences, and career development activities.

Research Education Component (REC)

Leader 1:   Lewis A. Lipsitz, MD   lipsitz@hsl.harvard.edu

Leader 2:   Amy Wagers, PhD

Leader 3:   Edward Marcantonio, MD

The overall goal of the Research Education Component (REC) of the Boston OAIC is to train future independent research scientists who have the knowledge and the skill to translate fundamental mechanisms of disease and disability into novel interventions that can improve the health, physical function, and well-being of people as they age. The REC achieves this by selecting the most promising early career scientists from clinical and basic science disciplines and providing them with both collective and individual educational activities, research experiences, mentoring, and career guidance that will enable them to acquire future career development or research awards and ultimately become leaders in translational research devoted to the discovery of function promoting therapies (FPTs).

Pilot and Exploratory Studies Core (PESC)

Leader 1:   Monty Montano, PhD   MMONTANO@bwh.harvard.edu

Leader 2:   Douglas P. Kiel, MD

Within the context of the OAIC's overall mission, the Pilot and Exploratory Studies Core (PESC) aims to provide catalytic support – seed funding, core support, and mentorship – for innovative pilot research projects that generate data on the mechanisms of FPT action to facilitate more definitive mechanistic studies, feasibility data to guide efficacy trials, hypothesis generating or proof-of-concept exploratory studies and retrospective analysis of existing epidemiologic data that inform FPT interventions.

Biostatistical Design and Analysis Core (BDAC)

Leader 1:   Thomas Travison, PhD   TGT@hsl.harvard.edu

Leader 2:   Karol Pencina, PhD

The BDAC provides collaborative support in the design, execution and analysis of clinical trials and epidemiology studies conducted at the Boston OAIC. Additionally, the BDAC provides mentoring and collaborative opportunities for students and junior faculty in quantitative aspects of the study of physical function and impairments in aging. The BDAC is equipped to provide critical services on a consulting basis (e.g. in an advisory capacity in critical review of study data collection procedures) and more formally (e.g. in conducting simulation studies and power calculation).

Furthermore, the BDAC provides support for ongoing projects by providing critical review and expertise in evaluating study conduct, or more extensive, pre-specified contributions to trial objectives. Support services for study completion are also available in providing guidance and assistance in statistical analyses, as well as co-authorship of abstracts and manuscripts describing study results.

Development Projects Core

Leader 1:   Shalender Bhasin, MD   sbhasin@bwh.harvard.edu

The Developmental Projects core funds pilot projects chosen based on their innovation and translational value, and the need and potential of novel methods to advance OAIC projects

Functional Assessment Core (FAC)

Leader 1:   Roger Fielding, PhD   roger.fielding@tufts.edu

Leader 2:   Kieran Reid, Ph.D.   Kieran.Reid@tufts.edu

The FAC represents a strategic interdisciplinary alliance between the Muscle Mechanics and Metabolomics Laboratory, the Laboratory of Exercise Physiology and Physical Performance and the Health and Disability Research Institute at Boston University and the Nutrition, Exercise Physiology and Sarcopenia Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University. The core provides standardized, state-of-the-art technologies to measure muscle performance, functional limitations, and disability in human and animal studies for OAIC's pilot and exploratory projects and for several OAIC related projects funded through other sources.

Translational Discovery Core (TDC)

Leader 1:   Ravi Jasuja, PhD

The ability to genetically modify rodents has increased the need to assess reproducibly and quantifiably, the phenotype of these animals with respect to body composition and physical function. In addition to utilizing the small animal resource services, the Translational Discovery Core (TDC) provides the infrastructural and consultative support for non-invasive measurements of alterations in body composition, muscle performance, physical function and metabolic performance to facilitate longitudinal studies of FPTs during aging and metabolic stress. The PDC is also continuing its mission to spearhead innovation- development of novel 7Tesla MRI techniques to provide mechanistic insights into FPT interventions.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications

Sandra Shi, MD
Instructor / Harvard Medical School and Hebrew SeniorLife
<u>Feasibility of a Multicomponent Frailty Intervention Adapted to the Post-Acute Nursing Setting</u>
Research focuses on improving patient centered outcomes and inform complex shared decision making in older adults with frailty requiring post-acute care at skilled nursing facilities.
- R03AG078894-01 (Aug 1, 2022 - Aug 1, 2024), NIH/NIA, Predicting and Identifying Risk Factors for Short Time at Home in Older Adults after Hospitalization

2022-2024 /
9 (total)
-4 (1st/Sr)

Jonathan Cunningham, MD MPH
Instructor / Harvard Medical School
<u>Proteomic Profiles of Aging in Heart Failure with Preserved Ejection Fraction</u>
He seeks to leverage large-scale proteomics to identify heart failure patients with distinct physiology and more precisely target heart therapies in clinical trials.
- KL2/Catalyst Medical Research Investigator Training (CMeRIT) / Boston Claude D. Pepper Older Americans Independence Center
- American Heart Association Career Development Award 4/1/2023-3/30/2026. Title Biomarkers and Treatment of Myocardial Fibrosis in HFpEF

2022-2024 /
25 (total)
3 (1st/Sr)

Heidi Kletzien, PhD
Postdoctoral Fellow / Harvard University
<u>Impact of biologic sex and age on epigenetic and regenerative capacity of head and neck stem cells</u>
Characterization and quantification of stem cells in the head and neck tissues of young and aged male and female mice and in isochronic and heterochronic parabionts.
- NIA NRSA F32: In vivo screening to identify cellular and (epi) genetic mechanisms driving sex- and age-biased development of head and neck cancers
- Aramont Fellowship Fund for Emerging Science Research: Uncovering clonal mechanisms of head and neck cancer initiation and progression

2022-2024 /
19 (total)
5 (1st/Sr)

Past Scholars
Jason Sanders, MD, Harvard Medical School (2020-2021)
Hao Zhou, MD, PhD, Harvard Medical School (2020-2022)
Daniel Roh, MD, Boston University (2021-2022)
Sari Reisner, DSc., Harvard Medical School (2021-2022)
Sanjay Divakaran, MD, Harvard Medical School (2021-2022)
Timothy Anderson, MD, Harvard Medical School (2021-2022)
Clark DuMontier, MD, Harvard Medical School (2021-2022)

PILOT/EXPLORATORY PROJECTS (4 Pilot Projects Listed)

1. Project Title: **PES-3: Stress-driven acceleration of epigenetic age and inflammation in transgender adults.**

Leader: **PIs: Sari Reisner, ScD and Monty Montano, PhD**

Results from this study will establish whether there is a link between exposure to gender-related psychosocial stress and epigentic age (DNA methylation score) and inflamm-aging (e.g., elevated CRP, IL-6 levels); and whether epigentic age and inflammation are related to levels of physical function. The study outcomes will inform a followup R01 to evaluate a combined behavioral and exercise intervention to reverse accelerated aging and inflamm-aging due to life course exposure to psychosocial stressors.

2. Project Title: **REC-4: Skeletal Muscle Perfusion and Energetics in Patients with Symptomatic Peripheral Artery Disease. Joint Boston OAIC-Harvard Catalyst C-MERIT Awardee.**

Leader: **Sanjay Divakaran, MD**

Dr. Divarkaran is an Instructor in Medicine in the Division of Cardiology, BWH. His research focuses on using perfusion and metabolic positron emission tomography (PET) and magnetic resonance spectroscopy (MRS) to uncover changes in oxygen delivery and metabolism in older individuals with peripheral artery disease. Studying patients with PAD at rest and post-exercise with PET and MRS has the potential to help better phenotype patients with PAD and address critical gaps in knowledge regarding the pathophysiology of intermittent claudication. For the OAIC REC, he proposes to use PET, MRS, and omics technologies to study 10 older adults with PAD before and after endovascular revascularization procedures. He will perform novel pre- and post-exercise plasma biomarker discovery by measuring differential microRNA expression and targeted protein biomarkers. His mentors are Dr. Marcelo Di Carli, a world-expert in perfusion and metabolic PET imaging, and Dr. Mark Feinberg, Director of the Program of Cardiovascular RNA Biology at BWH. He will utilize the OAIC Functional Assessment, Preclinical Discovery, and Biostatistical Design and Analysis Cores.

3. Project Title: **Reversing aging-induced wound healing via androgen-estrogen modulation**

Leader: **Devin O'Brien-Coon, MD MS**

Dr. O'Brien-Coon had three aims for his project, which overall will be testing approaches to reverse aging-induced wound healing dysfunction via androgen-estrogen axis modulation. In Aim 1, Dr. O'Brien-Coon planned to characterize the effects of testosterone and estradiol on increased inflammation and delayed wound closure in his stented-wound model in young vs elderly mice. In Aim 2, he planned to study the differential effects of cross-sex testosterone on wound healing in elderly mice vs young controls. Towards these aims he developed and tested sustained-release estradiol implants and achieved desired levels in the wound healing group given the implants. He also developed and switched to a rat wound model due to the need for larger wounds than achievable in mice so that he could measure desired outcomes. Just prior to this progress report submission, he performed castrated rat wound healing model surgeries to finalize estradiol implant performance; if successful he will then repeat experiments with aged rats. Finally in Aim 3, he will be assessing the mechanisms and potential of sex hormone

receptor modulation as a therapeutic target to restore wound repair function in elderly mice. Progress in this aim was marked by Dr. O'Brien-Coon starting a new collaboration with Dr. Ameya Kirtane, who specializes in drug delivery, to formulate more reliable topical anti-androgen/pro-estrogen formulations for sustained wound delivery since existing topicals are for transdermal release which is the opposite goal of his project.

4. Project Title: **PHD2 modulation on muscular adaptation to exercise and functional improvement.**

Leader: **Yori Endo, MD**

Dr. Endo's project is focused on age-related elevations in PHD2 as the mechanistic link between the loss of hypoxia-dependent muscular adaptation to exercise and diminished functional gain in aged muscle. This project was based on the finding that prolyl hydroxylase domain enzyme (PHD2), an enzyme which leads to the degradation of hypoxia inducing factors and loss of hypoxia pathway signaling, was found to be elevated systemically in older adults and in skeletal muscle in old mice. In Aim 1, Dr. Endo is assessing whether increased skeletal muscle PHD2 limits response to aerobic exercise in aging mice. In specific Aim 2, Dr. Endo will evaluate whether pharmacologic inhibition of PHD2 improves muscle adaptation to aerobic exercise. Dr. Endo has made good progress so far, this first year. Using a hypoxia signaling hypomorphic mouse model, she is investigating the effect of blunted hypoxia signaling on exercise response in young and old mice. She has completed several rounds of exercise treatment and are analyzing and processing the physiological data. She will then begin to perform biochemical analyses to further characterize the effect of the loss of hypoxia signaling on muscle following exercise.

DEVELOPMENT PROJECTS (3 Development Projects Listed)

1. Project Title: **DP-2: Measuring intracellular NAD in skeletal muscle and brain using 7T magnetic resonance spectroscopy**

Leader: **Alex Lin, PhD and Ravi Jasuja, PhD**

Core(s):

The use of 7T MR spectroscopy to measure intracellular NAD in skeletal muscle and brain is novel and will be of value to ongoing and planned studies of NAD activators.

2. Project Title: **DP-3: A novel statistical method to compare interventions initiated over time.**

Leader: **Karo Pencina, PhD, Co-I: Thomas Travison, PhD.**

Core(s):

A novel statistical method to compare treatments initiated over time to enable epidemiological assessment of treatment disparities in older adults.

3. Project Title: **DP-1. Development of novel remote sensing technology to assess muscle performance in community dwelling older adults**

Leader: **Roger A. Fielding, Tufts-HNRCA, Kieran F. Reid, Brigham and Women's Hospital and Conor J. Walsh, Harvard University**

Core(s):

This project will focus on the refinement of prototypes to collect data from the appropriate body segments during strength training and assessment, develop algorithms to appropriately interpret the sensor data, and refine an initial web application. Finally, we will validate and evaluate the technology with established gold-standard assessment measures of muscle strength, power, and fatigue in older adults. Aim 1. Wearable technology development. Previously, the Biodesign Lab developed a modular and wearable hardware system, which includes two Inertial Measurement Units (IMUs). Aim 2. Validation study: The prototype technology platform will be developed to capture sensor-based measures of muscle performance (muscle force, contractile velocity, power and fatigue). The reliability, reproducibility and instrumental validity of muscle performance measures will be quantitively assessed and directly compared to several gold-standard, laboratory-based assessments of muscle performance and physical function. Aim 3. Single participant longitudinal case study: One participant will train three times per week for 8 weeks in their home. Since the technology is not yet suitable for independent home use, a member of the research team will visit the participant's home.

RESEARCH (3 Projects Listed)

1. Project Title: **UNCOVERING MOLECULAR EFFECTORS OF MAMMALIAN AGING**

Leader(s):   **WAGERS, AMY JO**
HARVARD UNIVERSITY
NIH DP1AG063419 / (2018 - 2023)

Core(s):

Aging is the single largest risk factor for most chronic degenerative diseases, including cardiovascular,musculoskeletal and neurodegenerative dysfunctions, and age-associated diseases now represent

2. Project Title: **AGING-ASSOCIATED DYSREGULATION OF THE HYPOXIA PATHWAY LIMITS SKELETAL MUSCLE REGENERATION**

Leader(s):   **SINHA, INDRANIL**
BRIGHAM AND WOMEN'S HOSPITAL
NIH K76AG059996 / (2018 - 2023)

Core(s):

Project Summary/Abstract This proposal describes a five-year training program and career development plan for Dr. IndranilSinha. Dr. Sinha is a prior trainee of a National Institute of Aging-sponsored Postdoctoral Individual NationalResearch Service Award (F32). He is a current awardee of a Research and Education Core Grant through theBoston Pepper Center and the National Institute of Aging. He has completed clinical training in Plastic andReconstructive Surgery and is board-certified through the American Board of Plastic Surgery. He is nowembarking on a research and career development program under the mentorship of Amy Wagers, Ph.D.,Professor of Medicine, Harvard Medical School. Dr. Wagers is an accomplished researcher in skeletal muscleregeneration and has a history of mentoring trainees who go on to successful, independent research careers.Additional mentoring will be provided by Dr. Shalender Bhasin, a world-renowned researcher on sarcopenia,and Dr. Laurie Goodyear, an expert on exercise physiology. Dr. Sinha's career development plan includesutilization of educational resources at Brigham and Women's Hospital, Joslin Diabetes Center, and HarvardMedical School. Career development support will also be provided by the Brigham and Women's HospitalDepartment of Surgery, where the principle investigator will serve as an attending physician during the periodof funding. Dr. Sinha has developed a clear timeline for publication of his work in peer-reviewed journals,presentations at national meetings, establishment of an Aging Interest Group within Plastic Surgery, and plansfor the development of independent research projects and continued research funding. Dr. Sinha is interested in developing novel treatment strategies for aging-associated loss of skeletalmuscle regeneration. He is investigating mechanisms by which aging alters hypoxia pathway signaling andskeletal muscle regenerative potential in a murine model. He found that two key factors in the hypoxiapathway, aryl hydrocarbon receptor nuclear translocator (ARNT) and vascular endothelial growth factor(VEGF), are severely dysregulated in skeletal muscle in aging and may lead to a loss of skeletal muscleregenerative potential. Furthermore, using a genetically modified mouse model, he demonstrated that musclespecific loss of ARNT recapitulates diminished skeletal muscle regeneration as associated with aging. Buildingon these intriguing preliminary data, the central goals of this project are to (1) mechanistically define the role ofhypoxia pathway signaling and its impact on muscle regeneration in aging, (2) identify interventions to restoreARNT and VEGF signaling to preserve skeletal muscle myogenic potential, and (3) determine whether musclehypertrophy in response to exercise, which is known to require skeletal muscle regeneration and hypoxiasignaling, is limited in aging secondary to loss of ARNT.

3. Project Title: **PROSPECTIVE MONITORING OF NEWLY APPROVED CARDIOVASCULAR DRUGS IN OLDER ADULTS WITH FRAILTY**

Leader(s):   **KIM, DAE HYUN**
BRIGHAM AND WOMEN'S HOSPITAL
NIH R01AG062713 / (2019 - 2023)

Core(s):

PROJECT SUMMARY/ABSTRACTCardiovascular disease (CVD) affects 70% of older adults and remains the leading cause of morbidity and mor-tality in the United States. Several new drugs have recently been approved for CVD, but not enough is knownabout their utilization, benefits and risks in frail older patients. Since conducting a clinical trial in frail older adultscan be costly and impractical, there is a pressing need for innovative strategies to generate evidence on newCVD drugs in a timely manner. The objective of this application is to establish a near-real-time prospectivemonitoring program in Medicare data to evaluate the benefit of new CVD drugs for older adults with frailty. Aprospective monitoring program seeks to find early effectiveness and safety signals of new drugs by updatingthe analysis at regular intervals as new Medicare data become available. The investigators will incorporate anovel claims-based frailty index into the monitoring program to generate timely evidence on disease-specific andpatient-centered net benefit of new drugs by frailty status. The central hypothesis is that disease-specific benefitand net benefit are determined by a patient's degree of frailty. Disease-specific benefit will be evaluated usingclinical trial endpoints of effectiveness (e.g., CVD events) and safety (e.g., bleeding), and net benefit in terms ofthe number of days alive and spent at home, or home time . To conduct this work, the investigators will analyzeMedicare data on 6 new CVD drugs approved in 2011-2017: 3 anticoagulants vs warfarin for atrial fibrillation, 2antiplatelets vs clopidogrel for atherosclerotic CVD, and an angiotensin receptor-neprilysin inhibitor vs enalaprilfor systolic heart failure. The validity and reproducibility of the results will be enhanced through the linkage of asubset of Medicare data to electronic health records and a national survey to supplement clinical information,and external validation of the Medicare data analysis in 2 large commercial databases. In the next 4 years, theinvestigators will accomplish 3 specific aims: 1) evaluate the temporal trends and predictors of new CVD druguse in frail and non-frail older adults with CVD over 2011-2020; 2) determine disease-specific benefit (deaths,CVD and safety events) and net benefit (home time) of 6 new CVD drugs compared with alternative therapies;3) identify patient characteristics that can predict net benefit (home time) with new CVD drugs compared withalternative therapies. This proposal's innovative approach, which combines near-real-time prospective monitor-ing, a claims-based frailty score, and the patient-centered outcome of home time, offers a readily scalable andfeasible framework for comparative effectiveness and safety studies of newly approved medications. The impactof the proposed research is significant because timely evidence generated from real-world healthcare data canenable clinicians to optimize prescribing of new CVD drugs based on a patient's frailty and expected net benefit.

PUBLICATIONS

2023

1. **Optimizing the Design of Clinical Trials to Evaluate the Efficacy of Function-Promoting Therapies.**
   Bhasin S, Cawthon PM, Correa-de-Araujo R, Storer TW, Volpi E, Newman AB, Dioh W, Tourette C, Evans WJ, Fielding RA
   J Gerontol A Biol Sci Med Sci, 2023 Jun 16, 78(Supplement_1): 86-93
   https://doi.org/10.1093/gerona/glad024 | PMID: 37325959 | PMCID: PMC10272979
   Citations: 49 | AltScore: NA

2. **Androgens and Selective Androgen Receptor Modulators to Treat Functional Limitations Associated With Aging and Chronic Disease.**
   Bhasin S, Krishnan V, Storer TW, Steiner M, Dobs AS
   J Gerontol A Biol Sci Med Sci, 2023 Jun 16, 78(Supplement_1): 25-31
   https://doi.org/10.1093/gerona/glad027 | PMID: 37325955 | PMCID: PMC10272983
   Citations: 65 | AltScore: NA

3. **Benefits and Barriers of Technology for Home Function and Mobility Assessment: Perspectives of Older Patients With Blood Cancers, Caregivers, and Clinicians.**
   Clancy DD, Revette AC, Bahl NE, Ho KT, Manor B, Testa MA, Dieli-Conwright CM, Hshieh T, Driver JA, Abel GA, DuMontier C
   JCO Clin Cancer Inform, 2023 Apr, 7: e2200171
   https://doi.org/10.1200/CCI.22.00171 | PMID: 37098230 | PMCID: PMC10281405
   Citations: 56 | AltScore: NA

4. **Anorexia in Medicare Fee-for-Service Beneficiaries: A Claims-Based Analysis of Epidemiology and Mortality.**
   Dagenais S, Fielding RA, Clark S, Cantu C, Prasad S, Groarke JD
   J Nutr Health Aging, 2023, 27(3): 184-191
   https://doi.org/10.1007/s12603-023-1882-4 | PMID: 36973924 | PMCID: PMC9841141
   Citations: 34 | AltScore: 1

5. **Implementing 4-meter gait speed as a routine vital sign in a thoracic surgery clinic.**
   Deeb AL, Garrity M, Cooper L, Frain LN, Jaklitsch MT, DuMontier C
   J Geriatr Oncol, 2023 May, 14(4): 101481
   https://doi.org/10.1016/j.jgo.2023.101481 | PMID: 37060720
   Citations: | AltScore: 4.35

6. **Novel Potential Targets for Function-Promoting Therapies: Orphan Nuclear Receptors, Anti-inflammatory Drugs, Troponin Activators, Mas Receptor Agonists, and Urolithin A.**
   Dioh W, Narkar V, Singh A, Malik F, Ferrucci L, Tourette C, Mariani J, van Maanen R, Fielding RA
   J Gerontol A Biol Sci Med Sci, 2023 Jun 16, 78(Supplement_1): 44-52
   https://doi.org/10.1093/gerona/glad072 | PMID: 37325960 | PMCID: PMC10272986
   Citations: 60 | AltScore: NA

7. **Multi-modal profiling of peripheral blood cells across the human lifespan reveals distinct immune cell signatures of aging and longevity.**
   Karagiannis TT, Dowrey TW, Villacorta-Martin C, Montano M, Reed E, Belkina AC, Andersen SL, Perls TT, Monti S, Murphy GJ, Sebastiani P
   EBioMedicine, 2023 Apr, 90: 104514

https://doi.org/10.1016/j.ebiom.2023.104514 | PMID: 37005201 | PMCID: PMC10114155
Citations: 50 | AltScore: 748.704

8. **Geriatric Syndromes and Health-Related Quality of Life in Older Adults with Chronic Kidney Disease.**
Liu CK, Miao S, Giffuni J, Katzel LI, Fielding RA, Seliger SL, Weiner DE
Kidney360, 2023 Apr 1, 4(4): e457-e465
https://doi.org/10.34067/KID.0000000000000078 | PMID: 36790849
Citations: | AltScore: 5.85

9. **Association of Proinflammatory Diet With Frailty Onset Among Adults With and Without Depressive Symptoms: Results From the Framingham Offspring Study.**
Millar CL, Dufour AB, Hebert JR, Shivappa N, Okereke OI, Kiel DP, Hannan MT, Sahni S
J Gerontol A Biol Sci Med Sci, 2023 Feb 24, 78(2): 250-257
https://doi.org/10.1093/gerona/glac140 | PMID: 35830506 | PMCID: PMC9951064
Citations: 50 | AltScore: 256.81

10. **Maladaptive Immune Activation in Age-Related Decline of Muscle Function.**
Montano M, Correa-de-Araujo R
J Gerontol A Biol Sci Med Sci, 2023 Jun 16, 78(Supplement_1): 19-24
https://doi.org/10.1093/gerona/glad036 | PMID: 37325961 | PMCID: PMC10272988
Citations: 78 | AltScore: 2.5

11. **Mild Neurocognitive Disorder, Social Engagement, and Falls Among Older Primary Care Patients.**
Quach LT, Pedersen MM, Ogawa E, Ward RE, Gagnon DR, Spiro A, Burr JA, Driver JA, Gaziano M, Dhand A, Bean JF
Arch Phys Med Rehabil, 2023 Apr, 104(4): 541-546
https://doi.org/10.1016/j.apmr.2022.10.008 | PMID: 36513122 | PMCID: PMC10073260
Citations: 39 | AltScore: 0.5

12. **Association of Vascular Health Measures and Physical Function: A Prospective Analysis in the Framingham Heart Study.**
Sahni S, Dufour AB, Wang N, Kiel DP, Hannan MT, Jacques PF, Benjamin EJ, Vasan RS, Murabito JM, Newman AB, Fielding RA, Mitchell GF, Hamburg NM
J Gerontol A Biol Sci Med Sci, 2023 May 15, 78(7): 1189-1197
pii: glad097. https://doi.org/10.1093/gerona/glad097 | PMID: 37183502 | PMCID: PMC10329234
Citations: 46 | AltScore: 163.1

13. **Mortality and Heart Failure Hospitalization Among Young Adults With and Without Cardiogenic Shock After Acute Myocardial Infarction.**
Siddiqi HK, Defilippis EM, Biery DW, Singh A, Wu WY, Divakaran S, Berman AN, Rizk T, Januzzi JL, Bohula E, Stewart G, Carli MD, Bhatt DL, Blankstein R
J Card Fail, 2023 Jan, 29(1): 18-29
https://doi.org/10.1016/j.cardfail.2022.08.012 | PMID: 36130688
Citations: | AltScore: 32.6

14. **Dairy Food Intake Is Not Associated With Frailty in Adults From the Framingham Heart Study.**
Siefkas AC, Millar CL, Dufour AB, Kiel DP, Jacques PF, Hannan MT, Sahni S
J Acad Nutr Diet, 2023 May, 123(5): 729-739.e1
https://doi.org/10.1016/j.jand.2022.09.012 | PMID: 36108932
Citations: | AltScore: NA

15. **Exercise and Behavior: Adjuncts to Pro-Myogenic Compounds for Enhancing Mobility**

in Older Adults.
Storer TW, Pahor M, Woodhouse LJ, Lachman ME, Fielding RA
J Gerontol A Biol Sci Med Sci, 2023 Jun 16, 78(Supplement_1): 61-66
https://doi.org/10.1093/gerona/glad041 | PMID: 37325956 | PMCID: PMC10272978
Citations: 40 | AltScore: NA

16. **Testosterone replacement in prostate cancer survivors with testosterone deficiency: Study protocol of a randomized controlled trial.**
Valderr?bano RJ, Pencina K, Storer TW, Reid KF, Kibel AS, Burnett AL, Huang G, Dorff T, Privat F, Ghattas-Puylara C, Wilson L, Latham NK, Holmberg M, Bhasin S
Andrology, 2023 Jan, 11(1): 93-102
https://doi.org/10.1111/andr.13299 | PMID: 36181480 | PMCID: PMC9771994
Citations: 70 | AltScore: 9.25

17. **Association Between Systemic Vasculitis and Coronary Microvascular Dysfunction in the Absence of Obstructive Coronary Artery Disease.**
Weber B, Wallace ZS, Parks S, Cook C, Huck DM, Garshick M, Brown JM, Divakaran S, Hainer J, Dorbala S, Blankstein R, Liao KP, Aghayev A, Choi HK, Di Carli M
Circ Cardiovasc Imaging, 2023 Jan, 16(1): e014940
https://doi.org/10.1161/CIRCIMAGING.122.014940 | PMID: 36649456 | PMCID: PMC9999265
Citations: 5 | AltScore: NA

18. **Effect of Long-term Exercise Training on Physical Performance and Cardiorespiratory Function in Adults With CKD: A Randomized Controlled Trial.**
Weiner DE, Liu CK, Miao S, Fielding R, Katzel LI, Giffuni J, Well A, Seliger SL
Am J Kidney Dis, 2023 Jan, 81(1): 59-66
https://doi.org/10.1053/j.ajkd.2022.06.008 | PMID: 35944747 | PMCID: PMC9780154
Citations: 25 | AltScore: 59

2022

1. **Design and analysis of cluster randomized trials with time-to-event outcomes under the additive hazards mixed model.**
Blaha O, Esserman D, Li F
Stat Med, 2022 Oct 30, 41(24): 4860-4885
https://doi.org/10.1002/sim.9541 | PMID: 35908796 | PMCID: PMC9588628
Citations: 58 | AltScore: 1.85

2. **Treating Myocardial Inflammation in Cardiac Sarcoidosis: Why, With What, and for How Long?**
Blankstein R, Divakaran S
JACC Cardiovasc Imaging, 2022 Nov, 15(11): 1956-1959
https://doi.org/10.1016/j.jcmg.2022.07.016 | PMID: 36357137 | PMCID: PMC9758976
Citations: 16 | AltScore: 7.75

3. **Low coronary flow relative to myocardial mass predicts heart failure in symptomatic hypertensive patients with no obstructive coronary artery disease.**
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Citations: 3 | AltScore: 13.95

EXTERNAL ADVISORY BOARD MEMBERS

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RECOGNITION AND AWARDS (2022-2023)

<u>Amy Wagers</u> (2023)

- Recipient of NIH Director's Pioneer Award; Member of the NIA Council

<u>Kei Ouchi, MD</u> (2022)

- Beeson Award

<u>Lew Lipsitz</u> (2023)

- Appointed Editor-in-Chief of the Journal of Gerontology Series A Medical Sciences

<u>Monty Montano</u> (2023)

- Appointed Editor-in-Chief, Aging Cell
- Recipient of a Merck Investigators Study Program Award

<u>Roger Fielding</u> (2023)

- The ESCEO-IOF Herbert Fleisch Medal, awarded annually by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the International Osteoporosis Foundation (IOF). Chair, ASG Study Section; Appointed Associate Director of the Jean Mayer USDA Human Nutrition Research Center on Aging

<u>Shalender Bhasin</u> (2023)

- Member of the NIA Council
- Appointed Co-Director, Center for Transgender Health, Brigham and Women's Hospital

<u>Tim Anderson, MD</u> (2022)

- Beeson Award

MINORITY RESEARCH

General Brief Description of Minority Activities:
Not defined.

Minority Trainee(s):

- Rodrigo Valderrabano, MD, MSc., Assistant Professor of Medicine
  Dr. Valderrabano was recruited to Mass General Brigham from the University of Miami, Miami, FL, where he was an Assistant Professor of Medicine at the University of Miami, Miami, FL. Dr. Valderrabano received his medical degree from the Medical School in Puerto Rico and did a fellowship in Bone Health at Stanford University. Dr. Valderrabano is currently interested in muscle / bone dysfunction in people with diabetes and spinal cord injury. Integrating aging and outcomes of physical activity interventions is planned. Dr. Valderrabano is also coinvetigator on two research projects with Dr. Montano that are focused on HIV and Aging and COVID-19, respectively. Received a career development award in 2022

Minority Grant(s):

1. **Project Title:** **ROLE OF MICRORNAS ON AGE AND CONTRACTION-INDUCED SKELETAL MUSCLE GROWTH**

   Leader(s): **RIVAS, DONATO A**
   TUFTS UNIVERSITY BOSTON
   NIH K01AG047247 / (2015-2020)

DESCRIPTION (provided by applicant): The age-associated loss of skeletal muscle mass and function (sarcopenia) is associated with substantial social and economic costs. The plasticity and adaptability of skeletal muscle to contraction (i.e. resistance-exercise) is a fundamental physiological event leading to larger and more robust skeletal muscle. However, muscle growth in response to resistance exercise (RE), like other anabolic stimuli, is attenuated in older adults The cause of aberrant muscle adaptation with aging is complex. Recent work has revealed a novel role for small non-coding RNAs, called microRNAs (miRNA) in the regulation of gene expression. Using an integrated bioinformatics analysis of protein-coding gene and miRNA array data from young and older men, I identified ten specific miRNAs as important regulators of muscle plasticity (Plasticity Related miRs [PR-miRs]) leading to the transcriptional response to exercise and lean mass in young and older men. However, the precise mechanisms underlying the expression of PR-miRs on age-related changes in muscle anabolism and sarcopenia are currently unknown. Thus, the overall objective of this K01 application will be to determine the mechanistic role(s) of these PR-miRs in skeletal muscle adaptation to anabolic stimulation in 1) healthy young, 2) sarcopenic older and 3) age- and functionally-matched non-sarcopenic older males and females. This will be accomplished by determine the differences in expression of PR-miRs with aging and sarcopenia in response to anabolic stimulation (AIM 1). Mechanistically determine the extent to which manipulation of PR-miR levels in vitro, in human primary myocytes, can reverse anabolic resistance observed with age and sarcopenia (AIM 2) and the effect of altering PR-miRs levels on skeletal muscle growth and development (AIM 3). This project will improve our understanding of the molecular mechanisms that contribute to the loss of skeletal muscle and eventually leading to the

development of drug therapies for the treatment of sarcopenia in the ever growing aging population. The mentorship team includes, Dr. Roger Fielding, a leader in aging research and muscle biology, Dr. Kenneth Walsh, a cardiovascular researcher and leading molecular biologist, Dr. Laurence Parnell a computational biologist and authority in gene and miRNA expression analysis, Dr. Thomas Gustafsson a physician-scientist and clinical researcher and Dr. Thomas Travison an expert in biostatistics. The mentorship team has a variety of know-how in every facet of this project including, conducting human clinical trials and skeletal muscle biology, computational biology and genomics and molecular biology and mechanisms. The proposed career development plan includes research-oriented and didactic training at Tufts University, Boston University and the Karolinska Institute in Stockholm,Sweden. The pursuit of the specific aims of the research project, the multidisciplinary mentorship team and the career development plan will facilitate a transition to an independent research career.

2. Project Title: **THE ENRGISE STUDY**
Leader(s): **PAHOR, MARCO ; AMBROSIUS, WALTER T ;**
UNIVERSITY OF FLORIDA
NIH U01AG050499 / (2015-2019)

Growing evidence from our group and others shows that low-grade chronic inflammation, characterized by elevations in plasma C-reactive protein, tumor necrosis factor alpha, and particularly Interleuk

DUKE UNIVERSITY MEDICAL CENTER
Claude D. Pepper Older Americans Independence Center

Kenneth Schmader, M.D.   919-660-7500   kenneth.schmader@duke.edu
Principal Investigator

Michelle Cooley   919-660-7551   michelle.cooley@duke.edu
Program Administrator

CENTER DESCRIPTION

The overall goal of the Duke Claude D. Pepper Older Americans Independence Center (Duke OAIC) is to support research and training that improves the independence of older Americans by focusing on our theme to understand and optimize reserve and resilience. This theme is founded on the insight that independence in older adults is related to an individuals ability to withstand or recover from functional decline following acute or chronic health stressors. We conceptualize resilience as a dynamic response observed and measured after a stressor is applied. We define resilience as the ability to resist or recover from adverse effects of a stressor; reserve is the pre-stressor capacity, in multiple domains, to adapt to a stressor. Our approach includes better understanding of the underlying mechanisms as well as the creation of new interventions for optimizing reserve and resilience across the lifespan

Our overall strategy for the OAIC is to serve as a sustained resource to our investigators through a broad range of training and research studies; the goal is to address knowledge gaps in our focus with an emphasis on translational and interdisciplinary research. We recruit and develop early stage investigators in aging research related to our focus and utilize the substantial strengths of the Duke academic and health system environment to advance our focus.

The Duke Pepper Center has been at the forefront of geriatric research and training focused on the development of interventions to improve the functional status of older adults and the support of research that identifies risk factors predictive of functional decline. The Duke Pepper Center originally began its funding as a Geriatric Research and Training Center (GRTC) in 1991. The GRTC was originally funded with three research cores and support for junior faculty and pilot projects, which reflects the organization of the current OAIC structure. One year later, Duke was awarded a Pepper Center and, at the direction of the National Institute on Aging, the two programs were combined into one. Initial Pepper Center support focused on the development of promising interventions to promote the independence of older Americans and faculty development. Since then, the Duke OAIC has produced an impressive portfolio of relevant research and innovations in faculty development.

The goals of the Duke Pepper Center are:

1. To advance our knowledge of measures, mechanisms and analyses of reserve and resilience in older adults through an integrated research program
2. To develop and evaluate interventions that optimize reserve and resilience in older adults.
3. To identify and develop the next generation of researchers who will become leaders in aging and geriatrics research related to the Duke OAIC focus.
4. To support pilot studies needed to design successful, more definitive research studies related to the Duke OAIC focus.

CORES

Leadership and Administrative Core (LAC)

Leader 1:   Kenneth Schmader, MD   kenneth.schmader@dm.duke.edu

Leader 2:   Cathleen Colón-Emeric, MD, MHS   cathleen.colonemeric@duke.edu

The Leadership and Administrative Core (LAC) provides the scientific leadership and administrative infrastructure to create a robust environment for aging and geriatrics research in our theme. The Leadership and Administrative Core promotes the development of early investigators with interests in aging and geriatrics research and ensures the coordination, integration, funding, and translation of research within the Duke OAIC, a mission that supports our ultimate goal of improving the independence of older adults. The specific aims of the Leadership and Administrative Core are to: 1) to provide overall coordination and administration of the Duke OAIC 2) to stimulate, monitor, sustain and evaluate the progress of the OAIC towards achieving its research and education goals 3) to assess scientific opportunities for innovative research in our theme with an emphasis on translational and interdisciplinary research 4) to utilize and develop resources effectively to meet the goals of the Duke OAIC.

Research Education Component (REC)

Leader 1:   Cathleen Colón-Emeric, MD, MHS   colon001@mc.duke.edu

Leader 2:   Kimberly Johnson, M.D.   kimberly.s.johnson@duke.edu

Leader 3:   Barrett Bowling, M.D.   barrett.bowling@duke.edu

The objective of the Research Education Component (REC) is to develop the next generation of researchers who will become leaders in integrating basic science and clinical insights into innovative interventions promoting reserve and resilience in late life. Guided by educators in the Aging Center with nationally recognized expertise in curriculum development and evaluation, the REC measures the impact of OAIC programs on Scholars' career progression using innovative evaluation methods such as nominal group sessions. We have well established, close partnerships with multiple partner programs across the university (e.g., the Duke Clinical Translational Science Award Center (CTSA) KL2 program, NIA T32 aging training grant, NIA Roybal Center, NIMHD REACH EQUITY Center) . The School of Medicine offers excellent professional development programs, research leadership training, and grant-writing education and support services that are utilized by our scholars. Examples of REC training activities include our Intervention Development in Elderly Adults (IDEA) Workshop, Works-In-Progress sessions, Health Care Disparities Research Curriculum and "Pepper Shakers" networking events with faculty and scholars The specific aims of the Research Education Component are to: 1) to deliver an aging research curriculum around promoting physical reserve and resilience, while providing multiple opportunities for feedback, networking, and peer support; 2) to train and support mentors to enhance the quality of translational research mentoring across disciplines; 3) to provide mentored research experiences to prepare a diverse group of aging researchers focusing on physical resilience in older adults

Pilot and Exploratory Studies Core (PESC)

Leader 1:   Heather E. Whitson, MD   heather.whitson@duke.edu

Leader 2:   Susan N. Hastings, MD   susan.hastings@duke.edu

The Pilot/Exploratory Studies Core (PESC) emphasizes physiological reserve at the cell/tissue/organ level, which we hypothesize is a key contributor to resilience at the whole person level. The PESC impacts public health by performing studies that develop knowledge to maintain or recover independence in older Americans, by promoting reserve and resilience in the face of chronic and acute stressors. The PESC places emphasis on the development of novel interventions that will bolster resilience. PESC continues to support studies that conduct crucial resilience-related pilot work prior to the stage of intervention (e.g., development of measures or model systems). Our mentoring approach and OAIC environment train awardees to strategize as to how their lines of research may translate into improved human outcomes. We use small exploratory pilot monies as a rapid response mechanism to take advantage of cutting edge areas. The PESC solicits and selects high quality pilot studies from across Duke University Medical Center using a rigorous, multi-stage process that incorporates internal and external review. The PESC carefully monitors study progress and assists in the development of larger grant proposals from pilot study findings. The Duke PESC includes several highly innovative features: 1) the Pilot Grants Workshop, developed by OAIC Director Kenneth Schmader and frequently requested in national venues, 2) the inclusion of patient/community representatives on the Review Panel that selects pilots, 3) the Data Integration Working Group, which is a central hub for scientific development, oversight, and translation, and 4) mechanisms that support the science and careers of unfunded pilot study applicants. The specific aims of the Pilot/ Exploratory Studies Core are to: 1) to advance top quality science related to late-life reserve and resilience; 2) to attract and nurture a diverse cadre of outstanding investigators equipped to pursue promising new directions in aging research related to our theme; 3) to build and sustain relationships with critical stakeholders to maximize the impact and translation of the work conducted through this and future OAICs

Analysis (AC)

 Leader 1:   Sarah Peskoe, PhD   sarah.peskoe@duke.edu

The Analysis Core (AC) serves as the central resource for data management and biostatistical analyses for research to understand and optimize reserve and resilience. The AC provides specialized research expertise in study design, data collection and management, development of statistical analysis plans, analytic support, and interpretation/dissemination of results to OAIC scholars and faculty. The AC promotes novel lines of research by developing new methods specifically targeted to detect and measure reserve and resilience. Finally, the AC supports training objectives by developing fellow and faculty understanding of biostatistics and research methodology—critical areas of the research enterprise that are typically a knowledge gap in basic, translational, and clinical researchers. The AC works closely with OAIC investigators, the two Resource Cores (Molecular Measures Core and Physical Measures Core), the PESC and REC to direct study design and analysis and to insure studies are properly powered and address targeted research questions. Furthermore, the AC is uniquely positioned to expand studies to evaluate additional or emerging hypotheses, including those that support methodologic investigations in statistical science, a unique goal of this Core. The specific aims of the Analysis Core are to: 1) to provide data management and analytic support to funded and proposed projects, pilots, and OAIC investigations 2) to provide training and mentoring to OAIC Scholars and faculty 3) to develop and disseminate biostatistical analytic methodologies to advance the study of resilience and reserve.

Health and Mobility Measures Core (HMC)

Leader 1:   Katherine Hall, Ph.D.   katherine.hall@duke.edu
Leader 2:   Amy Pastva, PT, MA, PhD   amy.pastva@duke.edu

The Health and Mobility Measures Core (HMC) provides whole-person health and mobility measurement capabilities to advance our theme of understanding and optimizing physical reserve and resilience. The HMC serves as a central resource for Duke OAIC investigators and the broader Duke community seeking consultation, mentoring, training, and innovation for valid, sensitive, and reliable whole-person level health and mobility measures. A panel of 8 members, with complementary expertise in measurement across multiple domains, comprises the Core and provides highly integrated, customized support to investigators supported by our Research Education Component, Pilot/Exploratory Studies Core, Externally Funded Projects, and the larger Duke Community engaged by the Duke OAIC. The HMC supports investigators by meeting regularly throughout the full spectrum of project development, from early phase planning, to final interpretation of findings, to subsequent grant preparations, to dissemination and/or implementation. These meetings concurrently involve members of the Analysis and Molecular Measures Cores to assure maximal synergy. The specific aims of the Health and Mobility Measures Core are to: 1) to provide centralized intervention development and measurement expertise, including consultation and mentoring to advance our thematic investigations of physical reserve and resilience 2) to develop measurement protocols and train personnel in administration and data collection 3) to identify gaps in reserve and resiliency measures and develop and/or adapt innovative new measurement approaches for related outcomes

Molecular Measures Core (MMC)

Leader 1: Virginia B. Kraus, MD, PhD vbk@duke.edu

Leader 2: James Bain, PhD james.bain@duke.edu

Molecular profiling can uniquely discover biomarkers, and predict and monitor traits and processes to understand and optimize reserve and resilience. The goal of the Molecular Measures Core (MMC) is to promote an understanding of the means to optimize whole person reserve and resilience through analyses of molecular factors indicative of cellular and tissue level ability to withstand and recover from stressors. The MMC complements the whole person level analyses offered through the Health and Mobility Measures Core and is inter-dependent with the Analysis Core, which is responsible for statistical analysis and modeling of data generated by the Health and Mobility Measures Core and MMC. The MMC has extensive molecular profiling capabilities for body and cell-culture fluids and tissue extracts, including inflammatory, metabolic, biochemical, senescent, genomic/epigenomic, and extracellular vesicle markers. The MMC has capabilities to expand and adapt existing core capabilities to facilitate the many needs of the novel investigator-initiated research projects affiliated with our Duke OAIC. The current development project is a translational research project to test in vivo and in vitro resilience to stressors that uses a senescent model system to test interventions to promote resilience, The specific aims of the Molecular Measures Core are to: 1) to perform molecular analyses to support researchers and scholars, and harmonize markers across Duke OAIC research projects 2) to develop new molecular profiling and testing capabilities to evaluate resiliencies in the setting of stressors including SARS-CoV2 3) to conduct systems pathway analyses to identify biological pathways indicative of resilient phenotypes 4) to provide research-oriented mentorship, consultation and training on principles and methods of molecular analyses, in collaboration with PESC and REC

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications

Sonali Advani, MBBS, MPH
Assistant Professor of Medicine / Department of Medicine
<u>Deprescribing intervention to reduce inappropriate antibiotic exposure and improve resilience in older adults</u>

2022-2024 /
5 (total)
4 (1st/Sr)

Specific Aim 1: To develop and implement a deprescribing intervention to reduce inappropriate treatment of ASB in hospitalized older adults. Hypothesis 1: Our deprescribing intervention leveraging the UA with pharmacist support will reduce inappropriate antibiotic use in older adults with ASB. Specific Aim 2: To assess the feasibility, safety, and acceptability of this deprescribing intervention in older adults. Hypothesis 2: Our deprescribing intervention focusing on older adults with ASB will be safe, feasible, and acceptable. Reducing inappropriate treatment of ASB is a key priority for the American Geriatrics Society, CDC, and AHRQ. The CDC has identified "urinalysis" as a key opportunity to improve antibiotic use, and recommends developing criteria to differentiate between ASB and symptomatic urinary tract infection (UTI).

- SHEA Research Scholar Award (Society for Healthcare Epidemiology of America)

Leah Acker, MD, PhD
Medical Instructor / Department of Anesthesiology
<u>Pilot testing of a non-invasive neuroimmune modulation tool— transcutaneous auricular vagus nerve stimulation (taVNS)—to enhance perioperative cognitive resilience in older adults</u>

2022-2024 /
3 (total)
0 (1st/Sr)

The objective of this pilot proposal is to identify and quantify barriers to a feasible, high-fidelity randomized controlled trial (RCT) of self-administered taVNS to prevent POD in older surgery patients. The rationale for this pilot study is that understanding feasibility challenges early will allow us to carefully design a future RCT with maximal clinical impact. Aim 1: Measure the fidelity and tolerability of preoperative self-administered taVNS in anxious surgery patients age = 65. Aim 2: Quantify the feasibility of recruiting and retaining anxious surgery patients age = 65 to self administer preoperative taVNS with high fidelity. Exploratory aim: Assess the dose-relationship between taVNS and anxiety, heart rate, and inflammation.

- The Role of the Aging Brain-Heart-Immune Axis in Postoperative Delirium

Kimberly Hreha, EdD, OTR/L
Assistant Professor / Department of Orthopaedic Surgery
<u>Evaluating Physical Resilience and Best Practices in Vision Rehabilitation of Stroke Patients: A Mixed Methods Approach</u>

2022-2024 /
1 (total)
0 (1st/Sr)

Aim 1: Identify which strategies best support accessibility and tolerability of assessment and study enrollment protocols. Aim 2: Obtain feasibility data and explore facilitators and barriers of physical resilience measurement.

- Influence of Vision Impairments on Dementia in Stroke Survivors: A Longitudinal Analysis

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Past Scholars
Corey Simon, Orthopaedic Surgery (2018-2020)
Nazema Siddiqui, MD, MHS, Obstetrics and Gynecology (2018-2020)
Anthony Sung, MD, Senior Fellow in the Duke Center for the Study of Aging and Human Development, Center for the Study of Aging and Human Development, Institutes and Centers

(2018-2020)

Brian James Andonian, MD MHSc, Department of Medicine, Division of Rheumatology and Immunology (2020-2022)

Ming-Feng Hsueh, PhD, Department of Orthopaedic Surgery (2020-2022)

Daniel Parker, MD, Department of Medicine (2020-2022)

PILOT/EXPLORATORY PROJECTS (8 Pilot Projects Listed)

1. Project Title: **ApoE: A new target to improve aged bone healing**

Leader: **Gurpreet Baht, PhD**

Aim 1: Develop a therapeutic intervention to improve aged bone fracture healing. In our recent study, we showed that lowered circulating ApoE levels in knockout mice were associated with improved aged fracture repair. To test whether temporarily lowering circulating ApoE levels during fracture healing will improve fracture outcome, we will perform fracture studies with small molecule reverse agonists to a nuclear receptor that controls ApoE expression. Aim 2: Identify the immunophenotypic differences in the fracture calluses of aged mice treated with inhibitors of ApoE expression. We hypothesize that ApoE-based age-associated changes in fracture repair are due to changes in the immunophenotype of the fracture callus.

2. Project Title: **Resilience after heart transplant or LVAD in patients with advanced heart failure**

Leader: **Adam DeVore, MD MHS**

Aim 1: Determine the feasibility of a comprehensive assessment to predict resilience and to describe normative values in patients with advanced heart failure. We will enroll approximately 50 patients undergoing evaluation for heart transplant or LVAD at Duke. We will collect information on the completion rate of each assessment during the study protocol and collect qualitative data from the study teams on feasibility and study burden. Aim 2: Describe at what time point after surgery patients with advanced heart failure recover using assessments of physical, cognitive and psychosocial health.

3. Project Title: **Mechanisms underlying variation in primate physiological reserve**

Leader: **Elaine Gomez Guevara, PhD**

Aim 1: Measure oxidative stress and telomere dynamics across the lifespan in species of Lemur (fast maturation, shorter lifespan than Propithecus, while sympatric) and Propithecus (extreme longevity for body size in nature, very slow development, low rate of actuarial senescence, evidence for enhanced somatic maintenance). Lemur catta, the ring-tailed lemur, and Propithecus coquereli, Coquerel's sifaka, will be monitored at the Duke Lemur Center. Aim 2: Validate inflammatory biomarkers as age-related markers in these models.

4. Project Title: **Understanding the role of IL-15 signaling in podocyte resilience and survival**

Leader: **Gentzon Hall, MD PhD**

Hypothesis: A functioning IL-15/IL-15R axis is essential for homeostatic prosurvival signaling in podocytes, and impaired IL-15 signaling reduces podocyte resiliency to proapototic stimuli, increasing risk of glomerulosclerosis .Aim 1: To characterize the effects of IL-15/IL-15R knockdown a) on podocyte resiliency and loss in response to proapoptotic stimuli and b) on signaling through three prosurvival transcriptional regulatory pathways. Aim 2: To characterize the effects of targeted IL-15/IL-15R KD on pronephric integrity and function in DBP-GFP zebrafish.

5. Project Title: **Personalized Targeted Nutrition via StructurEd Nutrition Delivery Pathway to Improve Resilience in Older Adult Trauma Patients – SeND Home**

Leader: **Krista Haines, DO, MABMH**

Our long-term goal is to improve resilience for critically ill older adults who suffer trauma. The overall objective of the current proposal is to fully develop the SeND Home program through a formal feasibility, acceptability, and fidelity trial using an iterative design. We will accomplish our goals through the following aims: Aim 1: Assess the feasibility, fidelity, and acceptability of SeND Home for older adult trauma patients. We will enroll 40 older patients and follow them post-discharge using SeND Home using a 3:1 randomization. We will determine feasibility by measuring the ability to recruit and enroll the target number of patients, maintain 90% enrollment over a three-month period, and adherence rates to the study protocol. We will test acceptability by interviewing patients and stakeholders. We determine fidelity by measuring the proportion of inventions delivered according to the study protocol. Aim 2: Establish a plausible range of nutrition related outcomes for patients participating in SeND Home. Aim 3: Identify key barriers to nutrition delivery for older adult trauma patients in the hospital and discharge setting.

6. Project Title: **Individual and dyadic factors associated with older dialysis patients' physical resilience**

Leader: **Nicole DePasquale, PhD, MSPH**

Aim 1. Explore and describe individual (patient and care partner) and dyadic factors influential for patients' physical resilience. Each member of the care dyad will separately complete semi-structured, qualitative interviews to allow for an in-depth exploration of experience, feelings, perceptions, attitudes, and behaviors regarding patients' physical resilience, or ability to maintain, regain, or optimize physical function, following dialysis initiation and factors influencing it. Aim 2. Identify dyadic care types associated with different degrees of physical resilience. Each member of the care dyad will separately complete a survey containing measures that complement interview questions in Aim 1. Quantitative survey data obtained from Aim 2 will facilitate examination of similarities and differences in care dyads' qualitative accounts. These patterns will enable identification of dyadic care types, or groups of care dyads distinguished by contributing factors to and demonstrated levels of physical resilience.

7. Project Title: **Development of a Risk Assessment Tool to Enhance Physical Resilience in Older Adults following Orthopedic Surgery for Acute Injury: A Feasibility and Acceptability Pilot Study**

Leader: **Laura Pietrosimone, PhD and Trevor Lentz, PhD**

Aim 1: Determine the feasibility and acceptability of remotely measuring multidimensional psychological distress, social needs, mobility, and physical function following surgery for lower extremity fracture in older adults. We will conduct a pilot observational cohort study of older adults (?65 years-old) undergoing surgery for ankle fracture (n=15) at Duke Health. Subaim 1a will establish the feasibility of recruitment and retention of older adults in a study that uses remote assessment methods post-surgery. Subaim 1b will assess the feasibility and responsiveness of remotely administered patient-reported measures not commonly used older adults including psychological measures (grit scale, OSPRO Yellow Flag Assessment Tool,

SPARE psychological screening tools, STarT MSK tool) and social needs screening (HealthLeads screening tool). Subaim 1c will determine the feasibility and acceptability of remote mobility monitoring and functional assessments (e.g., TUG, gait speed) to establish functional recovery. Pilot data will inform the suitability of using these methods and measures in a future fully-powered cohort study.

8. Project Title: **The role of pericytes in postoperative neurocognitive disorder during aging**

Leader: **Ting Yang, MD, PhD**

The central hypothesis is that pericytes are a key cellular target in protecting the BBB integrity and ensuring neurologic sequalae from systemic inflammatory injury in the aging brain. The Objective is to identify the role and the molecular mechanisms for preserving pericytes function following a predictable stressor (i.e. surgery) thus enhancing brain resilience to long-term cognitive decline during aging. Aim 1: Determine the role of pericyte loss in transitioning from acute to long-lasting cognitive decline during aging. Aim 2: Identify the impacts of aging related pericytes transcriptomic changes on BBB function.

DEVELOPMENT PROJECTS (3 Development Projects Listed)

1. Project Title: **Cellular senescence burden as a molecular indicator of resilience**

    Leader: **Virginia Kraus, MD PHD**

    Core(s):

Stress elicits the Senescence Associated Secretory Phenotype (SASP) and the upregulation of lysosomal hydrolases. These cellular senescence responses have recently been discovered to be physiological tissue repair and remodeling responses. The complex systems of tissue repair and remodeling comprise the molecular foundation for resilience. We established the model system and markers in the classic @I38 human fibroblast cell line. These recent exciting insights define a beneficial role in tissue repair for SASP, the increased expression and secretion of a suite of inflammatory cytokines, growth factors, and proteases. When senescence reverts from an acute and transient state, such as in wound healing, to a chronic state with accumulation of senescent cells, the well-known phenomena of aging, including loss of reserve and resilience, are observed. In fact, the SASP is very similar to the inflammatory and coagulation markers associated with frailty and mortality in the elderly. Clearance of senescent cells in mouse models reduces expression of SASP factors in tissue and delays aging. The Specific Aims of this project are: Aim 1) To develop a panel of molecular markers indicative of senescent cell burden based on markers associated with SASP, soluble lysosomal exoglycosidases able to be detected in serum that might be a marker of a senescence process, and microRNAs we identified, through Duke OAIC pilot funding, as associated in elders with high function and longevity; and Aim 2) To evaluate the expression and interdependence of these factors in an *in vitro* model system followed by analyses of these factors in the CALERIE cohort and in future collaborations with other Duke OAIC projects. We hypothesize that methods that are senomorphic (change senescence) promote resilience.

2. Project Title: **Testing the resilience of the latent class trajectory model when the conditions of the model are not met**

    Leader: **Carl Pieper, DrPH and Jane Pendergast, PhD**

    Core(s):   Analysis (AC)

The objective of this project is to examine factors which impact the validity of discovering and defining latent classes of change under two types estimation models: commonly latent class trajectory model and Generalized mixed models. Both models are in wide use in assessing latent classes of trajectories, but make different underlying assumptions about the data structure. Initially, in the analysis of a panel data set, we observed that the 2 model types gave different results. We were surprised by the magnitude of the differences and research implications of these initial findings. In a deeper dive into the causes of the differences we observed, we learned that mis-specification of the error structure of the replicate observations led to incorrect definition of the number of classes contained in the data. The mis-classification occurred even in the presence of small correlations (0.1). These findings have implications for the validity of the findings derived under statistical packages used in the field. We demonstrated this both in simulations, where external factors could be controlled, and in real data. Using simulation, we plan to extend these investigations into other analytic issues commonly observed in longitudinal investigations change.

3. Project Title: **Developing Resiliency Related Health Data Science Capacity**
   Leader: **Juliessa Pavon, Katherine Hall**
   Core(s):

The goal of this DP is to (Aim 1) develop and build resiliency related health data science capacity in our OAIC, and (Aim 2) grow geriatric and resilience-focused research capacity within the larger Duke community. (Aim 1): This work is directed at two vulnerable, high-risk patient populations in which we intend to identify physical and psychosocial stressors as a potential target for intervention, to identify a resilience phenotype, and to work with key stakeholder providers to translate findings to practice. The DP is housed in the HMC because of Dr. Pavon's HMC role, but represents an inter-core (HMC and AC) collaboration with Duke's Center for Actionable Health Data Science (Duke Forge). Methods. We will link Duke geospatial data with EHR clinical data to identify patterns of potentially modifiable clinical factors that may be most characteristic of patients recovering from hip fracture or congestive heart failure who exhibit resilience (days out of hospital, that approximates time spent in good health between hospitalizations) within/across geographic areas identified as disadvantaged. DP methods will be guided and developed by HMC Core faculty Pavon and Dupre, AC Core faculty, and Dr. Ricardo Henao (Forge's Principal Data Scientist) in collaboration with Forge's expert informaticists, biostatisticians, and electrical and computer engineers. Forge teams are renowned for signal processing, pattern recognition, machine learning, and predictive modeling of complex biological and clinical data. This project will employ machine learning techniques, e.g., relevance vector machines, to develop descriptive and probabilistic models. Methods (Aim 2): We will use the synergy of our OAIC to grow and develop resilience focused capacity within the OAIC and larger Duke community. AC faculty and Forge will provide the quantitative expertise and use machine learning and other advanced analytic techniques to develop descriptive and predictive models (Data to Knowledge) which will subsequently be shared with OAIC scholars and clinicians (Knowledge to Practice) for dissemination and development of promising data-driven interventions. The proposed DP will build an infrastructure and system-wide relationship that will serve investigators and clinical practice in the years to come and further one of Dr. Pavon's career goals as a Geriatrics Health Informatics Scientist.

RESEARCH (22 Projects Listed)

1. Project Title: **PHYSICAL RESILIENCE PREDICTION IN ADVANCED RENAL DISEASE**

Leader(s): **BOWLING, CHRISTOPHER BARRETT**
DURHAM VA MEDICAL CENTER
VA I01HX002704 / (2019 - 2023)

Core(s):

ABSTRACTBackground: Older Veterans with advanced chronic kidney disease (CKD) face complex decisions to initiateor forgo dialysis in the context of uncertainty about their future health and physical function. Making thesedecisions is complicated by the course of advanced CKD which is characterized by frequent health events thatfurther worsen function. Decisions support tools are needed that are specific to the clinical course of advancedCKD and predict outcomes that matter most to these patients, such as physical function. Characterizing howpatients bounce back from health events, such as illnesses or injuries that result in emergency department(ED) visits or hospitalizations may be key to predicting future functional status. This approach draws from thenovel geriatric concept of physical resilience, defined as one s ability to resist or recover from functional declinefollowing a health stressor. Objectives: To help older Veterans make informed decisions about kidneydisease treatment by better characterizing physical resilience and identifying patient factors associated withphysical resilience to develop a prediction tool for physical resilience in advanced CKD. This addresses theHSR&D priority of Patient-Centered Care domain. To do this, we propose Physical REsilience Prediction inAdvanced REnal Disease (PREPARED), a prospective cohort study of older Veterans with advanced CKD withthe following Aims:1. To characterize physical function trajectories before and after an acute health stressor in order to define physical resilience among older Veterans with advanced CKD.2. To identify associations between patient characteristics and physical resilience trajectory and potential candidate variables for prediction model development.3. To develop a prediction tool for physical resilience (where this quantity has been defined in Aim 1).4. To determine the association of physical resilience with short-term mortality.Methods: We will conduct a longitudinal cohort study of 800 Veterans = 70 years old, with an estimatedglomerular filtration rate (eGFR) < 30 ml/min/1.73 m2 (excluding dialysis or transplant), and 90-day probabilityof hospitalization = 50% (based on the Care Assessment Needs [CAN] score). Telephone assessments willinclude brief validated measures of function every 8 weeks, and within 14 days following a stressor for up to 6calls. In Aim 1, we will characterize physical resilience, first by identifying latent classes of physical resiliencetrajectories using general growth mixture modeling. Next, among the subset from the physical resilience latenttrajectory class we will fit a piecewise linear mixed effects model to quantify resilience. In Aim 2, we willdetermine how the physical function trajectory is moderated by person-level health and psychosocial factorsand organ system-level physiologic factors. This information will be used to identify potential candidatevariables for our prediction model in Aim 3. The purpose of Aim 4 is to determine the prognostic importance ofphysical resilience by examining the relationship between experiencing a stressor and physical resilience with6-month mortality. Impact: The proposed study addresses the most pressing clinical dilemma in this complexcondition that disproportionately affects older Veterans. Data on physical resilience from the proposed studywill be used to develop a practical tool to address a vital question that CKD patients, their families, andproviders face when making treatment decisions. Limiting uncertainty about future health by predictingresilience will support individualized and patient-centered decision-making for kidney disease. Next steps: Wewill develop a clinical trial to test the use of our physical resilience prediction tool and work with our local andnational operations partners (Durham VA Renal Service, Office of Geriatrics and Extended Care, Renal FieldAdvisory Committee) to implement physical resilience assessment into care for these patients.

2. Project Title: **EXPLORING THE EFFECTS OF EXERCISE TRAINING ON PTSD SYMPTOMS AND PHYSICAL HEALTH IN OLDER VETERANS WITH PTSD**

Leader(s): **HALL, KATHERINE SHEPARD**
DURHAM VA MEDICAL CENTER
VA I01RX003120 / (2020 - 2024)

Core(s):

Posttraumatic stress disorder (PTSD) is prevalent among military Veterans, and affects over 30% of older, Vietnam-era Veterans. These servicemembers have endured nearly 40 years with these symptoms, and as a result, have significantly poorer health, higher rates of chronic disease and obesity, and an excess mortality rate 3 times higher than the general population. Clearly PTSD is more than just a psychological disorder. There is evidence to suggest that the pathway from PTSD to poor health is mediated by behavioral risk factors, such as exercise. Structured exercise is a highly effective, pluripotent strategy for the prevention, treatment, and management of chronic physical and psychological health conditions in older adults. To date, only a few pilot studies of exercise and PTSD have been published, and all suffer a major limitation: a singular focus on outcomes above the neck. These studies do not report the impact of exercise on physical health- and mobility-related outcomes that contribute to long-term impairment and disability in Veterans with PTSD. There have been no studies of exercise and PTSD done in older adults, representing a significant research gap. This research examines a wellness-based approach to promoting health in older Veterans with PTSD, targeting exercise, a major modifiable risk factor. The objective of this study is to compare the impact of a supervised exercise program on PTSD symptoms and related health outcomes versus a healthy aging attention control group (HA-ATC). This study will be a randomized controlled trial of a 6-month, supervised exercise program among 188 Veterans 60 years of age with PTSD at the Durham VAHCS. Participants will be randomly assigned to Supervised Exercise or HA-ATC. The exercise arm will include 3 weekly exercise sessions, each one lasting approximately 60 minutes, led by an exercise specialist. The HA-ATC will receive a health education program and materials modeled on the 10 KeysTM to Healthy Aging curriculum and the National Council on Agings Aging Mastery Program. The HA-ATC will include an 8-week face-to-face group program followed by 4 monthly sessions, the latter of which will be further supplemented with mailed informational packets, email newsletters, webinars, and group video telehealth sessions. Participants in the Exercise intervention arm will receive an individualized exercise prescription based on the individual s exercise history, current exercise capacity, personal preferences, and current health status. This will be a multicomponent program that includes a selection of 8 to 12 strengthening, balance, and flexibility exercises targeting the major muscle groups as well as primary joints. Participants will also be instructed in endurance exercise, including treadmill walking or recumbent bicycle. The exercise protocol will consist of a 5-10 minute warm-up, followed by a series of progressive aerobic and strengthening exercises, and will end with a 5 minute cool-down. The primary outcome for this study will be PTSD symptoms assessed with the CAPS-5. Physical function, another outcome of primary interest will be measured objectively with a Physical Performance Battery. This test battery assesses aspects of daily function including balance (single leg stance), gait speed (4 meter walk), and chair stands (# in 30 seconds). Aerobic endurance, the investigators primary functional outcome, will be assessed with the 6-minute walk test (6MWT). Secondary outcomes include depression, sleep, and cognitive function. Outcomes will be assessed at baseline, 3 months, and 6 months. Assessments will be repeated 12 weeks post-intervention (9 months) to examine whether any observed exercise intervention effects are maintained. Mixed linear models will be used to compare outcomes for the two study arms.

3. **Project Title:**	**Novel mechanisms of microRNA-mediated anabolic effects in age-related osteoarthritis**
Leader(s):	**HSUEH, MING-FENG**
	DUKE UNIVERSITY
	NIH K01AG078445 / (2023 - 2028)

Core(s):

Abstract Osteoarthritis (OA) is the most prevalent degenerative disease in older adults with the incidence rising rapidly after age 50 and leveling off after age 70. OA is also one of the common causes of chronic pain and the leading cause of physical disability in older adults. Currently, there is an unmet need for therapeutic strategies to improve the outcome for patients with OA. Our latest work identifies a list of microRNAs (miRNAs) in human cartilage and demonstrates a strong association with a robust anabolic effect. This effect is joint-specific and follows a distal-proximal axis gradient (high in ankle and low in hip). Studies show that a joint's identity is maintained by synovial cells and that there is a distinct miRNA profile in different joints. Together, this suggests that the miRNAs we identified in cartilage may originate from synovium and be involved in maintaining joint homeostasis. In Aim 1, I will determine the synovial cell types that express these regenerative miRNAs within human joints and the effects of age on the expression of these miRNAs. In Aim 2, I will determine the signaling pathways responsible for the miRNA-mediated anabolic effects in cartilage and the effects of age on these pathways. I will conduct gene set enrichment analysis to determine miRNA-mediated pathways and then use proteomics to validate these pathways. Through this project, I will determine the miRNA-mediated mechanisms by which synovial cells promote endogenous anabolic effects in the human joint. The key career enhancement of this award will be the training in computational bioinformatics to analyze the complex datasets generated by the project, and further training in aging biology to understand how aging impacts the regeneration process. To facilitate progress toward independence, the training plan will include the coursework/workshops in computational bioinformatics and aging biology, extensive internal and external scientific meetings, and career professional development activities and mentorship. The research and career development

plan detailed in this proposal will be conducted with a team of outstanding mentors. Dr. Yi-Ju Li, a professor of Biostatistics & Bioinformatics and an expert in statistics and bioinformatics, will serve as the primary mentor and focus on the training in bioinformatics, statistics, and professional skill development. Drs. Cathleen Col n -Emeric, Virginia Kraus (Duke), and Patrik nnerfjord (Lund University, Sweden) will serve as co-mentors; they will facilitate training in translational aging research, OA research, and proteomics, respectively. The environment at the Duke University and Duke Molecular Physiology Institute, where the main research activities are located, are ideal for the research and training activities outlined in this proposal. This award will enable me to elucidate the novel contributions of miRNAs to joint tissue homeostasis. Advancements in this area of research have the potential to develop as new therapeutic strategies aimed at improving the quality of life for patients with OA.

4. Project Title: Influence of Vision Impairments on Dementia in Stroke Survivors: A Longitudinal Analysis

Leader(s):   HREHA, KIMBERLY PATRICE
DUKE UNIVERSITY
NIH K01HD106010 / (2023 - 2026)

Core(s):

PROJECT SUMMARY/ ABSTRACT This is an application for a K01 Mentored Research Scientific Development Award. The goal of the proposed project is to provide the candidate with the advanced skills needed to establish an independent research program examining the visual health needs of stroke survivors also living with dementia. To facilitate this long-term goal, the candidate proposes a comprehensive training plan, combining formal coursework and meetings overseen by her mentors, participation in applied training experiences and involvement in seminars and workshops. Specific training goals include: (1) gain advanced knowledge in the epidemiology and mechanisms of post-stroke dementia, (2) learn neuropsychological and clinical assessment of dementia, (3) acquire skills and training in clinical research methodology and statistical analysis, using both cross sectional and longitudinal data and (4) productively participate in career advancement and leadership development activities. The training plan will be executed in coordination with the set of research activities mentioned above, which are based on preliminary data collected by the applicant. The preliminary data show a lack of research on whether the presence of specific types of vision impairment and ocular deficits increase the risk of post-stroke dementia. The candidate will expand on these findings by using data from the Atherosclerosis Risk in Communities stroke cohort to complete the following aims: (1) characterize the prevalence and outcomes associated with vision impairment(s) among stroke survivors with and without dementia; (2) determine how pre-existing vision impairments impact the development of dementia, among those with stroke; and (3) determine the effect and downstream consequences of post-stroke vision impairment in persons without pre-existing vision impairment. The primary hypotheses include that: (1) the odds of developing dementia are higher for stroke survivors with pre-existing vision impairment, compared to stroke survivors with normal vision; (2) stroke survivors with vision impairment preceding the stroke are more likely to develop dementia earlier, compared to stroke survivors with normal vision; and (3) the impact of post-stroke vision impairment on dementia development is stronger for those with functional impairment, compared to those without functional impairment. The expected findings will provide critical insight into the types of vision impairment and ocular deficits experienced by people with post-stroke dementia, including more information on the significance of distinguishing between pre- and post-stroke visual impairments and the expected differential impact on dementia. Results from this research will be used to develop a subsequent R01 research proposal that will facilitate the candidate s transition into an independent researcher focused on analysis of existent data and prospective enrollment to optimize the independence and community participation of stroke survivors with vision impairments and dementia.

5. Project Title: DEPRESCRIBING CENTRAL NERVOUS SYSTEM MEDICATIONS IN HOSPITALIZED OLDER ADULTS

Leader(s):   PAVON, JULIESSA M
DUKE UNIVERSITY
NIH K23AG058788 / (2019 - 2024)

Core(s):

This K23 Career Development Award in Aging focuses on the development of Dr. Juliessa Pavon, a hospital-based geriatrician, and on reducing central nervous system (CNS) medication use in hospitalized older adults.Dr. Pavon s long-term goal is to improve the resilience of older adults against the acute stressors ofhospitalization. She has built her research program on investigating hazards of hospitalization, and a majorthreat is high-risk medication exposure. Sub-optimal CNS medication use during hospitalization is a keymodifiable risk factor for poor health outcomes; common classes include opioids, anxiolytics, anti-depressants,antipsychotics, and hypnotics. Our preliminary data suggests that nearly 40% of hospitalized older adults areexposed to anxiolytics and 60% to opioids during their hospital stay. De-prescribing is a systematic process oftapering or reducing medications. Interventions to facilitate de-prescribing that target specific medicationclasses, like CNS medications, or specific populations, like those with existing cognitive impairment, have notbeen well-studied in the inpatient setting. This gap represents a key opportunity to reduce potentiallyinappropriate CNS medications and their debilitating side effects in vulnerable patients--in line with the NationalInstitute of Aging s priorities to improve medication use in older adults. Dr. Pavon s K23 award proposes todevelop and pilot test a de-prescribing intervention that is informed by a theoretical model of behavioralchange. Aim 1 results will inform the epidemiology of the problem and identify target populations forrecruitment. Aim 2 will use qualitative methods to examine barriers and facilitators of hospital de-prescribing.Results will inform the intervention delivery strategies best suited to facilitate CNS medication de-prescribing ina well-tolerated, feasible manner. Aim 3 will develop and pilot test a multi-component hospital-based de-prescribing intervention that uses health informatics for content delivery, and provider behavior change andpatient activation strategies. This work will advance understanding of 1) which patients and CNS medicationclasses to target for de-prescribing interventions, 2) whether there are unique barriers to de-prescribing in thehospital setting, and 3) the optimal delivery strategy for safely de-prescribing. During this K23 grant period, Dr.Pavon will also complete additional training in Markov modeling statistical techniques, interventiondevelopment, health informatics, and leadership. Dr. Pavon s mentor team will provide scientific support withexpertise in aging, pharmacology, hospital medicine, and research methodology. This career developmentplan will give Dr. Pavon the skills in conducting intervention development studies within the hospital setting.This training and resulting data will establish Dr. Pavon as a strong candidate for an R01 intervention designedto facilitate de-prescribing of CNS medications for the nearly 1 in 2 older adults that will experience exposure toa CNS medication during hospitalization.

6. Project Title: METABOLOMIC & RADIOGRAPHIC MARKERS OF FRACTURE RISK AMONG OLDER ADULTS WITH DIABETES
Leader(s): LEE, RICHARD H.
DUKE UNIVERSITY
NIH K23AG058797 / (2018 - 2023)

Core(s):
ABSTRACTAmong its medical complications, type 2 diabetes mellitus in older adults is associated with atwo-fold increase in the risk of hip and other low-trauma bone fractures. Paradoxically, thisincreased risk occurs despite a higher average bone mineral density. This increased fracturerisk is likely multifactorial, stemming from metabolic dysfunction that results in both increasedfalls risk and decreased bone strength. However, fracture risk stratification currently is limitedlargely to bone density testing and clinical risk tools that do not perform adequately for adultswith diabetes. Because bone is both a metabolic and structural tissue, metabolomics andbiomechanical analyses would be particularly useful for developing and assessing newmeasures of fracture risk. The objective of this application is to develop and evaluateradiographic and laboratory biomarkers of fracture risk among older adults with diabetes,utilizing biomechanical and translational measures. The proposed research has the followingaims: 1) Determine the association between metabolomic profiles and incident clinical fractureamong older adults with diabetes; 2) Compare geometric and biomechanical measures at thefemoral neck and intertrochanteric region among older adults with diabetes, with and without hipfracture. This application builds upon the prior published work and clinical expertise of thePrinciple Investigator, Dr. Richard Lee, and provides him additional research skills to assist withhis career development goal of understanding the interaction of chronic medical conditions onthe bone health of older adults, focusing on diabetes. Dr. Lee is a dual-trained Geriatrician andEndocrinologist with expertise in metabolic bone disease. The primary training goals of thisproposal include the following: 1) Develop laboratory and analytical skills in translational sciencethat will be used in the development and evaluation of clinical biomarkers, including omicstechnologies; 2) Acquire principles and skills in biomechanical engineering and materialsscience to integrate with clinical and epidemiological analyses. By integrating biomechanicalengineering and metabolomics approaches with epidemiologic research to identify new markersof fracture risk, this application addresses a significant source of morbidity and mortality amongan increasing proportion of older adults.

7. Project Title: **Longitudinal Characterization of the Older Adult Trauma Patient Experience**

Leader(s):   **HAINES, KRISTA**
                     DUKE UNIVERSITY
                     NIH K23AG065464 / (2020 - 2025)

Core(s):

PROJECT SUMMARY This proposal presents a five-year research career development program focused on describing the comprehensive long-term experience of trauma from the perspective of older adults and their family caregivers. The candidate is currently an Assistant Professor of Surgery at Duke University and acute and critical care trauma surgeon, with previous research experience in trauma-related outcomes and healthcare disparities, and has now chosen to focus on aging research, qualitative analysis, and health-related quality of life (HRQoL) research with a diverse mentoring committee of investigators with expertise in geriatrics, gerontology, surgery, critical care, and qualitative research. The proposed experiments and didactic training will provide the candidate with a unique set of skills that will help her transition to independence as a surgeon-scientist and enable her to fill a significant experience gap in the field of research dedicated to the older adult trauma patient population. Traumatic injury currently effects 5.4 million older adults each year in the United States representing 23% of all trauma admissions, and these numbers are projected to climb as the population ages. The consequences resulting from trauma to older adults are magnified when compared to younger age groups. Older adults have an increased likelihood of death as a result of trauma, with one-third of patients with presenting with multisystem trauma dying prior to leaving the hospital. Indeed, trauma is the 5th leading cause of death in older adult patients. Recent research suggests that the impact of trauma on older patients, their family members, and health care systems is dramatic. Despite these findings, very few high-quality studies have been conducted to describe the long-term experience of trauma from the perspective of these patients and their respective caregivers. Indeed, very little is known from the patient perspective regarding post-discharge trajectories through care facilities, the impact of functional limitations, and what factors are associated with poor outcomes. Compounding this problem is that it remains unknown which existing quality of life measurement instruments may be optimal for older adult trauma patients. These gaps in knowledge regarding this patient population serve to make the process of informed, shared decision making about goals of care challenging for older patients, their family caregivers, and clinicians. This proposal will characterize the one-year patient healthcare experience of older adult trauma patients and their family caregivers using a concurrent nested mixed-methods study design, using both qualitative and quantitative methods consisting of a survey and concept elicitation interviews. Specifically, the work of this proposal will 1) identify aspects of quality of life (QoL) among older adult trauma patients and how these change over time, 2) characterize the caregivers experience over one year, and 3) identify a core set of both patient- and caregiver-reported HRQOL measures that address key domains identified through the interviews, and determine which measures are most effective at different time points post-trauma.

8. Project Title: **DEPRESCRIBING FOR OLDER DIALYSIS PATIENTS**

Leader(s):   **HALL, RASHEEDA K**
                     DUKE UNIVERSITY
                     NIH K76AG059930 / (2018 - 2023)

Core(s):

ABSTRACTThis is a Beeson Emerging Leaders in Aging career development award (K76) for Dr. Rasheeda Hall, MD,MBA, MHS. Dr. Hall is a nephrologist who conducts aging research at Duke University, and her long-term goalis to become a leader in geriatric nephrology and develop effective interventions targeting geriatric conditionsin older dialysis patients. Compared to older adults without kidney disease, older dialysis patients are morelikely develop severe cognitive impairment, experience more falls, and have more frequent hospitalizations.These adverse outcomes are also known to be associated with potentially inappropriate medications, and olderdialysis patients are highly susceptible to adverse effects of potentially inappropriate medications because ofaltered medication clearance due to absent kidney function and common occurrences of hypotension and mini-strokes. Given this susceptibility, reduction of potentially inappropriate medications is a logical goal forimproving quality of care for these vulnerable patients. The objective of Dr. Hall s proposed research is todevelop an evidence-based strategy to reduce inappropriate prescribing in older dialysis patients. Theresearch aims are to: 1) identify the prevalence of specific potentially inappropriate medications and the extentto which there is an association with hospitalization risk in prevalent older dialysis patients, 2) identify elementsof a deprescribing intervention that are acceptable to nephrologists, primary care providers, and patients, and3) determine the feasibility of a deprescribing intervention tailored for older dialysis patients. This work willprovide evidence to support a definitive clinical trial of

deprescribing in dialysis units. Effective deprescribinginterventions have the potential to reduce hospitalizations and ameliorate geriatric syndromes in dialysispatients which is consistent with NIA s mission. Complementary to this research, this career developmentaward will solidify Dr. Hall s transition to research independence through coursework and mentoring to: a) fillknowledge gaps in directing a team of statisticians, interpretation of pharmacoepidemiologic data, advancedmethods in handling bias in observational data, timely qualitative analyses, execution of a pilot study, andclinical trial design; b) enhance her leadership skills; and c) successfully compete for a R01. Duke University isthe ideal environment for Dr. Hall to pursue this research career development because of the strong agingresearch expertise housed in its Center for Aging and affiliated Pepper Center, as well as, rich resourcesavailable through Duke s Clinical and Translational Institute.

9. Project Title: Stress Reactivity and Low Back Pain in Older Adults: Influences on Disability (ReLOAD)

Leader(s): **SIMON, COREY**

DUKE UNIVERSITY

NIH K76AG074943 / (2022 - 2027)

Core(s):

PROJECT SUMMARY/ABSTRACT This application for the Paul B. Beeson Emerging Leaders Career Development Award in Aging (K76) is for Dr. Corey Simon, a physical therapist and geriatric pain researcher specializing in low back pain. Low back pain is one of the world s most disabling conditions for older adults, with more than 75% reporting persistent disability 1-2 years after onset. A novel disability mechanism among older adults with low back pain is high stress reactivity, which is an acute physiologic response characterized by abnormal changes in blood biomarkers after stressful encounters. High stress reactivity is linked to poorer health outcomes including disability in other chronic conditions; and accumulating research suggests high stress reactivity is mediated by abnormal thoughts and feelings and is modifiable through biobehavioral interventions. However, stress reactivity research in older adults with low back pain is lacking. This proposal in an innovative 5-year research program that builds upon Dr. Simon s pilot study demonstrating exciting preliminary associations between stress reactivity, physical function, and psychological distress. This proposal will utilize novel laboratory stress reactivity tests, patient-reported outcomes, and qualitative interviews to: 1) Identify and quantify stress reactivity in older adults with low back pain; and 2) For the purpose of reducing disability risks, develop a biobehavioral intervention that targets high stress reactivity in older adults with low back pain. This program will test his central hypothesis that older adults with low back pain and high stress reactivity are at greater risk for disability due to negative thoughts and feelings and poor coping strategies. In addition, this program will provide Dr. Simon with advanced career development in stress reactivity science, behavioral intervention development, and research leadership. Upon completion of this program, Dr. Simon will be poised to facilitate the development of an NIA-funded clinical trial (R34/R01) to test the efficacy of his innovative biobehavioral rehabilitation intervention for older adults with low back pain that targets high stress reactivity. Collectively, this program is the next step in Dr. Simon s long-term goal to become an international leader in the development of targeted interventions to eradicate disability in older adults with low back pain.

10. Project Title: Duke Roybal Center

Leader(s): **COLON-EMERIC, CATHLEEN S; STRAUMAN, TIMOTHY J;**

DUKE UNIVERSITY

NIH P30AG064201 / (2019 - 2024)

Core(s):

DUKE ROYBAL SUMMARY: Mobility is fundamental to active aging. Intimately linked to health status and quality of life, the self-initiated day to day movements of older adults are shaped by their behavior and their environment. The number of older Americans is rapidly increasing and there is a critical need to build and accelerate research capacity to test and scale behavioral interventions, programs and practices that promote healthy aging in general and mobility in particular. To address this need, we propose to establish an NIA Edward R. Roybal Center at Duke University with the theme of Accelerating Translational Behavioral Intervention Research on Aging and Mobility. Our goal is to catalyze researchers across disciplines to develop and test innovative behavioral interventions to optimize mobility for older adults. These interventions will aim to foster independence and community participation, reduce unplanned health service use, and enhance quality of life. Our center aims are to (1) develop the next generation of scientists committed to programs of translational research using interventions grounded in behavioral or social science principles to improve mobility and

promote independent living of older adults; (2) use an experiential learning-based approach to behavioral intervention development and implementation; and, (3) accelerate translation so interventions can be successfully developed, validated, and scaled across NIH Stage Model levels. Our three overarching aims will be met by the Center s two cores, designed to enhance the research infrastructure for behavioral intervention development, stimulate new research collaborations, and promote translational behavioral research in aging and mobility. The Management and Administrative Core will coordinate the Center s activities; promote interactions and networking among pilot awardees, Center scientists who represent all levels of the NIH Stage Model, and collaborating partners; integrate with our long-standing NIA-funded Pepper and Demography and Economics of Aging Centers; and use experiential learning activities (e.g. intensive lab- based intervention development and grant writing workshops) to engage investigators in learning the practical research skills necessary for conducting intervention research from problem conception to implementation. Our Pilot Core will use a novel accelerator model that provides awardees with support and practical experience in working with a dedicated research team to conduct pilot research that is feasible, rigorous, and informs theory- based intervention development. We will leverage a skilled implementation team to foster the development and testing of behavioral interventions to benefit older adults with efficient project management for progression to more advanced levels in the NIH Stage Model. This approach was proven effective in our CTSA and builds from the Pepper Center s success on innovation in aging and mobility. The Duke Roybal Center will become a central resource for behavioral intervention development and implementation, accelerating the translation of research into practice, products, and policies that positively impact the daily activities of older adults.

11. Project Title: EPIGENETIC MECHANISMS PROMOTING LONGEVITY
Leader(s): **KRAUS, VIRGINIA**
DUKE UNIVERSITY
NIH R01AG054840 / (2018 - 2023)

Core(s):

AbstractCirculating small regulatory RNAs (sRNAs) are short non-coding RNAs (typically ~19-25nt in size). They mediatea broad spectrum of biological processes through regulation of gene expression. Our experimental evidenceindicates that serum levels of miRNAs (one form of sRNA) change considerably, the vast majority increasingwith age. The ability of circulating sRNAs to travel among tissues enables them to transmit signals and regulatea broad spectrum of biological functions. sRNAs exist in a variety of RNase-insensitive ribonucleoprotein or lipidcomplexes, or are encapsulated inside different types of extracellular vesicles. Consequently, in contrast tomessenger RNA, sRNAs are protected from extracellular RNases and are measurable and stable in samplesstored for decades. Despite numerous recent developments, we are far from understanding the role of sRNAsin aging. An understanding of their role in aging mammals, and in humans in particular, is still very limited dueto the increased complexity and longer life-spans of mammals compared with invertebrates. This projectleverages existing human sample resources from three completed NIH-funded studies (EPESE, STRRIDE andCALERIE), to discover and validate longevity-associated miRNAs in humans. Our preliminary analysis of 175circulating microRNA--in the NIA-funded Duke Established Populations for Epidemiologic Studies of the Elderly(Duke EPESE) community-based cohort of elders--identified 32 differentially expressed circulating miRNAs(p 10 years) compared with age, sex and race matched but short-term survivors (

12. Project Title: GENOMIC ANALYSIS OF THE CALERIE TRIAL TO GENERATE NEW KNOWLEDGE FOR GEROSCIENCE
Leader(s): **BELSKY, DANIEL WALKER**
COLUMBIA UNIVERSITY HEALTH SCIENCES
NIH R01AG061378 / (2019 - 2024)

Core(s):

SUMMARYThe graying global population makes interventions to extend healthy lifespan (healthspan) a public heathpriority. Therapies targeting basic biological processes of aging show proof-of-concept in animals: early-to-midlife intervention can delay disease onset and prolong healthspan. But translating these geroprotectivetherapies to humans faces the barrier that human clinical trials of midlife geroprotective therapy wouldrequire decades of follow-up to measure healthspan extension. An alternative is a short-term acceleratedgeroprotector trial that tests if geroprotective intervention can slow the rate of biological aging. Biologicalaging is the gradual and progressive decline in system integrity that occurs with advancing chronologicalage. This process is thought to be the root cause of increases in morbidity and disability in

later life. Newresearch shows that biological aging can be measured in humans and that measures of biological agingpredict human healthspan. Geroprotective therapies that target basic biological processes of aging arehypothesized to slow the rate of biological aging. But this has not been tested. Our study will test if the best-established geroprotective intervention in animals, long-term caloric restriction, slows the rate of biologicalaging in midlife humans, who are still young enough for age-related disease to be delayed or prevented.We will conduct new assays of stored biospecimens from the National Institute on Aging's recently-completed CALERIE Trial, which randomized 220 non-obese adults to 25% caloric restriction (CR, N=145)or ad libitum normal diet (AL, N=75) for a period of 2 years. We have already shown that CR slows aging-related deterioration in organ-system integrity. Now, we propose to extend this test to genomic measures ofbiological aging. We will assay whole-genome DNA methylation (using Illumina chips) and gene expression(using RNA sequencing) from blood samples collected at CALERIE baseline, and at 12-, and 24-monthfollow-ups. We will use this 3-time-point repeated-measures multi-omics dataset to test (i) Does CR slowsthe rate of biological aging as measured from DNA methylation (ii) Does CR cause changes to geneexpression in the pathways known to mediate healthspan-extending effects of CR in animals, e.g. themTOR pathway (iii) Do changes to DNA methylation and gene expression mediate effects of CR on organsystem functioning We will share the multi-omics data we generate with the CALERIE Biorepository,making the resource freely available to all interested researchers. The proposed project will generate newknowledge about effects of caloric restriction on biological aging in humans and test proof of concept for anaccelerated geroprotector trial design that can speed translation of new age-delaying therapies fromanimals to humans. Open data sharing through the CALERIE Biorepository will enable research beyond thescope of this project to improve understanding of caloric restriction and advance the field of geroscience.

13. Project Title: FUNCTIONAL LIMITATIONS AND DISABILITY AMONG MIDDLE-AGED ADULTS

Leader(s):   **BOWLING, CHRISTOPHER BARRETT**
DUKE UNIVERSITY
NIH R01AG062502 / (2020 - 2023)

Core(s):

Project summary/Abstract The burden of functional limitations (restrictions in basic physical actions) and disability (problems with daily activities and life participation) may be more common in middle-aged US adults than previously recognized. However, studies of middle-age populations have not typically included functional assessments. The Coronary Artery Risk Development in Young Adults (CARDIA) study provides a unique opportunity to study functional status in a diverse, aging cohort. The Year 35 in-person exam is scheduled for 2020 and 2021, at which time, participants will be 53 to 65 years old. We propose a CARDIA ancillary study to obtain measures of function by self-report and physical performance to be paired with the existing data collected from early adulthood through middle age to address the following aims: 1. To quantify the burden of functional limitations and disability in middle age and assess the degree to which this can be attributed to the accumulation of chronic conditions, 2. To assess domains of functional limitations and disability captured by physical performance versus self-report, 3. To identify health-related risk factors in early adulthood for functional limitations and disability in middle-age, 4. To identify health-related, socioeconomic, and psychosocial factors that contribute to between- and within- race differences in functional limitations and disability among middle-aged adults. We will add measures of physical performance (fast and usual gait speed, single leg balance, timed chair stands, 6-minute walk test, and grip strength) to the CARDIA Year 35 exam (projected N=3,270; 1,563 black, 1,707 white). Also, self-reported functional limitations (Patient-Reported Outcomes Measurement Information System [PROMIS] Physical Function Short Form 20a) and disability measures (basic and instrumental activities of daily living) will be added to the Year 35 exam and annual telephone calls (1 call prior to and 2 after the Year 35 exam). As studies of younger populations have not often included functional assessments, the conceptualization, measurement approaches, risk factors, and implications of functional limitations and disability are poorly understood. Filling this knowledge gap by adding appropriate functional measures to an ongoing population based cohort, that represents the next wave of aging black and white adults will lead to new approaches to prevent functional decline and improve population health.

14. Project Title: Physical Rehabilitation for Older Patients with Acute HFpEF-The REHAB-HFpEF Trial

Leader(s):   **KITZMAN, DALANE W**
WAKE FOREST UNIVERSITY HEALTH SCIENCES
NIH R01AG078153 / (2022 - 2027)

Core(s):

Acute decompensated heart failure (ADHF) is the leading cause of hospitalization in older persons, and is associated with marked physical disability, poor health-related quality of life (HRQOL), frequent rehospitalizations, loss of independence, high mortality, and enormous health care costs. However, most of the trials testing a wide range of medications and strategies in ADHF have been neutral. In our recently completed NIA-funded phase 2 trial (REHAB-HF), an innovative, early, transitional, tailored, and progressive multi-domain physical rehabilitation intervention produced a large improvement in the primary outcome of Short Physical Performance Battery (+1.5 points) in older patients with ADHF. At baseline, the participants (53%) with HF with preserved ejection fraction (HFpEF), had significantly worse impairments in physical function, frailty, HRQOL, and depression than those with HF with reduced EF. They also appeared to derive greater benefit from the intervention, with ~50% larger effect sizes in physical function, frailty, HRQOL, and depression. Patients with HFpEF also appeared to have much greater reductions in rehospitalizations and death and potential for reduced medical resource use. The finding of potentially greater benefit in HFpEF is noteworthy as HFpEF is highly relevant to older persons and has the most urgent need for new treatments since it is: 1) the most common form of HF, nearly unique to older persons, and disproportionately affects older women and Black persons; 2) increasing in prevalence; 3) accepted as a geriatric syndrome; 4) associated with marked impairments in physical function and HRQOL and high rates of frailty; 5) has high morbidity and mortality which are worsening over time; and 6) has limited evidence-based treatments. The phase 3 REHAB- HFpEF trial will focus on this large, growing, vulnerable, underserved population. The 5-year, randomized, attention-controlled, single-blinded trial will enroll 880 older adults age >60 years with ADHF and HFpEF across 20 geographically dispersed clinical centers. We will test the hypothesis that the innovative REHAB-HF intervention will improve the clinically compelling combined primary endpoint of all-cause rehospitalizations and mortality during 6-month follow-up, the most vulnerable time period following ADHF hospitalization (Aim 1) and the secondary endpoint of prevalence of major mobility disability, a clinically meaningful outcome in trials of older adults, at 6-months (Aim 2). We will also assess the intervention s impact on HRQOL, frailty, depression, physical activity, and health care costs. Our diverse, cohesive, multi-disciplinary team and experience from the phase 2 trial will ensure efficient and effective execution and dissemination. REHAB-HFpEF directly addresses the key recommendations of several recent NIA and NHLBI sponsored workshops. Its results could improve key outcomes that are meaningful to patients, caregivers, health systems, and payers. The trial has strong potential to change clinical guidelines, reduce health care costs, and influence national coverage decisions for the large, growing, underserved, high-risk population of older patients with acute HFpEF.

15. Project Title: MECHANOTRANSDUCTION IN MENISCUS HEALTH AND REPAIR
Leader(s): MCNULTY, AMY L
DUKE UNIVERSITY
NIH R01AR073221 / (2019 - 2023)

Core(s):

ABSTRACT.Meniscal injuries are a significant clinical problem as each year 850,000 meniscal surgeries are performed in theUnited States and nearly twice as many worldwide. Meniscal tears in the avascular inner zone of the tissue donot heal well with suturing or conservative treatments and can ultimately lead to the development of osteoarthritis(OA). Therefore, new strategies are needed to enhance endogenous meniscus repair and tissue regeneration.The menisci play a critical biomechanical role in the knee, providing load support, joint stability, and congruity.Meniscus tissue is maintained through a balance of anabolic and catabolic activities of meniscus cells. Thesecellular activities are controlled not only by biochemical factors in the joint but also by physical factors associatedwith joint loading. Mechanobiology, which is the influence of mechanical factors on the biologic response of cells,is important in converting physical signals into metabolic and inflammatory responses in meniscus. However,the mechanisms by which mechanical signals are transduced in meniscus cells have yet to be identified. Ouroverall goal is to identify critical meniscus mechanotransduction pathways and modulate thesepathways to promote meniscus repair and prevent OA development.Our work has shown that transient receptor potential vanilloid 4 (TRPV4) is a critical component in cartilagemechanotransduction and metabolism. The activation of TRPV4 can block IL-1 induced catabolic responses andalso increases cell migration and proliferation, which are important processes to enhance tissue repair. Whilewe have found that TRPV4 is expressed in the meniscus, the function of this mediator in meniscus health anddisease is currently unknown. In this proposal, we will determine how mechanotransduction occurs throughTRPV4 in meniscus and identify modulators of this pathway that will be used to enhance tissue repair and preventOA development. We hypothesize that mechanotransduction by TRPV4 plays a key role in meniscus metabolismand can be modulated to enhance meniscus repair and prevent the development of OA. In this proposal, we willdetermine the effects of mechanical stimulation on TRPV4-mediated metabolism in healthy meniscus

cells.Next, we will elucidate alterations in TRPV4-mediated mechanotransduction pathways in meniscus pathology.Finally, we will enhance integrative meniscus repair and prevent the development of OA by modulation ofmechanotransduction pathways. In this proposal, we will identify the key signaling pathways downstream ofTRPV4 that may function as novel drug targets to 1) treat patients with immobilized joints to simulate exerciseand maintain joint health; 2) enhance meniscus tissue regeneration using tissue engineering strategies; and 3)enhance meniscus repair and prevent the development of OA. Novel therapeutic targets identified in thisproposal can subsequently be developed into drugs to enhance meniscus repair and prevent the developmentof OA.

16. Project Title: The role of kidney epithelial cells specific EP4 receptors in blood pressure control

Leader(s): **YANG, TING**
DUKE UNIVERSITY
NIH R01DK132619 / (2022 - 2027)

Core(s):

Hypertension is a common chronic disease with a significant impact on public health, yet its basic pathogenesis is not fully understood, and new therapeutic targets are needed. A beneficial role for prostanoids in hypertension was suggested because non-steroidal anti-inflammatory drugs (NSAIDs), which block the production of all prostanoids, can cause sodium retention and exacerbate hypertension. Among prostanoids, PGE2 and its EP4 receptor (EP4R) have been implicated in blood pressure control, but these mechanisms are unknown. Our previous work showed that conditional deletion of EP4R from all tissues in adult mice dramatically exacerbated Ang II-dependent hypertension. However, the elimination of EP4R from vascular smooth muscle cells, endothelial cells, and macrophages had no impact on hypertension development. By contrast, specific removal of EP4R from whole renal epithelia recapitulated the phenotype of exacerbated hypertension, indicating that EP4R attenuates hypertension by direct actions in the renal epithelium. Recent single-cell sequencing studies demonstrated that EP4R expression in renal epithelia is enriched in the collecting duct (CD). CDs have pivotal roles in final urinary sodium excretion through the actions of the epithelial sodium channel (ENaC). Our preliminary studies showed that mice with EP4R deletion in renal epithelia throughout the nephron had increased responsiveness to ENaC inhibitor, and PGE2 inhibits the ENaC activity in isolated CDs. Thus, we hypothesize that EP4R resists the development of hypertension through actions in the CD to reduce sodium reabsorption via ENaC. The project s objective is to identify mechanisms underlying the anti-hypertension effects of EP4R and to exploit them for new treatments of human hypertension. Our Aims are: 1) Identify cell specificity for EP4R actions in kidney epithelia to resist hypertension. We will generate mice with EP4R deleted from entire CDs, principal cells, or intercalated cells, respectively, to assess the consequences of these genetic alterations on blood pressure, sodium homeostasis, and ENaC function in hypertension; and 2) Determine the mechanisms of ENaC regulation by EP4R. We will perform patch-clamp electrophysiology in isolated CDs to characterize EP4R downstream signaling pathways that mediate its powerful effects on attenuating the development of hypertension. Successful completion of the proposed research is expected to identify the mechanisms underlying the antihypertensive actions of EP4R. The long-term goal is to identify novel therapeutic targets for essential hypertension.

17. Project Title: Role of pericytes in postoperative neurocognitive disorder during aging

Leader(s): **YANG, TING**
DUKE UNIVERSITY
NIH R03AG078882 / (2022 - 2024)

Core(s):

ABSTRACT Perioperative neurocognitive disorders (PNDs) include acute delirium and long-lasting cognitive decline. These complications have become highly prevalent in our geriatric population, especially following common surgical procedures such as orthopedic fracture repairs. Delirium impacts over 50% of older adults after orthopedic surgery, which is often performed in frail patients including those with pre-existing dementia. Delirium and dementia have bidirectional relationships even though they have distinct pathophysiologies. To-date it remains unknown how a transient episode of delirium can contribute to the development of Alzheimer s Disease and related dementia (ADRD). We have established and validated a clinically relevant mouse model to study the acute impact of surgery on delirium-like pathology in rodents. With this model we found significant changes in blood-brain barrier (BBB) function and neuroinflammatory markers. Our Preliminary Results indicate that surgery induces vascular dysfunction in the central nervous system (CNS), with a rapid

loss of ~58% of pericytes in the hippocampal microvasculature. Pericytes in the CNS play key roles in neurovascular integrity and supporting communication and signaling with other cell types. Recent studies from Alzheimer s disease (AD) samples demonstrated that pericyte dysfunction can promote neurodegeneration. The role of pericytes in delirium and their putative contribution to long-lasting cognitive decline and ADRD remain unknown This proposal will begin to investigate whether protracted loss of pericytes after surgery in aged mice predisposes to long-term cognitive decline and neurodegeneration. The Objective is to define the role of pericytes in postoperative neurocognitive disorders. Our Central Hypothesis is that aging prolongs pericytes dysfunction after surgery leading to enduring neurovascular disorders and dementia. The hypothesis will be tested in 2 aims: 1) Identify the effects of surgery- induced pericyte loss on acute and long-term neuroinflammation and neuronal loss; and 2) Determine the role of pericytes in postoperative neurocognitive disorder. We will subject adult (3-months) and aged (18-mo-old) male and female mice to orthopedic surgery, and evaluate changes in pericytes, neuronal loss, and neurodegenerative markers at 24 hr and 3 months after surgery. We will also treat aged mice with PDGF-BB to boost PDGFRb signaling and promote pericytes recruitment to possibly prevent long-lasting cognitive pathology sequalae, focusing on PNDs behaviors and neurodegenerative biomarkers 3 months after surgery. Overall, results from this project will provide a foundation to identify novel and specific targets to prevent PNDs and curtail the effects of surgery on vulnerable older adults with AD or other forms of dementia and neurodegeneration.

18. Project Title: **The Role of the Aging Brain-Heart-Immune Axis in Postoperative Delirium**

Leader(s):   **ACKER, LEAH**
              DUKE UNIVERSITY
              NIH R03AG078891 / (2022 - 2024)

Core(s):

ABSTRACT Postoperative delirium (POD) is a syndrome of acute fluctuating changes in attention and consciousness that affects up to 50% of surgery patients 65 and older, increases the risk for Alzheimer's disease (AD) and AD-related dementias (ADRD), and accelerates dementia progression. Yet, interventions for POD are limited because its pathophysiologic mechanisms are poorly understood. The vagus nerve mediates the brain-heart-immune axis, which allows the brain to suppress systemic inflammation via the cholinergic anti-inflammatory reflex. Advanced age, preoperative stressors, the condition requiring surgery, and surgery and anesthesia themselves all decrease vagal tone. Without sufficient vagal tone to keep inflammation in check, excessive inflammation will result, including neuroinflammation. Excessive postoperative inflammation is thought to play a role in POD pathogenesis. Furthermore, excessive postoperative inflammation can injure neurons, providing a plausible mechanistic link between POD and AD+ADRD. Thus, there is a critical need to evaluate the role of the brain-heart-immune axis in POD among older adults. To interrogate the aging brain-heart-immune axis as a possible contributor to POD pathogenesis, heart rate variability (HRV), the standard measure of vagal tone, will be measured before general surgery in 100 patients 65 and older. Specifically, the prospective, observational HIPPIE - HRV In POD and Postoperative Inflammatory Endpoints - study will quantify the relationship between preoperative vagal tone and (1) POD incidence and (2) postoperative increase in serum biomarkers of inflammation and neuronal injury. Successful completion of the HIPPIE study will demonstrate the involvement of the brain-heart-immune axis in POD pathogenesis and will provide novel biomarker(s) of POD risk. Furthermore, a mechanistic link between POD and the brain-heart-immune axis is anticipated to provide strong scientific justification for future trials of vagal tone enhancement as an intervention for POD. Finally, this work will provide a rich new perioperative geriatric data set including measurements of the previously unexplored perioperative brain-heart-immune axis. The data, experience, and training from this proposal will lay the foundation of a successful career in geriatrics research.

19. Project Title: **Feasibility Trial of a Novel Integrated Mindfulness and Acupuncture Program to Improve Outcomes after Spine Surgery (I-MASS)**

Leader(s):   **LENTZ, TREVOR ; GOERTZ, CHRISTINE MARIE;**
              DUKE UNIVERSITY
              NIH R34AT012082 / (2023 - 2025)

Core(s):

ABSTRACT Spine pain consistently ranks first or near the top in global rankings of disease burden, and epidemiological data suggest the burden is worsening. The number of low back surgeries has increased by 300% over the past 2 decades, accounting for approximately 30% of spine-related costs in the US. While it can provide cost- effective pain relief to some patients, up to 25% of those who undergo spine surgery will develop persistent pain requiring additional surgery, imaging, or other invasive interventions. Moreover, many patients will experience persistent opioid use, which carries significant risks of misuse, addiction, and overdose. Clinical practice guidelines strongly recommend the use of multimodal or mind and body treatments for effective pain management after surgery. This approach combines interventions with analgesic or physical therapeutic inputs alongside interventions with psychological or behavioral inputs to better address the multifaceted risk factors for persistent pain and opioid use following surgery. Integration of Mindfulness delivered via mobile app (mHealth) with auricular Acupuncture (AA) in individuals undergoing Spine Surgery (I-MASS) is a highly promising multimodal treatment approach given the distinct yet complementary mechanisms by which mindfulness and AA influence pain after surgery. Establishing the effectiveness of I-MASS requires a rigorously designed pragmatic trial comparing it to usual medical care in adults who undergo spine surgery. However, trials of this size and scope require careful preparation. This proposed mixed methods R34 project is designed to answer important preparatory questions regarding the feasibility and acceptability of I-MASS through the following Specific Aims: 1) Conduct interviews with patient and care delivery stakeholders to refine and finalize the I-MASS intervention protocol by integrating mHealth mindfulness training and AA for use in patients age 18-80 undergoing spine surgery; 2) Conduct a single-site, exploratory randomized controlled clinical trial to assess the feasibility and acceptability of I-MASS in patients undergoing single-level laminectomy, discectomy or fusion; and 3) Use feasibility trial results to develop and submit a competitive research proposal to NIH for a multi-site, pragmatic, randomized comparative effectiveness clinical trial designed to rigorously evaluate I-MASS compared to mHealth mindfulness, AA, and usual care augmented with standard education. The results of this R34 project will provide the information needed to successfully execute on such a study and create new knowledge regarding the feasibility and acceptability of a highly innovative non-pharmacological multimodal approach designed to improve the lives of patients undergoing spine surgery.

20. Project Title: Improving physical function and quality of life in older adults with prediabetes utilizing interactive small-group resistance training through video conference technology

Leader(s): **LEVITAN, ERIC ; STARR, KATHRYN N;**
IMPACTIV, INC.
NIH R44AG076087 / (2022 - 2023)

Core(s):

Vivo is a virtual small group exercise program designed for adults 55 and over that is unique in the increasingly popular digital fitness market. Vivo offers 3 key market differentiators: 1) a personalized and individualized live training experience with feedback from a certified trainer, 2) a community of older adult exercisers which enhances motivation and social support, and increase accountability and fun, and 3) the Vivo training experience focuses on improving physical function using performance feedback, goal setting, and a system to measure perceived exertion. Most older adults experience a 30% loss in muscle mass between ages 50 70. Resistance training is the most effective strategy for improving both muscle mass and function and managing sarcopenia. Vivo s programming is based on the scientific evidence that even in the absence of chronic disease, resistance training that is customized to meet the individual s needs and level of functioning is a feasible and evidence-based approach to improve physical function, regulate glucose handling, reduce the risk for falls, and prolong independent living and aging in place. To date 92 people have participated in Vivo (age range 44-93). In our pilot study of 34 older adults (74% women; mean age 70.9 y; range 60-84y) after 8 weeks of participating in Vivo with a certified trainer (average of 12 hours of training per person) we observed +25.8% improvement in upper body strength as measured by the 30 second arm curl test; +25.9% improvement in lower body strength as measured by the 30 second chair stand test; and +28% improvement in endurance as measured by the 2-minute knee raise test. The aims for this SBIR FastTrack are as follows: Phase I Aim 1: Evaluate the acceptability, feasibility, and fidelity of current Vivo prototype in sedentary older adults with prediabetes Milestone 1: Assess a) attendance, benefits and barriers/facilitators of participation; b) ease of use; and c) overall satisfaction. Milestone 2: Assess trainer fidelity. Aim 2 : Design and develop a multifunctional platform prototype for Vivo 2.0 Milestone 1: Create functional specifications of the client-centered approach (results, goals, adherence, upcoming workouts), and social engagement and support. Milestone 2: Develop a clickable prototype of the platform. Phase II Aim 1: Design and build the Vivo 2.0 platform a unified web/mobile application. Milestone 1: Assess prototype usability. Milestone 2: Iterate the design on the software and hardware to increase usage, accuracy and usability. Milestone 3: Develop and test a minimum viable software product based on the new prototype and functional design to include a mobile front-end and web front-end app and a backend database. Aim 2: Conduct a RCT to determine effectiveness of Vivo 2.0 v. wait list control. Primary outcomes will be change in lower

extremity strength after 12 weeks measured by the number of chair stands in 30 seconds and average glycemic level (HgA1c). Secondary outcomes will include improvements in quality of life, and effect of adherence and social engagement on physical function outcomes.

21. Project Title: Trajectories of blood-based biomarkers of AD, their determinants, and ability to predict cognitive impairment

Leader(s): **LIU, YONGMEI ; LUO, SHENG ;**
DUKE UNIVERSITY
NIH R56AG076622 / (2022 - 2023)

Core(s):

The AT(N) framework uses PET and/or CSF biomarkers to define Alzheimer s Disease (AD) pathology and continuum; however, its broad implementation is restricted by high cost and limited accessibility. Recent advances in primarily Caucasian samples have identified plasma AD biomarkers namely, the ratio of A 42/A 40 and phosphorylated tau (p-tau, e.g. p-tau181, p-tau217) that are highly sensitive and specific for detecting abnormal A and Tau. Plasma p- tau is particularly promising for AD diagnosis and prediction of conversion to AD; yet, their potential as markers of disease progression and risk predictors for mild cognitive impairment (MCI)/AD, especially among racial/ethnic minorities who are disproportionately affected by AD, remains largely unexplored. Here, our objective is to use trajectories of promising plasma AD biomarkers to 1) define their natural history, 2) their ability to predict the risk of developing AD- specific cognitive impairment, and 3) to identify their molecular determinants. We propose to measure A 42/A 40 and p-tau217 in 3,810 MESA participants, across five time points (Exam 1, 4, 5, 6 & 7) spanning 22 years, and human neuronal cell lines to achieve the following specific aims: Aim 1. To quantify two plasma AD biomarkers (p-tau217 and A 42/A 40) and determine their changes with age starting from age 45 to 100+. Aim 2. To determine the ability of baseline and longitudinal changes in plasma AD biomarkers to predict future cognitive impairment. Aim 3. To examine effects of vascular aging and cognitive decline-associated genomic features, that we have previously identified, on AD biomarkers. The proposed MESA longitudinal study combining plasma AD biomarkers with multi-omics data, cardiometabolic measures, brain imaging, cognitive testing, and clinical MCI/AD data across the mid- to late-life transition period is a critical next step to evaluate the utility of plasma AD biomarkers to predict future risk of cognitive impairment in a racially and ethnically diverse population, and to identify candidate causal molecular processes in early AD pathogenesis that could serve as targets for disease- modifying interventions.

22. Project Title: PRAGMATIC EVALUATION OF EVENTS AND BENEFITS OF LIPID-LOWERING IN OLDER ADULTS (PREVENTABLE)

Leader(s): **ALEXANDER, KAREN P; AMBROSIUS, WALTER T ;**
HERNANDEZ, ADRIAN ; WILLIAMSON, JEFF DOUGLAS ;
DUKE UNIVERSITY
NIH U19AG065188 / (2019 - 2026)

Core(s):

There is an urgent need for evidence to guide clinical care of older adults due to demographic shifts, includinglonger life expectancy and a recent doubling of the older adult population. Statins reduce recurrent CVD eventsand prevent initial events in patients younger than 75 years. However, clinical research has often excludedpersons older than 75 years due to a higher prevalence of comorbidity and frailty so little to no evidence isavailable to guide care in this population. For older adults living longer, the promise of preventing cognitiveimpairment is as compelling as preventing a CVD event, but some evidence suggests statins maycontribute to memory difficulty or muscle symptoms. There is equipoise regarding the usefulness of statinsfor primary CVD, dementia, and disability prevention in adults older than 75 years, especially in the settingof multiple chronic conditions, advanced age, or frailty. Evidence to improve cognitive and functionaloutcomes in older populations with diverse race/ethnicity and health status will require new clinical trialapproaches with sustainable methodology and infrastructure. We propose PREVENTABLE (PRagmaticEValuation of evENTs And Benefits of Lipid-lowering in oldEr adults), the first statin trial with a non-CVDprimary outcome survival free of dementia or persisting disability. Using a placebo-controlled pragmaticclinical trial (PCT) design across PCORnet and VA network, the trial will be under the leadership of Dr. KarenAlexander at DCRI, Dr. Jeff Williamson at WFSM, Dr. Adrian Hernandez at DCRI, and Dr. Walter Ambrosius atWFSM. This team has established experience and track-record of accomplishment in the design and conductof PCTs, trial expertise in ascertaining cognitive and disability outcomes in older adults, and is

supported by arobust administrative infrastructure for coordinating these shared responsibilities for success. The overarchinggoal of PREVENTABLE is to generate knowledge about the role of statins in older adults, a population in whichrisk/benefit for primary prevention has been under studied. The hypothesis is that a large trial conducted in anolder adult population will demonstrate the benefit of statins for reducing dementia, disability, and CV events.We further hypothesize that extensive genomic, biochemical and imaging ancillary studies will offer uniqueinsights into these key outcomes. PREVENTABLE has the following specific aims: AIM 1: Determine the roleof a moderate-intensity statin in preventing dementia and prolonging disability-free survival in patients 75 yearsand older without clinically evident coronary heart disease, including those with frailty, impaired physicalfunction, mild cognitive impairment, polypharmacy, and multi-morbidity. AIM 2: Determine the role of moderate-intensity statin in preventing hospitalization for myocardial infarction/acute coronary syndrome, stroke, heartfailure, revascularization or cardiovascular-related death, and preventing either mild cognitive impairment ordementia. AIM 3: Test the safety and tolerability of statins in older adults and collect 17,000 bio-specimens toadvance precision health.

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Berger M, Eleswarpu SS, Cooter Wright M, Ray AM, Wingfield SA, Heflin MT, Bengali S, Udani AD
Anesth Analg, 2022 Jan 1, 134(1): 159-170
https://doi.org/10.1213/ANE.0000000000005677 | PMID: 34709008 | PMCID: PMC8678191
Citations: 40 | AltScore: 18.3

8. **Associations between longitudinal changes in sleep disturbance and depressive and anxiety symptoms during the COVID-19 virus pandemic among older women with and without breast cancer in the thinking and living with breast cancer study.**
Bethea TN, Zhai W, Zhou X, Ahles TA, Ahn J, Cohen HJ, Dilawari AA, Graham DMA, Jim HSL, McDonald BC, Nakamura ZM, Patel SK, Rentscher KE, Root J, Saykin AJ, Small BJ, Van Dyk KM, Mandelblatt JS, Carroll JE
Cancer Med, 2022 Mar 22, 11(17): 3352-3363
https://doi.org/10.1002/cam4.4682 | PMID: 35315588 | PMCID: PMC9110906
Citations: 52 | AltScore: 15.5

9. **Reserve and resilience in CKD: concept introduction and baseline results from the Physical REsilience Prediction in Advanced REnal Disease (PREPARED) study.**
Bowling CB, Olsen MK, Berkowitz TSZ, Smith B, Floyd B, Majette N, Miles AL, Crowley SD, Wang V, Maciejewski ML, Whitson HE
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https://doi.org/10.1186/s12882-022-03033-w | PMID: 36585609 | PMCID: PMC9803898
Citations: 30 | AltScore: 0.5

10. **Preoperative dysphagia risk in community-dwelling adults aged =50 years: Prevalence and risk factors.**
Canick J, Campbell JC, Cohen SM, Jones HN, Leiman DA, Raman S, Porter Starr KN
Nutr Clin Pract, 2022 Jul 5, 38(1): 157-166
https://doi.org/10.1002/ncp.10889 | PMID: 35788985 | PMCID: PMC10026185
Citations: 55 | AltScore: 1

11. **Hevin/Sparcl1 drives pathological pain through spinal cord astrocyte and NMDA receptor signaling.**
Chen G, Xu J, Luo H, Luo X, Singh SK, Ramirez JJ, James ML, Mathew JP, Berger M, Eroglu C, Ji RR
JCI Insight, 2022 Dec 8, 7(23):
https://doi.org/10.1172/jci.insight.161028 | PMID: 36256481 | PMCID: PMC9746899
Citations: 46 | AltScore: NA

12. **CBX4 Regulates Replicative Senescence of WI-38 Fibroblasts.**
Chen YH, Zhang X, Ko KY, Hsueh MF, Kraus VB
Oxid Med Cell Longev, 2022, 2022: 5503575
https://doi.org/10.1155/2022/5503575 | PMID: 35251476 | PMCID: PMC8890863
Citations: 50 | AltScore: 1

13. **Economic Outcomes of Rehabilitation Therapy in Older Patients With Acute Heart Failure in the REHAB-HF Trial: A Secondary Analysis of a Randomized Clinical Trial.**
Chew DS, Li Y, Zeitouni M, Whellan DJ, Kitzman D, Mentz RJ, Duncan P, Pastva AM, Reeves GR, Nelson MB, Chen H, Reed SD
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Citations: 34 | AltScore: 33

14. **A Processed Electroencephalogram-Based Brain Anesthetic Resistance Index Is Associated With Postoperative Delirium in Older Adults: A Dual Center Study.**
Cooter Wright M, Bunning T, Eleswarpu SS, Heflin MT, McDonald SR, Lagoo-Deenadalayan S, Whitson HE, Martinez-Camblor P, Deiner SG, Berger M
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Citations: 46 | AltScore: 7.2

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Couch E, Belanger E, Gadbois EA, DePasquale N, Zhang W, Wetle T
Aging Clin Exp Res, 2022 Dec 9, 35(2): 387-397
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Citations: 23 | AltScore: 2.85

16. **The potential link between obstructive sleep apnea and postoperative neurocognitive disorders: current knowledge and possible mechanisms.**
Devinney MJ, VanDusen KW, Kfouri JM, Avasarala P, Spector AR, Mathew JP, Berger M
Can J Anaesth, 2022 Oct, 69(10): 1272-1287
https://doi.org/10.1007/s12630-022-02302-4 | PMID: 35982354 | PMCID: PMC9924301
Citations: 108 | AltScore: 17.55

17. **A Multidimensional Bioinformatic Platform for the Study of Human Response to Surgery.**
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KW, Rocke DJ, Gilner JB, Parker DC, Bain JR, Muehlbauer MJ, Ilkayeva OR, Corcoran DL, Modliszewski JL, Devos N, Foster MW, Moseley MA, Dressman HK, Chan C, Huebner JL, Chasse S, Stempora L, Aschenbrenner ME, Joshi MB, Hollister B, Henao R, Barfield RT, Ellison MA, Bailey S, Woody S, Huang ES, Kirk A, Hwang ES
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Citations: 22 | AltScore: 6

19. **Biomarker clusters differentiate phenotypes of lumbar spine degeneration and low back pain: The Johnston County Osteoarthritis Project.**
Goode AP, Hu D, George SZ, Schwartz TA, Kraus VB, Huebner JL, Cleveland RJ, Taylor KA, Jordan JM, Golightly YM
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Citations: 43 | AltScore: 6.05

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Citations: 49 | AltScore: NA

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Huang ZY, Luo ZY, Cai YR, Chou CH, Yao ML, Pei FX, Kraus VB, Zhou ZK
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Citations: 19 | AltScore: 2.85

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Citations: 34 | AltScore: 223.068

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Citations: 32 | AltScore: NA

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Liu H, Lutz M, Luo S, Alzheimer?s Disease Neuroimaging Initiative
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Citations: 24 | AltScore: 1.25

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Citations: 37 | AltScore: 8.45

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Peters AE, Kitzman DW, Chen H, Nelson MB, Pastva AM, Duncan PW, Reeves GR, Upadhya B, Whellan DJ, Mentz RJ
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https://doi.org/10.1017/S1478951521001747 | PMID: 36942584 | PMCID: PMC10032330
Citations: 34 | AltScore: 1.5

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Ramaker ME, Corcoran DL, Apsley AT, Kobor MS, Kraus VB, Kraus WE, Lin DTS, Orenduff MC, Pieper CF, Waziry R, Huffman KM, Belsky DW
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Citations: 50 | AltScore: 22.8

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Root JC, Zhou X, Ahn J, Small BJ, Zhai W, Bethea T, Carroll JE, Cohen HJ, Dilawari A, Extermann M, Graham D, Isaacs C, Jacobsen PB, Jim H, McDonald BC, Nakamura ZM, Patel SK, Rentscher K, Saykin AJ, Van Dyk K, Mandelblatt JS, Ahles TA
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Citations: 44 | AltScore: 1.25

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Siamakpour-Reihani S, Cao F, Lyu J, Ren Y, Nixon AB, Xie J, Bush AT, Starr MD, Bain JR, Muehlbauer MJ, Ilkayeva O, Byers Kraus V, Huebner JL, Chao NJ, Sung AD
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Citations: 74 | AltScore: 11.5

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Singhal S, Walter LC, Smith AK, Loh KP, Cohen HJ, Zeng S, Shi Y, Boscardin WJ, Presley CJ, Williams GR, Magnuson A, Mohile SG, Wong ML
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Citations: 58 | AltScore: 9.95

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Citations: 41 | AltScore: NA

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Thompson JC, Ren Y, Romero K, Lew M, Bush AT, Messina JA, Jung SH, Siamakpour-Reihani S, Miller J, Jenq RR, Peled JU, van den Brink MRM, Chao NJ, Shrime MG, Sung AD
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Citations: 21 | AltScore: 16.83

42. **Associating persistent self-reported cognitive decline with neurocognitive decline in older breast cancer survivors using machine learning: The Thinking and Living with Cancer study.**
Van Dyk K, Ahn J, Zhou X, Zhai W, Ahles TA, Bethea TN, Carroll JE, Cohen HJ, Dilawari AA, Graham D, Jacobsen PB, Jim H, McDonald BC, Nakamura ZM, Patel SK, Rentscher KE, Saykin AJ, Small BJ, Mandelblatt JS, Root JC
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Citations: 62 | AltScore: 5.35

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Vann CG, Zhang X, Khodabukus A, Orenduff MC, Chen YH, Corcoran DL, Truskey GA, Bursac N, Kraus VB
Front Physiol, 2022, 13: 937899
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Citations: 109 | AltScore: NA

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Wixted D, Neighbors CE, Pieper CF, Wu A, Kingsbury C, Register H, Petzold E, Newby LK, Woods CW
Diagnostics (Basel), 2022 Jul 31, 12(8):
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Citations: 39 | AltScore: NA

45. **Impact of a Novel Training Approach on Hemodynamic and Vascular Profiles in Older Adults.**
Woessner MN, Welsch MA, VanBruggen MD, Johannsen NM, Credeur DP, Pieper CF, Sloane R, Earnest CP, Ortiz De Zevallos Munoz J, Church TS, Ravussin E, Kraus WE, Allen JD
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https://doi.org/10.1123/japa.2020-0509 | PMID: 34348230 | PMCID: PMC9182940
Citations: 35 | AltScore: 2.85

46. **Severity of functional impairments by race and sex in older patients hospitalized with acute decompensated heart failure.**
Ye F, Nelson MB, Bertoni AG, Ditzenberger GL, Duncan P, Mentz RJ, Reeves G, Whellan D, Chen H, Upadhya B, Kitzman DW, Pastva AM
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Citations: 52 | AltScore: 1.5

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Zhang X, Baht GS, Huang R, Chen YH, Molitoris KH, Miller SE, Kraus VB
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Citations: 45 | AltScore: 3.35

48. **Glucosamine use, smoking and risk of incident chronic obstructive pulmonary disease: a large prospective cohort study.**
Zhang XR, Zhang PD, Li ZH, Yang P, Wang XM, Liu HM, Liang F, Wang JD, Sun Y, Shen D, Chen PL, Zhong WF, Huang QM, Liu D, Wang ZH, Kraus VB, Mao C
Br J Nutr, 2022 Aug 28, 128(4): 721-732
https://doi.org/10.1017/S000711452100372X | PMID: 34526168 | PMCID: PMC9892851
Citations: 59 | AltScore: 8.2

49. **Albumin-Corrected Fructosamine Predicts All-Cause and Non-CVD Mortality Among the Very Elderly Aged 80 Years or Older Without Diabetes.**
Zhou J, Lv Y, Zhao F, Wei Y, Gao X, Chen C, Lu F, Liu Y, Li C, Wang J, Zhang X, Gu H, Yin Z, Cao Z, Kraus VB, Mao C, Shi X
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Citations: 41 | AltScore: 1.25

50. **Geriatric Preoperative Optimization: A Review.**
Zietlow KE, Wong S, Heflin MT, McDonald SR, Sickeler R, Devinney M, Blitz J, Lagoo-Deenadayalan S, Berger M
Am J Med, 2022 Jan, 135(1): 39-48
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Citations: 73 | AltScore: 104.75

51. **Application of longitudinal item response theory models to modeling Parkinson's disease progression.**

EXTERNAL ADVISORY BOARD MEMBERS

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RECOGNITION AND AWARDS (2022-2023)

<u>Harvey J. Cohen, MD</u> (2022)

- Inaugural winner of Duke Department of Medicine Career Achievement Award

<u>Heather Whitson, MD, MHS</u> (2023)

- Neil Spector Humanism in Medicine Award, Duke Department of Medicine
- Translation Research Mentor Award, Duke School of Medicine

<u>Heather Whitson, MD, MHS</u> (2022)

- Outstanding Committee Service Award, Research Committee, American Geriatrics Society

<u>James R. Bain, PhD</u> (2022)

- Visiting Professor in the Department of Pharmacology and Nutritional Sciences, University of Kentucky College of Medicine, Lexington

<u>Katherine Hall, PhD</u> (2022)

- Inducted as a Fellow to the Society of Behavioral Medicine

<u>Kenneth Schmader, MD</u> (2022)

- Appointed to CDC ACIP Work Group on Respiratory Syncytial Virus vaccines

<u>Leah Acker, MD, PhD</u> (2023)

- American Delirium Society New Investigator Award
- Duke University LEADER Program Award

<u>Leah Acker, MD, PhD</u> (2022)

- AGS-NIA R13 Bench-to-Bedside Resilience "Rising Star" Award
- Society for Neuroscience in Anesthesia and Critical Care, John D. Michenfelder New Investigator Award

<u>Susan N. Hastings, MD</u> (2022)

- National VHA Diffusion Award

<u>Virginia Byers Kraus, MD, PhD</u> (2023)

- Elected to The American Clinical and Climatological Association

MINORITY RESEARCH

General Brief Description of Minority Activities:

Physical Rehabilitation for Older Patients with Acute HFpEF-The REHAB-HFpEF Trial (1R01AG078153-01) NIA

Dalane W. Kitzman, MD, PI, Amy Pastva, Intervention Coordinator

The REHAB-HFpEF trial will determine whether a novel physical rehabilitation intervention will improve the primary outcome of combined all-cause rehospitalizations and mortality and the secondary outcome of major mobility disability during 6-month follow-up in patients hospitalized for heart failure and preserved ejection fraction (HFpEF), **which is nearly unique to older persons, particularly women and Black persons**, and for which there are few treatment options.

Access to and effectiveness of community-based rehabilitation after stroke (5R01HD101493-02) NICHD

Janet Freburger, PI, Sara Bingham Jones, PI, Amy Pastva, PI

This study will fill gaps in our understanding of access to and effectiveness of rehabilitation care for patients discharged home following stroke. It will also determine the potential effectiveness of a transitional care model in improving access to and appropriate delivery of rehabilitation care. Findings from this study will inform care delivery at the patient-, provider-, health system-, and policy-levels and may have a significant impact on the health of the nearly 800,000 persons per year who experience a stroke.

Duke/UNC Alzheimer's Disease Research Center (5P30AG072958-02) NIA

Heather Whitson, MD, PI and Gwenn Garden, MD, PhD, PI

The Duke/University of North Carolina (UNC) Alzheimer's Disease Research Center (Duke/UNC ADRC) is a collaboration of leading researchers in aging and Alzheimer's disease. The Center's primary objective is to catalyze and support research and innovation that will ultimately reduce the prevalence and impact of Alzheimer's disease and related dementias. Leveraging the diversity of Eastern North Carolina and our strong scientific environment, we will enable novel research to identify opportunities to intervene in the years before Alzheimer's disease symptoms arise and to **reduce racial and urban/rural disparities** associated with dementia.

Duke Center for REsearch to AdvanCe Healhcare Equity (REACH EQUITY) (3U54MD012530-05S2) NIHMD

Kimberly S. Johnson, MD, MHS, PI

African Americans, Hispanics and other minorities receive lower quality healthcare and have poorer health than Whites. The Duke Center for REsearch to AdvanCe Healthcare Equity (REACH Equity) will test

interventions to improve the quality of care that minorities receive in the healthcare setting.

Minority Trainee(s):

- Charity Oyedeji, MD, PESC Scholar, Assistant Professor of Medicine (Hematology)
  Dr. Charity Oyedeji's research focuses on implementing a geriatric assessment into clinical assessments of older adults with sickle cell disease. Due to advances in care and access, patients with sickle cell disease (SCD) are living longer than they have in previous generations. SCD is recognized as a condition that mimics accelerated aging, but little is known about aging with SCD. In particular, SCD patients face frequent health stressors including hypoxia, pain crises, and frequent hospitalizations, but little is known about how aging with SCD affects one's resilience to these stressors. The objective of this study is to test the feasibility and safety of focused geriatric assessment and provocative tests that measure physiological reserve in SCD patients over age 50 and to determine the feasibility of a protocol to assess resilience to the stressor of hospitalization in older SCD patients. In addition, biomarkers of inflammation, coagulation, and longevity will be compared in 20 older (age 50-70) people with SCD and 20 younger (age 18-49) people with SCD. Thus far, the study has demonstrated that focused geriatric assessment, including provocative performance measures was safe and well-tolerated by older SCD patients. 50% of the older participants experienced a hospitalization within 12 months of a baseline assessment, indicating the feasibility of a future study to prospectively measure resilience after hospitalization by following a cohort of well-characterized participants for 2 years. Measures of physiological reserve in older SCD patients, on average, were consistent with normative measures from healthy seniors 20-30 years older. In 2020, Dr. Oyedeji used these findings to support a successful application for funding from the American Society of Hematology. She was also the recipient of 3 outstanding abstract awards at national meetings, and the recipient of the 2019 Duke Maddox Award for Aging Research. In 2021, Dr. Oyedeji received a Duke REACH Equity Career Development Award, an invitation to present at the American Society of Hematology Annual Meeting in December, and submitted a manuscript to the ASH Education Program.

- Gentzon Hall, MD, PhD, Assistant Professor of Medicine (Nephrology)
  Dr. Hall is an Assistant Professor of Medicine (Nephrology) whose lab utilizes sophisticated genetic studies to better understand contributors to glomerulosclerosis (AAGS), a common cause of chronic kidney disease (CKD) in older adults. His ultimate goal is to identify targets for pharmacological intervention that will protect kidney function, especially in populations at highest risk for AAGS. Progressive loss of glomerular visceral epithelial cells (i.e. podocytes) with age is thought to be the principal driver of AAGS. Based on his own previous findings, Dr. Hall hypothesizes that impaired IL-15/IL-15R axis signaling reduces podocyte resiliency to proapototic stimuli, increasing risk of AAGS across the lifespan. In Aim 1 of his pilot study, he utilizes immortalized human podocyte lines to quantify podocyte apoptosis in gene knockdown and controls after exposure to two well-validated proapototic stimuli. In Aim 2, he will utilize targeted gene deletion in zebrafish embryos to understand the role of the IL-15 signaling in vivo. A validated surrogate model for albuminuria in humans will be used to detect and quantify proteinuria in knockdown IL-15 and IL-15R zebrafish compared to controls. If these experiments confirm the role ofIL-15 signaling in podocyte survival and function after nephrotoxic stressors, it will justify future research to develop IL-15 signaling agents to enhance kidney resilience and protect against AAGS.

- Katherine Ramos, PhD, Assistant Professor of Medicine, Psychiatry and Behavioral Sciences
  Dr. Ramos' research focuses on developing and implementing behavioral interventions for older adults to enhance both their psychological and physical well-being in the context of medical complexity and/ or metastatic cancer. Despite the availability of interventions to improve functioning and quality of life in older adults by targeting their behaviors and mental health, there is a scarcity of research that focuses exclusively on older adults living with serious, life-limiting illness such as late-stage lung cancer. The objective of the Roybal study was to provide 8-12 sessions of Self-System Therapy (an evidenced-based psychotherapy treatment for depression) adapted and implemented for older adults over 65 years of age with Stage III or Stage IV lung cancer. The intervention primarily focuses on teaching older adults how to integrate promotion-focused and prevention-focused goal setting to improve self-regulation and increase behaviors that promote mental health and physical well-being. The study was recently completed with a sample of 12 focus group members, 5 user testers, 5 advisory members, and 30 participants enrolled in the pilot. Analyses are underway. An extension of this work has been recently funding by the NIA Research Centers Collaborative Network (RCCN) via Wake Forest School of Medicine. This study is currently underway with a focus on piloting measures targeting physical and psychological resilience(including accelerometry data collection) as older adults with late-stage lung cancer participate in the Self-System Therapy for Lung Cancer Intervention. Study completion is anticipated by March 2022. Thus far, from this work Dr. Ramos has presented her findings in national and international conferences, these include the: Association for Behavioral and Cognitive Therapies (ABCT), the American Psychological Association (APA), and the International Society for Psychotherapy Research in Heidelberg, Germany. A special issue paper abstract has been submitted for a full manuscript submission and an NIH R21 grant submission is currently underway to test the initial efficacy of the intervention in a larger randomized control trial.
- Nicole DePasquale, PhD, Assistant Professor, Dept. of Medicine
  Nicole DePasquale's research addresses questions about health, well-being, and multiple role management in the context of middle and late adulthood, with the ultimate aim of informing intervention efforts. She addresses these questions through two lines of research that utilize quantitative and qualitative methodology. One line examines the ways in which patients with chronic kidney disease and their family care partners work together to self-manage the disease and the impact dyadic self-management has on their health both as individuals and as a unit. The second line examines the work/nonwork interface of long-term care employees with family caregiving roles, or double- and triple-duty caregivers. Recent research includes patient-family discussions about living-donor kidney transplantation, decisional conflict regarding kidney failure treatment modalities, and the work and nonwork benefits of family-supportive supervisor behavior among double- and triple-duty caregiving men. Dr. DePasquale has self-identified as an Individual from a disadvantaged background, as defined by the Notice of NIH's Interest in Diversity (NOT-OD-20-031) released in 2019 regarding Underrepresented Populations in the U.S. Biomedical, Clinical, Behavioral and Social Sciences Research Enterprise. Dr. DePasquale's OAIC funded research project titled, "Individual and dyadic factors associated with older dialysis patients' physical resilience" currently does not intentionally seek to examine minority groups or racial differences, but the nature of her work does heavily focus on African Americans given that they are disproportionately burdened with chronic kidney disease/renal failure. This pilot project serves as an add-on component to the Shared Kidney Care Study and expands the parent study's existing strengths by adding a new and unique focus on physical resilience. It will

examine how kidney failure dyads work together (or not) to maintain, regain, or optimize older patients' physical function amid dialysis initiation and its negative downstream effects for patients and family care partners alike.

Minority Grant(s):

1. Project Title: **FLUAD? vs. Fluzone? High-Dose Study**

Leader(s):   **SCHMADER, KENNETH**

DUKE UNIVERSITY

Centers for Disease Control and Prevention 200-2012-53663 / (2016-2021)

The objective of this randomized controlled clinical trial is to compare the reactogenicity, safety, and effect on functional status and quality of life in older adults of the high dose influenza vaccine (Fluzone?) versus the MF-59 adjuvanted influenza vaccine (FLUAD?). In this randomized safety trial of 757 older adults (adjuvanted inactivated influenza vaccine, trivalent [aIIV3], 378; high dose inactivated influenza vaccine [HD-IIV3], 379), the proportion of participants with moderate-to-severe injection-site pain (primary outcome) was not higher after aIIV3 than HD-IIV3. No vaccine-related serious adverse events occurred. Post-vaccination HRQOL impact was similar between aIIV3 and IIV3-HD groups. From a safety standpoint, aIIV3 or HD-IIV3 is an acceptable option to prevent influenza in older adults.

2. Project Title: **The Impact of Reactogenicity of the Recombinant Zoster Vaccine on the Physical Functioning and Quality of Life of Older Adults**

Leader(s):   **SCHMADER, KENNETH**

DUKE UNIVERSITY

Glaxo Smith Kline GSK Zoster 063 / (2017-2019)

Herpes zoster and its related complications are associated with significant medical burden, which negatively affects quality of life and daily functioning of older patients. The recently licensed recombinant zoster vaccine (RZV) offers high efficacy but is associated with local and systemic reactions. This study assessed the impact of RZV on the quality of life and daily functioning of 400 older participants. Grade 3 reactogenicity occurred in 9.5% of participants and was associated with a transient clinically important decrease in SF-36 Physical Functioning score (affecting activities such as walking, carrying groceries, climbing stairs) and the EQ-5D-5L on Days 1 and 2 post-first vaccination. No clinically meaningful reductions in mean SF-36 Physical Functioning scale scores from pre- to post-RZV dose-1 were observed over a 7 day period post-vaccination.

3. Project Title: **EXPLORING THE EFFECTS OF EXERCISE TRAINING ON PTSD SYMPTOMS AND PHYSICAL HEALTH IN OLDER VETERANS WITH PTSD**

Leader(s):   **HALL, KATHERINE SHEPARD**

DURHAM VA MEDICAL CENTER

VA I01RX003120 / (2020-2024)

Posttraumatic stress disorder (PTSD) is prevalent among military Veterans, and affects over 30% of older, Vietnam-era Veterans. These servicemembers have endured nearly 40 years with these symptoms, and as a result, have significantly poorer health, higher rates of chronic disease and obesity, and an excess mortality rate 3 times higher than the general population. Clearly PTSD is more than just a psychological disorder. There is evidence to suggest that the pathway from PTSD to poor health is mediated by behavioral risk factors, such as exercise. Structured exercise is a highly effective, pluripotent strategy for the prevention, treatment, and management of chronic physical and psychological health conditions in older adults. To date, only a few pilot studies of exercise and PTSD have been published, and all suffer a major limitation: a singular focus on outcomes ?above the neck.? These studies do not report the impact of exercise on physical health- and mobility-related outcomes that contribute to long-term impairment and disability in Veterans with PTSD. There have been no studies of exercise and PTSD done in older adults, representing a significant research gap. This research examines a wellness-based approach to promoting health in older Veterans with PTSD, targeting exercise, a major modifiable risk factor. The objective of this study is to compare the impact of a supervised exercise program on PTSD symptoms and related health outcomes versus a healthy aging attention control group (HA-ATC). This study will be a randomized controlled trial of a 6-month, supervised exercise program among 188 Veterans ?60 years of age with PTSD at the Durham VAHCS. Participants will be randomly assigned to Supervised Exercise or HA-ATC. The exercise arm will include 3 weekly exercise sessions, each one lasting approximately 60 minutes, led by an exercise specialist. The HA-ATC will receive a health education program and materials modeled on the 10 KeysTM to Healthy Aging curriculum and the National Council on Agings Aging Mastery Program. The HA-ATC will include an 8-week face-to-face group program followed by 4 monthly sessions, the latter of which will be further supplemented with mailed informational packets, email newsletters, webinars, and group video telehealth sessions. Participants in the Exercise intervention arm will receive an individualized exercise prescription based on the individual?s exercise history, current exercise capacity, personal preferences, and current health status. This will be a multicomponent program that includes a selection of 8 to 12 strengthening, balance, and flexibility exercises targeting the major muscle groups as well as primary joints. Participants will also be instructed in endurance exercise, including treadmill walking or recumbent bicycle. The exercise protocol will consist of a 5-10 minute warm-up, followed by a series of progressive aerobic and strengthening exercises, and will end with a 5 minute cool-down. The primary outcome for this study will be PTSD symptoms assessed with the CAPS-5. Physical function, another outcome of primary interest will be measured objectively with a Physical Performance Battery. This test battery assesses aspects of daily function including balance (single leg stance), gait speed (4 meter walk), and chair stands (# in 30 seconds). Aerobic endurance, the investigators primary functional outcome, will be assessed with the 6-minute walk test (6MWT). Secondary outcomes include depression, sleep, and cognitive function. Outcomes will be assessed at baseline, 3 months, and 6 months. Assessments will be repeated 12 weeks post-intervention (9 months) to examine whether any observed exercise intervention effects are maintained. Mixed linear models will be used to compare outcomes for the two study arms.

4. Project Title: THE AMPK/ULK1/P27KIP1 AXIS REGULATES AUTOPHAGY AND CELL SURVIVAL IN AGED SATELLITE CELLS

Leader(s): WHITE, JAMES P.

DUKE UNIVERSITY
NIH K01AG056664 / (2017-2022)

a. Project summary/abstract:Sarcopenia is the age-related loss in skeletal muscle mass and strength; it leads to a host of co-morbiditiesincluding loss of physical function and overall resilience. One such perturbation in persons with sarcopenia isthe diminished ability to regenerate muscle after injury. Muscle stem cells, referred to as satellite cells, arerequired to activate, proliferate and differentiate to regenerate muscle and restore physical function. Agedsatellite cells are slower to activate upon injury; susceptible to apoptosis; and less efficient in repairing injuredmuscle. The AMPK/ULK1/p27Kip1 pathway appears critical for successful transition from quiescence to entryinto the cell cycle. Our preliminary data identify perturbations in the AMPK/ULK1/p27Kip1 pathway withadvanced age. This award period will investigate the role of the AMPK/ULK1/p27Kip1 pathway in thephenotype of satellite cell aging in both human and mouse models. In Aim1, we will test the hypothesis thatactivation of AMPK and its downstream targets ULK1 and p27Kip1 regulate the autophagy/apoptosis decisionin aged satellite cells. We will use molecular assays to rescue the functional loss of this pathway in aged cellsand return proliferative capacity. In Aim 2, we will test the hypothesis that exercise, a physiological inducer ofAMPK and autophagy, stimulates the AMPK/ULK1/p27Kip1 pathway, thereby enhancing proliferation andmetabolic function in aging murine and human satellite cells. Aim 3 will test the hypothesis thatAMPK/ULK1/p27Kip1 signaling will regulate the beneficial effects of caloric restriction on aged satellite cells.Together, the experiments in this proposal will test the hypothesis that the AMPK/ULK1/p27Kip1 pathway isimpaired in aging satellite cells resulting in a reduction in autophagy and susceptibility to apoptosis. Keyaspects of Dr. White's career enhancement will be: to learn how to coordinate clinical exercise trials; to trainin methods of satellite cell isolation and metabolic analysis, especially in the context of the aging organism.The training program will entail dedicated internal and external scientific presentations; pertinent coursework/workshops in stem cell biology and aging; and intensive career mentorship to ensure progress towardindependence. The research and career development plan detailed in this proposal will be conducted with ateam of outstanding mentors. Dr. William E. Kraus, a professor at the Duke Medical School is an establishedexpert in clinical exercise studies and muscle/satellite cell biology; he will serve as the primary mentor. Drs.Kenneth Schmader, Deborah Muoio (Duke) and Amy Wagers (Harvard) will serve as co-mentors; they willfacilitate training in aging biology, cell metabolism and aging stem cell biology, respectively. The environmentat the Duke School of Medicine is ideal for the research and training activities outlined in this proposal. Thisaward will provide Dr. White with optimal training to ensure an outstanding start to his career as anindependent investigator.

5. Project Title: **DEPRESCRIBING CENTRAL NERVOUS SYSTEM MEDICATIONS IN HOSPITALIZED OLDER ADULTS**

Leader(s): **PAVON, JULIESSA M**
DUKE UNIVERSITY
NIH K23AG058788 / (2019-2024)

This K23 Career Development Award in Aging focuses on the development of Dr. Juliessa Pavon, a hospital-based geriatrician, and on reducing central nervous system (CNS) medication use in hospitalized older adults.Dr. Pavon?s long-term goal is to improve the resilience of older adults against the acute stressors ofhospitalization. She has built her research program on investigating hazards of hospitalization, and a majorthreat is high-risk medication exposure. Sub-optimal CNS medication use during hospitalization is a keymodifiable risk factor for poor health outcomes; common classes include opioids, anxiolytics, anti-depressants,antipsychotics, and hypnotics. Our preliminary data suggests that nearly 40% of hospitalized older adults areexposed to anxiolytics and 60% to opioids during their hospital stay. De-prescribing is a systematic process oftapering or reducing medications. Interventions to facilitate de-prescribing that target specific medicationclasses, like CNS medications, or specific populations, like those with existing cognitive impairment, have notbeen well-studied in the inpatient setting. This gap represents a key opportunity to reduce potentiallyinappropriate CNS medications and their debilitating side effects in vulnerable patients--in line with the NationalInstitute of Aging?s priorities to improve medication use in older adults. Dr. Pavon?s K23 award proposes todevelop and pilot test a de-prescribing intervention that is informed by a theoretical model of behavioralchange. Aim 1 results will inform the epidemiology of the problem and identify target populations forrecruitment. Aim 2 will use qualitative methods to examine barriers and facilitators of hospital de-prescribing.Results will inform the intervention delivery strategies best suited to facilitate CNS medication de-prescribing ina well-tolerated, feasible manner. Aim 3 will develop and pilot test a multi-component hospital-based de-prescribing intervention that uses health informatics for content delivery, and provider behavior change andpatient activation strategies. This work will advance understanding of 1) which patients and CNS medicationclasses to target for de-prescribing interventions, 2) whether there are unique barriers to de-prescribing in thehospital setting, and 3) the optimal delivery strategy for safely de-prescribing. During this K23 grant period, Dr.Pavon will also complete additional training in Markov modeling statistical techniques, interventiondevelopment, health informatics, and leadership. Dr. Pavon?s mentor team will provide scientific support withexpertise in aging, pharmacology, hospital medicine, and research methodology. This career developmentplan will give Dr. Pavon the skills in conducting intervention development studies within the hospital setting.This training and resulting data will establish Dr. Pavon as a strong candidate for an R01 intervention designedto facilitate de-prescribing of CNS medications for the nearly 1 in 2 older adults that will experience exposure toa CNS medication during hospitalization.

6. Project Title: **METABOLOMIC & RADIOGRAPHIC MARKERS OF FRACTURE RISK AMONG OLDER ADULTS WITH DIABETES**

Leader(s): **LEE, RICHARD H.**
DUKE UNIVERSITY
NIH K23AG058797 / (2018-2023)

ABSTRACTAmong its medical complications, type 2 diabetes mellitus in older adults is associated with atwo-fold increase in the risk of hip and other low-trauma bone fractures. Paradoxically, thisincreased risk occurs despite a higher average bone mineral density. This increased fracturerisk is likely multifactorial, stemming from metabolic dysfunction that results in both increasedfalls risk and decreased bone strength. However, fracture risk stratification currently is limitedlargely to bone density testing and clinical risk tools that do not perform adequately for adultswith diabetes. Because bone is both a metabolic and structural tissue,

metabolomics andbiomechanical analyses would be particularly useful for developing and assessing newmeasures of fracture risk. The objective of this application is to develop and evaluateradiographic and laboratory biomarkers of fracture risk among older adults with diabetes,utilizing biomechanical and translational measures. The proposed research has the followingaims: 1) Determine the association between metabolomic profiles and incident clinical fractureamong older adults with diabetes; 2) Compare geometric and biomechanical measures at thefemoral neck and intertrochanteric region among older adults with diabetes, with and without hipfracture. This application builds upon the prior published work and clinical expertise of thePrinciple Investigator, Dr. Richard Lee, and provides him additional research skills to assist withhis career development goal of understanding the interaction of chronic medical conditions onthe bone health of older adults, focusing on diabetes. Dr. Lee is a dual-trained Geriatrician andEndocrinologist with expertise in metabolic bone disease. The primary training goals of thisproposal include the following: 1) Develop laboratory and analytical skills in translational sciencethat will be used in the development and evaluation of clinical biomarkers, including ?omicstechnologies; 2) Acquire principles and skills in biomechanical engineering and materialsscience to integrate with clinical and epidemiological analyses. By integrating biomechanicalengineering and metabolomics approaches with epidemiologic research to identify new markersof fracture risk, this application addresses a significant source of morbidity and mortality amongan increasing proportion of older adults.

7. **Project Title:** **NEURO-INFLAMMATION IN POSTOPERATIVE COGNITIVE DYSFUNCTION: CSF AND FMRI STUDIES**

Leader(s): **BERGER, MILES**
DUKE UNIVERSITY
NIH K76AG057022 / (2017-2022)

This is a K76 Beeson career development award for Dr. Miles Berger, a geriatric neuro-anesthesiologist with a focus on postoperative cognitive disorders. Each year >16 million olderAmericans undergo anesthesia and surgery, and up to 40% of these patients developpostoperative cognitive dysfunction (POCD), a syndrome of postoperative thinking and memorydeficits. Although distinct from delirium, POCD (like delirium) is associated with decreased qualityof life, long term cognitive decline, early retirement, increased mortality, and a possible increasedrisk for developing dementia such as Alzheimer?s disease. We need strategies to prevent POCD,but first, we need to understand what causes it. A dominant theory holds that brain inflammationcauses POCD, but little work has directly tested this theory in humans. Our preliminary datastrongly suggest that there is significant postoperative neuro-inflammation in older adults whodevelop POCD. In this K76 award, we will prospectively obtain pre- and post-operative cognitivetesting, fMRI imaging and CSF samples in 200 surgical patients over age 65. This will allow us toevaluate the role of specific neuro-inflammatory processes in POCD, its underlying brainconnectivity changes, and postoperative changes in cerebrospinal fluid (CSF) Alzheimer?sdisease (AD) biomarkers, such as the microtubule-associated protein tau. This project willadvance understanding of neuro-inflammatory processes in POCD and clarify the potential link(s)between these processes and postoperative changes in AD pathology, in line with the NationalInstitute of Aging?s mission to understand aging and fight cognitive decline due to AD. During thisK76 grant period, Dr. Berger will also complete an individually tailored MS degree in TranslationalResearch that will include training in immunology methods, fMRI imaging, cognitive neuroscience,geroscience, and physician leadership. This career

development plan will give Dr. Berger thetransdisciplinary skills to pursue his longer term goal of improving postoperative cognitive functionfor the more than 16 million older Americans who have anesthesia and surgery each year.

8.	**Project Title:**	**NORTH CAROLINA DIABETES RESEARCH CENTER**
	Leader(s):	**NEWGARD, CHRISTOPHER B**
		WAKE FOREST UNIVERSITY HEALTH SCIENCES
		NIH P30DK124723 / (2020-2021)

PROJECT SUMMARY/ABSTRACT ? METABOLOMICS CORE Comprehensive metabolic analysis, or ?metabolomics?, is a technology that defines the chemical phenotype of living systems. Given that metabolic fluxes and metabolite levels are downstream of genomic, transcriptomic, and proteomic variability, metabolomics provides a highly integrated profile of biological status. As such, it has unique potential for discovery of biomarkers that predict disease incidence, severity, and progression, and for casting new light on underlying mechanistic abnormalities. Metabolomic analyses are challenging, however, due to the complexity inherent in measuring large numbers of intermediary metabolites with diverse chemical properties in a quantitatively rigorous and reproducible fashion. The DMPI Metabolomics Core Lab has a long history of collaborative research and has established a strong and reliable infrastructure for conducting measurements for investigators at Duke and at outside institutions. Thus, it is well poised to become the NCDRC Metabolomics Core. While Duke has world-renowned facilities for metabolomics, its use by diabetes investigators outside of Duke (such as WF and UNC researchers) has been limited by bottlenecks, particularly in the analysis and interpretation of data, which the NCDRC seeks to address by establishing the NCDRC Metabolomics Core with support from Research Navigators.

9.	**Project Title:**	**AGING IN 1000 HEALTHY YOUNG ADULTS: THE DUNEDIN STUDY**
	Leader(s):	**MOFFITT, TERRIE E ; CASPI, AVSHALOM ;**
		DUKE UNIVERSITY
		NIH R01AG032282 / (2009-2020)

DESCRIPTION (provided by applicant): Declining fertility rates, aging of the baby-boomers, and increasing life expectancy are leading to population aging. As the population ages, this increases the public-health burden of age-related conditions, such as cardiovascular disease, type 2 diabetes, and dementia. Treating un-prevented diseases in late life has proven costly and ineffective. It is now known that potentially preventable risk exposures and physiological causes of age-related disease emerge in childhood. This recognition lends new scientific significance to studies that have followed cohorts from childhood. It is also now known that the pathogenesis of age-related diseases involves gradually accumulating decline in organ systems, beginning in the first half of the life course. Consequently, new interventions aiming to prevent age-related diseases will have to be applied to individuals while they are yet young, before they reach midlife. Translation of basic-science geronotology discoveries into interventions for young humans is lacking because virtually nothing is known about the process of biological aging during the first half of the life course. This prompts our proposal to study the pace of biologicalaging from the twenties forward. We will use the Dunedin Multidisciplinary Health & Development Study, a longitudinal study of a birth cohort now entering its fifth decade. This

study combines methods of demographic/economic surveys, clinical- quality health assessments, biobanking, and linkage to nationwide administrative records (health, welfare, finances). We propose to administer a full-day data-collection protocol to the 1004 living members of the birth cohort. To assess each cohort member's pace of biological aging we will: (a) measure biomarkers across multiple organ systems, and (b) statistically model correlated change in these biomarkers assessed at ages 26, 32, 38, and 45 years. We will describe individual variation in the pace of aging, plus its developmental origins, genomic signatures, functional consequences, and economic costs. We will identify attributes that set apart individuals whose bodies are months or years younger than their chronological age. The proposed work will improve knowledge by generating findings to support future interventions to slow aging, prevent age-related disease, and improve the quality of longer lives.

10. Project Title: **NEURAL SIGNATURES OF HEALTHY AND UNHEALTHY AGING**

Leader(s):   **HARIRI, AHMAD R ; MOFFITT, TERRIE E ;**
DUKE UNIVERSITY
NIH R01AG049789 / (2015-2020)

DESCRIPTION (provided by applicant): Declining fertility rates, aging of the baby-boomers, and increasing life expectancy are leading to population aging. As the population ages, this increases the public-health impact of age-related conditions, such as cardiovascular disease, type 2 diabetes, and dementia. Treating un-prevented diseases in late life has proven costly and ineffective. Consequently, effective strategies are needed in midlife to prevent age-related diseases and to improve the quality of longer lives. It is now known that potentially preventable risk exposures and physiological causes of age-related disease emerge in childhood. This recognition lends new scientific significance to studies that have followed cohorts from childhood. It is also now known that the pathogenesis of age-related diseases involves gradually accumulating damage to organ systems, beginning in the first half of the life course. Of these organ systems, the central nervous system is integral, prompting our proposal to add neuroimaging to the Dunedin Multidisciplinary Health & Development Study, a longitudinal study of both problematic and positive processes of adult development and aging, in a birth cohort now entering its fifth decade. This study combines methods of demographic/economic surveys, clinical-quality health assessments, biobanking, and linkage to nationwide administrative records (health, welfare, finances). We propose to administer a multimodal MRI protocol to the 1004 living members of the birth cohort. Our proposed neuroimaging protocol will measure individual variation in brain function, structure, and connectivity. We focus on the hubs of four neural circuits and the core behavioral capacities each supports: (1) the amygdala and emotion/threat, (2) the ventral striatum and motivation/reward, (3) the hippocampus and memory, and (4) the dorsolateral prefrontal cortex and executive control. With the resulting midlife neural measures, we propose three primary aims that will generate findings about problematic and successful aging: Aim 1 tests whether prospectively ascertained early- life adversity is linked to midlife neural measures. Aim 2 tests whether neural measures are linked to real-world behaviors (e.g., saving behavior) necessary to prepare for successful aging. Aim 3 tests if neural measures are related to the accelerated pace of biological aging. The proposed work will improve knowledge by generating findings about the neural correlates of age-related diseases and successful healthy aging. These findings are expected to support preventing disease and enhancing preparedness

for wellbeing in late life. Beyond the proposed 5-year project, follow-up neuroimaging is envisaged. This project thus brings neuroimaging into three timely and vigorous areas of aging science: the study of early-life programming of lifelong health, the study of midlife preparation for successful aging, and mind-body research linking brain function to physical health.

11. Project Title: **EPIGENETIC MECHANISMS PROMOTING LONGEVITY**
Leader(s):   **KRAUS, VIRGINIA**
     DUKE UNIVERSITY
     NIH R01AG054840 / (2018-2023)

AbstractCirculating small regulatory RNAs (sRNAs) are short non-coding RNAs (typically ~19-25nt in size). They mediatea broad spectrum of biological processes through regulation of gene expression. Our experimental evidenceindicates that serum levels of miRNAs (one form of sRNA) change considerably, the vast majority increasingwith age. The ability of circulating sRNAs to travel among tissues enables them to transmit signals and regulatea broad spectrum of biological functions. sRNAs exist in a variety of RNase-insensitive ribonucleoprotein or lipidcomplexes, or are encapsulated inside different types of extracellular vesicles. Consequently, in contrast tomessenger RNA, sRNAs are protected from extracellular RNases and are measurable and stable in samplesstored for decades. Despite numerous recent developments, we are far from understanding the role of sRNAsin aging. An understanding of their role in aging mammals, and in humans in particular, is still very limited dueto the increased complexity and longer life-spans of mammals compared with invertebrates. This projectleverages existing human sample resources from three completed NIH-funded studies (EPESE, STRRIDE andCALERIE), to discover and validate longevity-associated miRNAs in humans. Our preliminary analysis of 175circulating microRNA--in the NIA-funded Duke Established Populations for Epidemiologic Studies of the Elderly(Duke EPESE) community-based cohort of elders--identified 32 differentially expressed circulating miRNAs(p 10 years) compared with age, sex and race matched but short-term survivors (

12. Project Title: **GENOMIC ANALYSIS OF THE CALERIE TRIAL TO GENERATE NEW KNOWLEDGE FOR GEROSCIENCE**
Leader(s):   **BELSKY, DANIEL WALKER**
     COLUMBIA UNIVERSITY HEALTH SCIENCES
     NIH R01AG061378 / (2019-2024)

SUMMARYThe graying global population makes interventions to extend healthy lifespan (healthspan) a public heathpriority. Therapies targeting basic biological processes of aging show proof-of-concept in animals: early-to-midlife intervention can delay disease onset and prolong healthspan. But translating these geroprotectivetherapies to humans faces the barrier that human clinical trials of midlife geroprotective therapy wouldrequire decades of follow-up to measure healthspan extension. An alternative is a short-term acceleratedgeroprotector trial that tests if geroprotective intervention can slow the rate of biological aging. Biologicalaging is the gradual and progressive decline in system integrity that occurs with advancing chronologicalage. This process is thought to be the root cause of increases in morbidity and disability in later life. Newresearch shows that biological aging can be measured in humans and that measures of biological agingpredict human healthspan. Geroprotective therapies that target basic biological processes of aging arehypothesized to slow the rate of biological aging.

But this has not been tested. Our study will test if the best-established geroprotective intervention in animals, long-term caloric restriction, slows the rate of biologicalaging in midlife humans, who are still young enough for age-related disease to be delayed or prevented.We will conduct new assays of stored biospecimens from the National Institute on Aging's recently-completed CALERIE Trial, which randomized 220 non-obese adults to 25% caloric restriction (CR, N=145)or ad libitum normal diet (AL, N=75) for a period of 2 years. We have already shown that CR slows aging-related deterioration in organ-system integrity. Now, we propose to extend this test to genomic measures ofbiological aging. We will assay whole-genome DNA methylation (using Illumina chips) and gene expression(using RNA sequencing) from blood samples collected at CALERIE baseline, and at 12-, and 24-monthfollow-ups. We will use this 3-time-point repeated-measures multi-omics dataset to test (i) Does CR slowsthe rate of biological aging as measured from DNA methylation? (ii) Does CR cause changes to geneexpression in the pathways known to mediate healthspan-extending effects of CR in animals, e.g. themTOR pathway? (iii) Do changes to DNA methylation and gene expression mediate effects of CR on organsystem functioning? We will share the multi-omics data we generate with the CALERIE Biorepository,making the resource freely available to all interested researchers. The proposed project will generate newknowledge about effects of caloric restriction on biological aging in humans and test proof of concept for anaccelerated geroprotector trial design that can speed translation of new age-delaying therapies fromanimals to humans. Open data sharing through the CALERIE Biorepository will enable research beyond thescope of this project to improve understanding of caloric restriction and advance the field of geroscience.

13. Project Title:	**FUNCTIONAL LIMITATIONS AND DISABILITY AMONG MIDDLE-AGED ADULTS**
Leader(s):	**BOWLING, CHRISTOPHER BARRETT**
	DUKE UNIVERSITY
	NIH R01AG062502 / (2020-2023)

Project summary/Abstract The burden of functional limitations (restrictions in basic physical actions) and disability (problems with daily activities and life participation) may be more common in middle-aged US adults than previously recognized. However, studies of middle-age populations have not typically included functional assessments. The Coronary Artery Risk Development in Young Adults (CARDIA) study provides a unique opportunity to study functional status in a diverse, aging cohort. The Year 35 in-person exam is scheduled for 2020 and 2021, at which time, participants will be 53 to 65 years old. We propose a CARDIA ancillary study to obtain measures of function by self-report and physical performance to be paired with the existing data collected from early adulthood through middle age to address the following aims: 1. To quantify the burden of functional limitations and disability in middle age and assess the degree to which this can be attributed to the accumulation of chronic conditions, 2. To assess domains of functional limitations and disability captured by physical performance versus self-report, 3. To identify health-related risk factors in early adulthood for functional limitations and disability in middle-age, 4. To identify health-related, socioeconomic, and psychosocial factors that contribute to between- and within- race differences in functional limitations and disability among middle-aged adults. We will add measures of physical performance (fast and usual gait speed, single leg balance, timed chair stands, 6-minute walk test, and grip strength) to the CARDIA Year 35 exam (projected N=3,270; 1,563 black, 1,707

white). Also, self- reported functional limitations (Patient-Reported Outcomes Measurement Information System [PROMIS] Physical Function Short Form 20a) and disability measures (basic and instrumental activities of daily living) will be added to the Year 35 exam and annual telephone calls (1 call prior to and 2 after the Year 35 exam). As studies of younger populations have not often included functional assessments, the conceptualization, measurement approaches, risk factors, and implications of functional limitations and disability are poorly understood. Filling this knowledge gap by adding appropriate functional measures to an ongoing population based cohort, that represents the next wave of aging black and white adults will lead to new approaches to prevent functional decline and improve population health.

14. Project Title: **QUALIFICATION OF PROGNOSTIC AND DIAGNOSTIC BIOMARKERS OF KNEE OSTEOARTHRITIS**

Leader(s):   **KRAUS, VIRGINIA**
                      DUKE UNIVERSITY
                      NIH R01AR071450 / (2017-2020)

AbstractA cure for osteoarthritis (OA) remains elusive. This is due in large part to two major obstacles, inability todetect OA sufficiently early before the onset of irreversible signs and recalcitrant symptoms, and inability toidentify individuals at high risk of progression based on traditionally used metrics (age, sex, body mass index,knee pain and joint space width). The latter challenge is responsible for low powering of clinical trials andnumerous drug trial failures. Using a systematic, unbiased and iterative approach, we have created a multiplereaction monitoring (MRM) proteomic panel for serum-based prediction of knee OA structural progression anddiagnosis of knee OA. The selection of proteins was based on results of extensive discovery proteomic studiesin synovial fluid, urine, and serum from knee OA radiographic progressors and non-progressors (with 3-4 yearfollow-up) and controls. The ultimate goals of this work are to qualify these new biomarker candidates in thecontexts of knee OA progression and OA diagnosis in larger well-phenotyped cohorts from the OsteoarthritisInitiative, the Johnston County Osteoarthritis Project and the Chingford cohorts. With this further qualification,these new biomarker tools will be very significant for their potential utility for clinical trial and clinical use toinform strategies for phenotyping and earlier identification and treatment of OA patients. We also intend topursue formal Food and Drug Administration (FDA) qualification of the optimal marker set yielded by thisproposal to facilitate their use as drug development tools.

15. Project Title: **MECHANOTRANSDUCTION IN MENISCUS HEALTH AND REPAIR**

Leader(s):   **MCNULTY, AMY L**
                      DUKE UNIVERSITY
                      NIH R01AR073221 / (2019-2023)

ABSTRACT.Meniscal injuries are a significant clinical problem as each year 850,000 meniscal surgeries are performed in theUnited States and nearly twice as many worldwide. Meniscal tears in the avascular inner zone of the tissue donot heal well with suturing or conservative treatments and can ultimately lead to the development of osteoarthritis(OA). Therefore, new strategies are needed to enhance endogenous meniscus repair and tissue

regeneration.The menisci play a critical biomechanical role in the knee, providing load support, joint stability, and congruity.Meniscus tissue is maintained through a balance of anabolic and catabolic activities of meniscus cells. Thesecellular activities are controlled not only by biochemical factors in the joint but also by physical factors associatedwith joint loading. Mechanobiology, which is the influence of mechanical factors on the biologic response of cells,is important in converting physical signals into metabolic and inflammatory responses in meniscus. However,the mechanisms by which mechanical signals are transduced in meniscus cells have yet to be identified. Ouroverall goal is to identify critical meniscus mechanotransduction pathways and modulate thesepathways to promote meniscus repair and prevent OA development.Our work has shown that transient receptor potential vanilloid 4 (TRPV4) is a critical component in cartilagemechanotransduction and metabolism. The activation of TRPV4 can block IL-1 induced catabolic responses andalso increases cell migration and proliferation, which are important processes to enhance tissue repair. Whilewe have found that TRPV4 is expressed in the meniscus, the function of this mediator in meniscus health anddisease is currently unknown. In this proposal, we will determine how mechanotransduction occurs throughTRPV4 in meniscus and identify modulators of this pathway that will be used to enhance tissue repair and preventOA development. We hypothesize that mechanotransduction by TRPV4 plays a key role in meniscus metabolismand can be modulated to enhance meniscus repair and prevent the development of OA. In this proposal, we willdetermine the effects of mechanical stimulation on TRPV4-mediated metabolism in healthy meniscus cells.Next, we will elucidate alterations in TRPV4-mediated mechanotransduction pathways in meniscus pathology.Finally, we will enhance integrative meniscus repair and prevent the development of OA by modulation ofmechanotransduction pathways. In this proposal, we will identify the key signaling pathways downstream ofTRPV4 that may function as novel drug targets to 1) treat patients with immobilized joints to simulate exerciseand maintain joint health; 2) enhance meniscus tissue regeneration using tissue engineering strategies; and 3)enhance meniscus repair and prevent the development of OA. Novel therapeutic targets identified in thisproposal can subsequently be developed into drugs to enhance meniscus repair and prevent the developmentof OA.

16. Project Title: ADHERENCE TO VENOUS THROMBOEMBOLISM PROPHYLAXIS GUIDELINES IN HOSPITALIZED ELDERS
Leader(s):   PAVON, JULIESSA M
DUKE UNIVERSITY
NIH R03AG048007 / (2014-2016)

DESCRIPTION (provided by applicant): There are important public health concerns related to inappropriate use of venous thromboembolism (VTE) prophylaxis among medically ill hospitalized elderly patients with low risk of VTE occurrence. Specifically, use of anticoagulants (heparin products) for VTE prophylaxis when not medically indicated may be harmful, and is a major patient safety issue that also has a significant cost effect on health systems. To this end, the American College of Chest Physician (ACCP) 9th Edition guidelines explicitly recommend a risk-stratification approach, rather than universal use of anticoagulants for VTE prophylaxis. Even though many medical inpatients are at high risk for VTE, there are others whom do not have sufficient risk to warrant prophylaxis, and use in this population is inappropriate. The firstaim of this application proposes to determine the magnitude and scope of inappropriate use of anticoagulant VTE prophylaxis in low risk older adults. This aim will

be achieved by using data abstraction from the Duke University Health System electronic records to determine (1) the prevalence of low risk elders using criteria proposed by ACCP guidelines, and (2) anticoagulant VTE prophylaxis use in this group. Guideline directed use of pharmacologic VTE prophylaxis also emphasizes mobility evaluation. Mobility is a key component of risk stratification. Poor mobility evaluation by providers may be a significant barrier to appropriate use of VTE prophylaxis. Our second aim proposes to determine whether level of mobility during hospitalization is being used to influence use and duration of VTE prophylaxis among medically ill hospitalized elders. To achieve this aim, we will collect prospective observational data to objectively measure inpatient mobility using patient mounted accelerometers during patient hospital stays. Our goal is to improve the appropriateness of use of VTE prophylaxis among those in which the risks of harm may outweigh the benefit. Results from our study will provide important insights about use of risk assessment, and the relationship between patient mobility and VTE prophylaxis. These results are critical to understanding how to take the next steps toward improving the appropriate use and safety of anticoagulants in hospitalized older adults. Information from this study could be used in future proposals to study interventions to ultimately improve hospital practice in the care of older adults. Our investigative team at Duke is unique since we have expertise in all key fields of study: geriatrics, hospital medicine, hematology, and physical activity, that also have a longstanding history of working well with each other. As such, this collaborative team and research plan is designed to provide the principal investigator with a foundation from which to pursue an independent career in geriatric and hospital medicine research.

17. **Project Title:** **METABOLOMICS OF LOW-TRAUMA FRACTURE AMONG OLDER WOMEN WITH DIABETES**

Leader(s): **LEE, RICHARD H.**
DUKE UNIVERSITY
NIH R03AG048119 / (2014-2017)

DESCRIPTION (provided by applicant): Among its associated medical complications, diabetes is associated with low-trauma bone fracture: Compared to older women without diabetes, older women with diabetes have 2-times the fracture risk. Paradoxically, this increased risk occurs despite diabetic women having a higher average bone mineral density. The long-term goal is to understand how diabetes among older adults contributes to osteoporosis and low-trauma bone fractures. The objective of this application is to identify, among older, diabetic women, candidate fracture-related metabolic profiles. The central hypothesis is that compared to older, diabetic women without a fracture history, the metabolic profiles of those women with a low-trauma fracture will be significantly different. As prior studie have shown, there are significant differences in metabolic profiles, related to fatty acid and amino acid metabolism, associated with diabetes. Additionally, in an animal-based model of osteoporosis, significant differences were observed in the levels of fatty acids and branched chain amino acids, using targeted metabolomics. The rationale for the proposed study is that the contribution to incident fracture risk among older women with diabetes can be determined in prospective studies, once candidate metabolic profiles are known in this population. In this proposed, cross-sectional study of diabetic women, age 65 years, recruited from general endocrine and primary care clinics, the following aims will be addressed: 1) Assess the levels of amino acids, organic acids, and acylcarnitines in older women with diabetes, both with and without a history of low-trauma fracture; 2) Compare the metabolic profiles of older, diabetic

women without a history of low-trauma fracture to those with a history of fracture. Under the firstaim, after controlling for both measures of bone metabolism and functional status, the association between a history of low-trauma fracture and the levels of branched-chain amino acids and acylcarnitines, will be measured using targeted metabolomics. Under the second aim, the association between a history of low-trauma fracture and other metabolite classes will be measured using non-targeted metabolomics. The approach is innovative in identifying candidate, fracture-associated metabolic profiles, by utilizing metabolomics. Given the increasing prevalence of diabetes and substantial fracture-related morbidity among older adults, the proposal is significant because it is critically important to understand the key factors in thi population that contribute to low-trauma fractures. The results from the proposed study will inform the design of future studies to develop clinically applicable prospective screening tools toidentify at-risk individuals.

18. **Project Title:**   **EFFECTS OF AGING AND THE URINARY MICROBIOME ON RECURRENT URINARY TRACT INFECTIONS**
    Leader(s):   **SIDDIQUI, NAZEMA Y**
                      DUKE UNIVERSITY
                      NIH R03AG060082 / (2018-2020)

PROJECT SUMMARY/ABSTRACT Urinary tract infections (UTIs) are one of the most commonly diagnosed infections in olderadults. UTIs cost $1.6 billion annually, impair health-related quality of life, and can have serioussequellae such as hospitalization, sepsis, or death. At all ages, UTIs are more prevalent inwomen than men, with up to 50% of all women experiencing a UTI during their lifetime. Theincidence of UTI rises in older women with over 10% of women older than 65 and almost 30% ofwomen older than 85 reporting a UTI within the prior 12 months. Among women with UTIs, there exists a subgroup with recurrent UTIs, defined as 3 or moreculture proven infections within 12 months, or >2 culture proven infections in a 6 month period.Recurrent UTI is not only more common in women, but especially more common in the post-menopausal life stage. In some women with recurrent UTIs, genetic factors facilitate bacterialadherence and repeated infection. However, recurrent UTI prevalence rises significantly in post-menopausal women, suggesting additional non-genetic mechanisms associated with aging. The urinary microbiome is one potential non-genetic factor that could influence recurrentUTIs with aging. We now have significant evidence that a urinary microbiome exists, and thatdysbiosis may be associated with health versus disease. Our long-term goal is to improve ourunderstanding of the microbes that occupy the urinary niche, how these microbes change withaging, and to determine whether particular microbial community types are associated withrecurrent UTI. We aim to compare urinary lactobacilli in populations of women without recurrentUTIs to assess how lactobacilli change with aging and with the presence of vaginal estrogentherapy. Next, we aim to assess whether urinary lactobacilli or other microbes are associatedwith recurrent UTI in postmenopausal women who are using vaginal estrogen. Finally, we aim todetermine whether there are distinct microbial community types that are associated withrecurrent UTI in older women.

19. **Project Title:**   **A PILOT STUDY TO ADVANCE TRANSLATION OF MOLECULAR SIGNATURES OF BIOLOGICAL AGING**

Leader(s):   **BELSKY, DANIEL WALKER**
                     COLUMBIA UNIVERSITY HEALTH SCIENCES
                     NIH R21AG054846 / (2017-2020)

PROJECT SUMMARYThe broad aim of this proposal is to determine if any of several proposed methods to quantify biological agingin humans are promising for use in trials of interventions to increase healthy lifespan. The biological processof aging is thought to drive risk for many disabling health conditions and mortality. There is evidence thattrajectories of aging begin to diverge as early in life as young adulthood. If this process can be measured, itwill speed development of interventions to prevent disease and disability and prolong healthy life. Onemeasurement approach is to calculate a ?biological age.? In contrast to a person's chronological age, whichcounts time since birth, a person's biological age reflects the condition of their body and mind relative to theirpeers. For example a 30-year-old person with the body and mind of an average 50-year-old would have abiological age of 50. Interventions shown to reduce biological age or slow its increase would thus be strongcandidates for increasing healthy lifespan. But in order to identify such interventions, measures of biologicalage are needed. Several algorithms have been proposed to calculate a person's biological age from panelsof clinical biomarkers and whole-genome data on blood DNA methylation and RNA expression. Thesealgorithms represent highly-scaleable methods ideal for implementation in intervention trials. But a criticalknowledge gap is whether the algorithms actually measure the process of biological aging that, if modified,would extend healthy lifespan. The research proposed in this application aims to fill that knowledge gap byimplementing and testing five of the most promising algorithms in an already-created database, the DunedinStudy. The Dunedin Study follows a population-representative birth cohort now in it's fifth decade of life. Thedatabase includes genome-wide DNA-methylation, RNA-expression, SNP, and clinical biomarker data on 954individuals along with extensive physical and cognitive function testing. Research aims will test if the differentalgorithms measure a common process of biological aging that drives disease and disability. Studying all ofthe algorithms together in a young, still-healthy cohort followed over time will answer three questions: 1) Arethe different algorithms related to one another, i.e. do they measure the same thing? 2) Can they measurechanges occurring in young adults as their trajectories of aging begin to diverge ? the time interventionswould likely have their greatest benefit? and 3) Do they measure real-life experiences of health decline inaging ? deficits in physical and cognitive functions and subjective perceptions of aging? Results will informwhich, if any, of the proposed biological aging algorithms show promise for implementation in interventiontrials. This could lead immediately to their implementation in archived biospecimens from completed trials.Results will also inform future approaches to developing measures of biological aging by identifying whatworks and what doesn't.

20. Project Title: EVALUATING EFFECTS OF AGE-RELATED MICROBIOTA MODULATIONS IN HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS

Leader(s):   **SUNG, ANTHONY ; CHAO, NELSON J. ;**
                     DUKE UNIVERSITY
                     NIH R21AG066388 / (2019-2021)

Allogeneic hematopoietic stem cell transplant (HCT) has the potential to cure patients with hematologicmalignancies. However, HCT is associated with significant treatment related mortality (TRM) ranging from 20-30%. (1). TRM is particularly high in patients with advanced age (hazard ratio 1.84, age >60 years vs.

21. Project Title: **DEVELOPING RESEARCH AT THE INTERFACE OF HIV AND AGING**

Leader(s):   **HIGH, KEVIN P.**
WAKE FOREST UNIVERSITY HEALTH SCIENCES
NIH R24AG044325 / (2013-2019)

DESCRIPTION (provided by applicant): Effective antiretroviral therapy (ART) has resulted in many people with chronic HIV surviving into middle and old age. However, even those with controlled HIV viral replication, are more likely than uninfected subjects to experience premature chronic illness, multi-morbidity and functional decline. For example, 58% of HIV-infected subjects age >= 50 years have one or more of the following: renal failure, diabetes mellitus, bone fracture, hypertension or overt cardiovascular disease vs. only 35% of HIV-uninfected controls. Further, geriatric syndromes such as frailty and falls are becoming more prevalent in HIV-infected adults. While the need for research in HIV and aging is widely recognized, challenges in methodology, data acquisition and sharing, and research workforce education/training have hampered this goal. Multi-morbidity, functional decline and disability are typically research domains of geriatrics and gerontology. The Claude D. Pepper Older Americans Independence Centers (OAlCs; aka 'Pepper Centers') were established to advance research into the causes, mechanisms, prevention and treatment of functional decline with age, but lack expertise in HIV. In contrast, the Centers for AIDS Research (CFARs) have unparalleled expertise in HIV- related basic, clinical and social/behavioral research, but lack resources or expertise in aging biology, clinical phenotypes, or functional measures. This proposal leverages CFAR/OAIC expertise to create a shared research platform, enhancing and accelerating investigation at the interface of HIV and aging by: 1) Harmonizing processes for data collection across OAlCs and CFARs and providing a coordinated platform for data collection; 2) Validating key instruments/measures of function and geriatric phenotypes in HIV- infected subjects age > 50 years; 3) Supporting pilot projects at the interface of HIV and aging; 4) Identifying and mentoring junior faculty with a research focus in HIV and aging; and 5) Disseminating information and data sharing opportunities to the larger scientific community. Accomplishing these aims will efficiently amplify NIAID investment in the CFARs, NIA investment in the OAlCs, and, more importantly, address critical healthcare needs in a rapidly growing population aging with HIV.

22. Project Title: **EPIGENETIC MECHANISMS PROMOTING LONGEVITY**

Leader(s):   **KRAUS, VIRGINIA**
DUKE UNIVERSITY
NIH R56AG054840 / (2017-2018)

AbstractCirculating sRNAs are short non-coding RNAs (typically ~19-25nt in size). They mediate a broad spectrum ofbiological processes through regulation of gene expression. Experimental evidence indicates that the serumlevels of sRNAs change considerably--the vast majority increasing?with age. The ability of circulating miRNAsto travel among tissues enables them to transmit signals and regulate a broad spectrum of biological functions.sRNAs exist in a variety of RNase-insensitive ribonucleoprotein or lipid complexes, or are encapsulated insidedifferent types of extracellular vesicles. Consequently, in contrast to messenger RNA, sRNAs are protectedfrom extracellular RNases and are measurable and stable in samples stored for decades. Despite numerousrecent developments, we are far from understanding the role of sRNAs in aging. An understanding of their rolein aging mammals, and humans in particular, is still very limited due to the increased complexity and longerlife-spans of mammals compared with invertebrates. This project leverages existing human sample resourcesfrom three completed NIH-funded studies (EPESE, STRRIDE and CALERIE) to discover and validatelongevity-associated sRNAs in humans. Our preliminary analysis of 175 circulating microRNA--in the NIA-funded Duke Established Populations for Epidemiologic Studies of the Elderly (Duke EPESE) community-based cohort of elders--identified 32 differentially expressed circulating miRNAs (p

23. **Project Title:**   **EXTRACELLULAR VESICLES AND THEIR ROLE IN HALLMARKS OF AGING**

Leader(s):   **KRAUS, VIRGINIA**
                    DUKE UNIVERSITY
                    NIH R56AG060895 / (2018-2019)

AbstractExtracellular vesicles (EVs) are membranous particles released from nearly all cell types into all bodily fluidsevaluated to date ? including serum and plasma. Depending on tissue of origin, health state and organismage, they carry a variety of complex cargo consisting of nucleic acids (5,000 microRNA documented to date),proteins (93,000 documented to date including cytokines) and metabolites. Due to their coordinate regulationof tissue homeostasis and biological processes through intercellular trafficking of microRNA and protein cargo,EVs are particularly attractive for this project because they can potentially serve as DIRECT biomarkers ofaging, namely indicators AND mediators of the aging process. The goal of this project is to establish EVswith their microRNA and protein constituents as biomarkers of healthspan and lifespan and to informbiological mechanisms promoting healthspan and lifespan. We focus particularly on three of the hallmarksof aging, epigenetic alterations, cellular senescence and altered inter-cellular communication. Increasingevidence suggests that EVs secreted from senescent cells have unique characteristics and contribute tomodulating the phenotype of recipient cells; thus, they have been newly deemed novel senescence associatedmolecular pattern (SASPs). We hypothesize expression of different amounts and different compositions of EVsare associated with different lifespan and healthspan of humans, and with different senescence states inmurine models. In collaboration with Meso Scale Diagnostics, LLC (MSD), a premier developer of highlyreliable and highly sensitive biomarker assays, we will develop new biomarkers of EVs informing agingmechanisms and test their function in vitro. These biomarkers will be qualified in the context of aging in ourexisting extensive human sample sets: individuals (n=3056) from multiple longitudinal cohort studies (EPESEaged >71 years; PALS aged 20-100 years) and NIH-funded controlled trials of geroprotective interventions(STRRIDE exercise aged 18-70 years; and CALERIE

caloric restriction aged 22-45 years). Complementingthis new biomarker development work, we will validate and qualify: the new S-PLEX high sensitivity (femtomolelevel detection) assays by MSD for soluble cytokines and circulating microRNAs we have identified asassociated with healthspan and lifespan in elders. Taken together, we believe our broad expertise inbiomarkers and aging, our interdisciplinary team and our partnership with a company with the capability tocommercialize assays provide a unique project responsive to RFA-AG-18-018 for ?Development of validreliable markers of aging-related biologic mechanisms for human studies?.

24. Project Title: **MOLECULAR TRANSDUCERS OF PHYSICAL ACTIVITY AND HEALTH: NC CONSORTIUM CLINICAL SITE**

Leader(s): **KRAUS, WILLIAM E ; HOUMARD, JOSEPH A ; NICKLAS, BARBARA J ;**
DUKE UNIVERSITY
NIH U01AR071128 / (2016-2022)

ABSTRACT Exercise is a powerful physiological stimulus contributing to disease prevention and intervention. Theprotective and preventive effects of exercise are well-documented for metabolic, neurodegenerative, andcardiovascular diseases, and certain cancers. While scientists acknowledge the extensive benefits ofexercise, there is still insufficient understanding about the underlying mechanisms by which exercise preventsdisease and improves health across diverse organ systems. The NIH Common Fund has developed aforward-looking funding mechanism ? six tethered RFA's tied to creating a research consortium, the MolecularTransducers of Physical Activity Consortium (MoTrPAC) ? to create resources and critical information forexercise and health investigators well into the future. Two products of the MoTrPAC collective efforts will be apublically available data resource that will enhance and accelerate subsequent mechanistic research ondiseases and conditions affected by physical activity; and a biorepository of clinical and animal model samplesto be used in studying exercise biology. Based on prior collaborative efforts, our group believes that we areideally positioned to propose a protocol that will respond directly to the RFA, while at the same time executethe large volume of tests to complete the ~450 people required at each site within the MoTrPAC consortium.To accomplish all of our Clinical Center goals, we have developed a consortium ? the North Carolina ClinicalSite Consortium (NCCSC). The NCCSC consists of the experienced research teams Duke University Schoolof Medicine; East Carolina University (ECU); and Wake Forest School of Medicine (WFSM). As described inthe study plan, the NCCSC weighed a number of alternatives for training regimens, timing, and type of tissuesampling, sample sizes for the four obligated study groups, and other factors, while staying within budgetconstraints. The following Aims will maximize the value of the data and sample repositories; this will beaccomplished with the enrollment of 540 individuals and finishing 450. ? Aim 1: To determine the response of molecular transducers to a single acute bout of either aerobic or resistance training. ? Aim 2: To determine the responses of molecular transducers to a chronic exercise training program of either aerobic or resistance training. ? Aim 3: To determine the responses of molecular transducers to a detraining period following either aerobic or resistance training.

25. Project Title: **PHYSICAL RESILIENCIES: INDICATORS AND MECHANISMS IN THE ELDERLY COLLABORATIVE**

Leader(s): **COLON-EMERIC, CATHLEEN S ; WHITSON, HEATHER E. ;
DUKE UNIVERSITY
NIH UH2AG056925 / (2017-2019)**

ABSTRACTThe overarching objectives of the PRIME Collaborative (Physical Resilience: Indicators and Mechanisms inthe Elderly) are to characterize specific resilience phenotypes, elucidate biological mechanisms, and validateclinically valuable predictive tools and measures of physical resilience. The application focuses on resilience inthree systems that are central to older adults' overall health: musculoskeletal, cognitive, and immune. Thecentral hypothesis of this application is that resilience to physical stressors is influenced by biologicalmechanisms at the molecular level. We will examine whether mechanisms associated with one or more of theseven ?Pillars of Aging,? which have been described by the trans-NIH Geroscience Interest Group, underlie amore generalized capacity for recovery that applies across multiple stressor/response scenarios. An inter-professional team of aging researchers from has been assembled to accomplish these objectives; the teamrepresents expertise from six NIA-funded Older American Independence Centers (OAICs) and leverages otherexisting resources. The PRIME Collaborative team will use a two-phased approach. In Phase 1, workgroupswill define specific resilience phenotypes in existing datasets using latent class trajectory analysis of sequentialoutcome measures following a stressor. The three resilience phenotypes, selected for their over-archingrelevance to late life health as well as our team's expertise, are: musculoskeletal recovery after orthopedicsurgery, immune recovery after infection, and cognitive recovery after surgery/anesthesia. We will conduct pilotstudies to identify novel clinical tests and biomarkers associated with each of these resiliencies. Feasibility andresponse data from pilot studies will inform the design of a larger cohort study in Phase 2. In the final 6months of Phase 1, the most promising predictive tests and markers will be selected and will inform twoparallel activities in Phase 2. First, a longitudinal cohort study of older patients undergoing elective surgery willbe conducted to validate predictors in a more diverse population. The Phase 2 cohort study will also allow us toassess synergy and interactions between different types of predictors (provocative tests, physiologic outputmeasures, biomarkers) and different types of resilience (musculoskeletal, cognitive, immune). Second,biological mechanisms underpinning resilience will be identified using newly developed mouse resiliencemodels, and in vitro human and mouse myotubule systems. These model systems are suitable for interventionstudies. The Phase 2 biological studies will be designed to identify pathways related to one or more Pillars ofAging so that they are likely to underpin multiple types of resilience, and suggest therapeutic targets and novel,resilience-bolstering interventions.

26. **Project Title:** **PHYSICAL RESILIENCIES: INDICATORS AND MECHANISMS IN
THE ELDERLY COLLABORATIVE**

Leader(s): **COLON-EMERIC, CATHLEEN S
DUKE UNIVERSITY
NIH UH3AG056925 / (2017-2022)**

ABSTRACTThe overarching objectives of the PRIME Collaborative (Physical Resilience: Indicators and Mechanisms inthe Elderly) are to characterize specific resilience phenotypes, elucidate biological mechanisms, and validateclinically valuable predictive tools and measures of physical resilience. The application focuses on resilience inthree systems that are central to older adults' overall health: musculoskeletal, cognitive, and immune. Thecentral hypothesis of this application is that resilience to physical stressors is influenced by biologicalmechanisms at the molecular level. We will examine whether mechanisms associated with one or more of theseven ?Pillars of Aging,? which have been described by the trans-NIH Geroscience Interest Group, underlie amore generalized capacity for recovery that applies across multiple stressor/response scenarios. An inter-professional team of aging researchers from has been assembled to accomplish these objectives; the teamrepresents expertise from six NIA-funded Older American Independence Centers (OAICs) and leverages otherexisting resources. The PRIME Collaborative team will use a two-phased approach. In Phase 1, workgroupswill define specific resilience phenotypes in existing datasets using latent class trajectory analysis of sequentialoutcome measures following a stressor. The three resilience phenotypes, selected for their over-archingrelevance to late life health as well as our team's expertise, are: musculoskeletal recovery after orthopedicsurgery, immune recovery after infection, and cognitive recovery after surgery/anesthesia. We will conduct pilotstudies to identify novel clinical tests and biomarkers associated with each of these resiliencies. Feasibility andresponse data from pilot studies will inform the design of a larger cohort study in Phase 2. In the final 6months of Phase 1, the most promising predictive tests and markers will be selected and will inform twoparallel activities in Phase 2. First, a longitudinal cohort study of older patients undergoing elective surgery willbe conducted to validate predictors in a more diverse population. The Phase 2 cohort study will also allow us toassess synergy and interactions between different types of predictors (provocative tests, physiologic outputmeasures, biomarkers) and different types of resilience (musculoskeletal, cognitive, immune). Second,biological mechanisms underpinning resilience will be identified using newly developed mouse resiliencemodels, and in vitro human and mouse myotubule systems. These model systems are suitable for interventionstudies. The Phase 2 biological studies will be designed to identify pathways related to one or more Pillars ofAging so that they are likely to underpin multiple types of resilience, and suggest therapeutic targets and novel,resilience-bolstering interventions.

THE JOHNS HOPKINS UNIVERSITY
Claude D. Pepper Older Americans Independence Center

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CENTER DESCRIPTION

Frailty is an age-related condition with a multifaceted etiology, in which older adults lose capacity to cope with stressors and become remarkably vulnerable to declines in health and functioning, loss of independence, and early mortality. Since its inception, the **Johns Hopkins University (JHU) Older Americans Independence Center (OAIC)** has pursued a highly productive program for the study of frailty through population-based, clinical, and biological research and for the training of the next generation of frailty-focused investigators. This has helped to create a vibrant and growing center with scientific vigor and a rich, diverse interdisciplinary milieu of experienced faculty and successful trainees focused on frailty research. The goals of this program are to ameliorate and prevent frailty, and by doing so, improve the health, well-being, and independence of older adults. During the current cycle this OAIC supported large bodies of research advancing understanding of the biology underlying frailty, the interplay between frailty and cognition, important distinctions in frailty manifestation for different assessments and subpopulations, implications of frailty for health management—overall, and in clinical subspecialties, and the development of interventions. Nonetheless, given the rapidly growing population of Americans over age 70, there remains an urgent need for further scholarship and its translation into modalities that facilitate the maintenance of independence. We envision great potential to further accelerate intervention development and delivery to older adults who can most benefit by increasing our attention to new areas of burgeoning opportunity: engineered / technological interventions, methods for pre-frailty ascertainment, and disparities in frailty and its ascertainment. We are dedicated both to further pursuing this work, and to infusing all of our work with the determination to address frailty and its health consequences equitably in older Americans.

This renewal application, hence, aims both to further our long-running progress and to expand into new areas where progress also is crucial if the Center's goals are to be met. The proposed OAIC benefits from experienced and committed frailty-focused leadership, interdisciplinary expertise, an active engagement in the OAIC network, and strong institutional commitment to research on aging and frailty at Johns Hopkins University. Its mission remains to make fundamental discoveries related to the genesis of frailty, move these towards frailty-focused interventions, develop evidence-based guidelines for the prevention and management of adverse outcomes in frail older individuals, identify new investigators and research fields dedicated to these ends, and provide supported investigators with the expertise, resources, and training necessary to lead the next generation of frailty-related scholarship and practice. We propose to accomplish it through tried and true strategies already present in this OAIC, the innovations we identify above, and the following **specific aims**—each to be pursued overall and through a specific lens on health equity:

1) To develop, lead and advance effective frailty-focused interdisciplinary research programs that

promote the maintenance of independence. This will include a new focus on engineering approaches, heightened priority on health equity, and emerging use of merged / massive cohort studies to investigate novel risk factors.

2) To translate new knowledge generated in this OAIC into targeted prevention and treatment strategies that help older adults maintain independence. This includes implementation of frailty into clinical practice, preventative strategies, new engineered technologies, and community-based interventions.

3) To provide the highest quality expertise, support, infrastructure and technology in biological, bioengineering, engineering, data analytic and clinical research methodologies to OAIC supported trainees and investigators. Four robust resource cores have been established to provide these resources to supported investigators.

4) To support the development of new and innovative methodologies, research strategies and technologies essential to the study of frailty. Aims 3 and 4 are organized through Biostatistics, Biological Mechanisms, Clinical Translation cores, and a new Technological Assessment and Solutions core. New expertise will be provided in machine learning and technology, and omics data science expertise will be strengthened.

5) To provide tailored training and mentorship to junior investigators interested in developing careers focused on frailty in older adults. The leadership team is committed to providing ongoing scientific, leadership, and career training to the next generation of frailty-focused investigators.

6) To attract a diverse group of outstanding investigators and trainees to frailty research from across the Johns Hopkins University and beyond. We will augment our prior successful efforts by providing leadership, locally, nationally, through the engagement of a diverse group of OAIC scholars, and through our OAIC Network, to promote and encourage research, educational and training activities related to frailty.

CORES

Leadership and Administrative Core (LAC)

<u>Leader 1:</u>   Karen Bandeen-Roche, PhD   kbandee1@jhu.edu

<u>Leader 2:</u>   Jeremy Walston, MD   jwalston@jhmi.edu

This Johns Hopkins University (JHU) Older Americans Independence Center (OAIC) Leadership and Administrative Core (LAC) was designed to provide the scientific leadership, organization and infrastructure necessary to lead and oversee the frailty-focused activities of this OAIC. The overall goal of the LAC is to ensure the ongoing success of this OAIC in stimulating and sustaining the next generation of frailty-related science and the next generation of frailty-focused investigators. The aims of this LAC are to: 1) provide the interdisciplinary intellectual leadership needed to stimulate and sustain the development of innovative frailty-focused research addressing diverse populations, facilitate translation between basic and clinical research on frailty, develop innovative intervention and prevention strategies from these biological and clinical discoveries, and ensure effective, high impact utilization of each OAIC core; 2) identify and attract the next generation of frailty-focused research leaders from diverse backgrounds at JHU and facilitate training, career development and access to resources to promote their emergence as independent, interdisciplinary investigators in this field; 3) organize independent panels for review of: Resource Core Developmental Projects, Pilot/Exploratory Studies, and for the selection of specific junior faculty to receive salary support from the Research Education Component, and progress towards OAIC goals, conducted annually by an External Advisory Board; 4) lead, administer, and oversee core functions to assure productivity, cost effectiveness, integration, and quality of all aspects of this OAIC program, and to well steward OAIC resources; 5) prepare reports for non-competing renewal applications, annually, and administrative documents as needed, including data safety monitoring documentation; 6) organize and conduct scientific sessions to propel the frailty-focused science and career development of participants in OAIC retreats, research in progress meetings, and research planning meetings; and 7) maximize JHU OAIC scholarly visibility locally and nationally via local programming and participation in the OAIC network, the annual OAIC scientific meeting and annual scientific meetings of aging or frailty focused organizations, and through OAIC-led information and dissemination resources. This Core will set goals with all other cores and ensure that goals are met. It will lead visioning discussions among the multidisciplinary Leadership Council as to scientific direction and clinical relevance; provide institutional leadership in identifying the investigators and mechanisms to accomplish the Center's scientific goals; and provide leadership and organization to ensure the successful development and implementation of the infrastructure and new methods needed to support investigators in furthering research on frailty and its translation to increase the independence of older adults.

Research Education Component (REC)

<u>Leader 1:</u>   Gary Gerstenblith, MD   gblith@jhmi.edu

<u>Leader 2:</u>   Esther Oh, MD, PhD   eoh9@jh.edu

The long-term objective of the Research Education Component (REC) is the establishment of a cadre of well-trained, highly motivated junior faculty who will become leaders and mentors in scholarship on frailty and aging and its translation to maintain independence, health and robustness for older adults. The REC accomplishes this objective through four specific aims: 1) It provides an education program combining subject-area, methodological and leadership training together with

mentorship having both team-based and one-on-one elements and a mentored research project, so as to promote, benchmark, and assure research progress and career development. 2) It partners with the Leadership Council to identify, attract, and select outstanding junior faculty from a diversity of disciplines with the interest and potential to become future scholarly leaders on frailty and aging. 3) It provides the research infrastructure, salary support and protected time essential to enable the selected trainees to successfully bridge the critical transition to independent grant funding. 4) It creates a welcoming academic home and 'stimulus zone' for junior faculty, postdoctoral fellows, and predoctoral students invested in frailty-related scholarship through a variety of forums for ongoing networking and intellectual enrichment where they can interact with each other together and senior OAIC faculty. Forums provided complement structured mentorship plans for supported faculty and include monthly sessions in which REC-, PESC- and DP-supported faculty present research-in-progress, twice-monthly meetings of the Frailty and Multisystem Dysregulation research working group, and sponsorship of other working group meetings, seminars and guest lectures in collaboration with partnering institutional resources on aging. REC-supported faculty receive full mentorial and material support from each resource core, as appropriate to their interests and needs. Information dissemination infrastructure overseen by the LAC provides supported faculty with avenues by which to disseminate their findings. Resources are prioritized, first, to K-eligible individuals, followed by R-eligible individuals and then to other trainees so as to direct Core efforts to provide support at a key transitional point, when research careers are often in jeopardy because of lack of funding and research infrastructure. The leadership of this Core and the OAIC as a whole will continue to emphasize training across disciplines and that bridges basic science and clinical investigation. Demographic diversity and inclusion are prioritized: A new working group will help us ascend yet further in this area. The overall approach we propose has achieved notable success as evidenced by the accomplishments and success in receipt of career development awards of previously supported faculty.

Pilot / Exploratory Studies Core (PESC)

Leader 1:   Neal Fedarko, PhD   ndarko@jhmi.edu

The overall goal of the Pilot / Exploratory Studies Core (PESC) is to cultivate and support cutting edge pilot and exploratory studies that will advance the development of effective prevention and/or therapies for frailty and hence facilitate independence in older adults. The PESC Core leaders, in close collaboration with other core leaders and congruent with the scientific vision of the OAIC, sets scientific goals for the next stages of pilot frailty research. They then work to identify investigators whose expertise and career goals would be applicable to furthering etiological and interventional knowledge in the targeted areas. Pilot and exploratory studies that can collect data required in order to select or design the future large-scale or confirmatory studies needed to establish frailty mechanisms, improve measurement and diagnosis, determine etiologies, or develop novel treatment approaches are prioritized. Studies selected for funding in the first year of this cycle include a study that uses video-based pose estimation to develop an automated, quantitative frailty and pre-frailty assessment in older adults, a multimodal approach to finding genetic signatures of frailty in TOPMed population studies, and a pilot study of provision of digital access to older, frail and underserved patients awaiting kidney transplant to facilitate improved health care in this most vulnerable group. The specific aims of the PESC are to 1) solicit, select, and support pilot studies that advance the science and translation of frailty research, 2) to support the development of well-designed and informative pilot studies, 3) to provide and conduct longitudinal mentorship to supported investigators as well as provide oversight through completion of the pilot award and pursuit of funding for the next stage of research, 4) to further guide the

translation of any pilot study results, and 5) to expand the research environment and network of frailty-focused investigators needed to accomplish the overall OAIC goals. These aims will be carried out in close collaboration with biostatistics, biological mechanisms, and clinical translational and recruitment core leaders to ensure optimal design and access to core resources needed for study success. A new Technology Assessment and Solutions Core (RC4) will bring new and unique engineering focused studies into this core. This core will also guide the translation of pilot work into a deeper understanding of the basic biology and population implications of frailty and into interventions that will prevent or treat frailty hence help maintain independence.

Resource Core 1 (RC1): Biostatistics Core (RC1)

Leader 1:   Qian-Li Xue, PhD   qxue1@jhu.edu
Leader 2:   Karen Bandeen-Roche, PhD   kbandee1@jhu.edu

Since mid-2003, this OAIC Biostatistics Core (RC1) has dedicated critically needed resources toward the quantitative challenges of research on frailty. Partnering in OAIC leadership, and working closely with other OAIC resource cores, it has helped develop the careers of an interdisciplinary cohort of junior faculty supported by the Research Education Component (REC)—and beyond—and ensured expert design and analysis of pilot, external, and de novo studies needed to advance science on frailty. It now proposes to continue in these efforts, by providing: (1) mentorship for junior faculty supported by our REC, and our broader OAIC, in developing careers focused on frailty and aging; (2) new data and computing infrastructure and software, including web-based data housing and acquisition tools; (3) expertise for science on frailty, through support for the design, statistical analysis, and data management of research projects, and through making available new data analytic methodologies that are essential to studying the complex syndrome of frailty; and (4) leadership and visibility for frailty-related scientific and health promotion endeavors at Johns Hopkins, throughout the OAIC network, and in the broader gerontological community. Our support and leadership in these areas have been significant and wide-reaching, and could not be provided without the resources of this Core. The leadership is experienced, expert, deeply immersed in scholarship on aging, and visible in both gerontology and statistics. The Core will continue to support every REC and pilot-supported investigator as per their need. The Core synergizes actively with other OAIC resource cores, as evidenced by progress over the last cycle. Our team includes a statistical genomics expert to enhance our collaborations with the Biological Mechanisms Core (RC2). We also have engaged an internal consultant with expertise in signal intensive measurement to enhance our interactions with our new Technological Assessment and Solutions Core (RC4). We will continue to provide design and analytic expertise and support a Registry collaboratively with the Clinical Translation Core (RC3). Regarding new methodologies: research will develop approaches needed to better (i) assess prefrailty, hence identify at-risk persons early enough to intervene successfully; (ii) delineate heterogeneous etiology underlying frailty; (iii) design studies to assess frailty intervention; (iv) characterize attributable fraction of frailty risk factors over the lifecourse, and (v) address frailty disparities. By efforts along all these lines, this Core will contribute crucially to the success of this OAIC in answering a next generation of questions on frailty, and achieving findings' translation toward increased independence of older persons.

Resource Core 2 (RC2): Biological Mechanisms Core (RC2)

Leader 1:   Peter Abadir, MD, PhD   pabadir1@jhmi.edu
Leader 2:   Dan Arking, PhD   darking@jhmi.edu

The identification of the etiologies of frailty and age-related vulnerability remains a crucial challenge for gerontological research. Key to this challenge are the development of a better understanding of the underlying biological basis that contributes to frailty and the identification of key biological pathways for the development of interventions that might help prevent or alleviate frailty and loss of independence. The goal of Johns Hopkins Older Americans Independence Center (OAIC) Biological Mechanisms Core (RC-2) is to enable the next generation of frailty-related etiological discovery and to promote the translation of these discoveries into clinically relevant diagnostic, preventive, and treatment modalities. This will be achieved through the provision of high-quality biological and bioengineering measurement expertise, incorporation of new technologies, analytical and computational expertise for genetics and omics analyses, and infrastructure necessary to attain this goal. In order to comprehensively encompass the biological expertise necessary to study frailty-related etiology, we have engaged a leadership team and internal consultants with complementary and synergistic biological and translational expertise needed to unravel the complex biological mechanisms that underpin frailty. They also all bring mentorship skills for trainees, and infrastructure to RC-2 and national prominence to frailty research. The specific aims of RC-2 are to: 1) provide state of the art scientific expertise, infrastructure, and technology necessary to advance biological and etiological research related to frailty, 2) provide access to biological samples from human subjects and from animal models necessary to test hypotheses related to frailty, 3) facilitate the translation of biological findings into interventions or prevention-focused clinical studies, 4) provide training, mentorship, and guidance to promising junior investigators around biological mechanisms that impact frailty, and 5) provide institutional and external visibility for RC-2 related science and activities. Our aims will be accomplished through close communication between the core leaders and their laboratories, close partnership with the other OAIC cores, and the engagement of expert consultants in the highly relevant areas of mitochondrial measurement, metabolomics, epigenetics, mouse model development, nanotechnologies for diagnostic and treatment development, and the development of multi-omic analyses related to frailty. By providing these resources, RC-2 will foster high quality research that elucidates clinically relevant biological pathways that underlie frailty and related interventions that hold promise to attenuate frailty, related conditions, and the loss of independence.

Resource Core 3 (RC3): Clinical Translation and Recruitment Core (RC3)

Leader 1:   Todd Brown, MD   tbrown27@jhmi.edu

The Johns Hopkins University (JHU) Older Americans Independence Center (OAIC) proposes to offer a resource core entitled Clinical Translation Core, or Resource Core 3 (RC3). This core—now in its 10th year—was designed to accelerate the translation of important biological findings related to frailty into clinical studies, and because of the need to train and support junior investigators proposing clinical investigations in frail, older adults. This initiative is closely aligned with the JHU Division of Geriatric Medicine and Gerontology's goals of integrating frailty-related research into clinical practice. The specific aims of RC3 are 1) to provide supported OAIC investigators with comprehensive training, mentorship and access to expertise in clinical research, 2) to provide the oversight necessary to ensure optimal and safe performance of clinical studies, 3) to provide clinical research space and assistance with all aspects of protocol development, data collection, and recruitment of human subjects as needed, and 4) to maintain and further develop an active registry of older adults characterized for frailty and consented to be contacted for additional aging and frailty related studies. A core leader with substantial clinical research expertise in aging and HIV-related metabolic studies, and who also leads a core and infrastructure in the JHU Institute of

Clinical and Translational Research (ICTR), will facilitate the development, implementation, and conduct of both clinical physiological studies and clinical trials in this core. A highly skilled and experienced research program manager with expertise in recruitment of minoritized older adults and in the measurement of frailty and mobility, along with a team of experienced recruiters, will facilitate completion of Core aims. These aims will be carried out in close collaboration with the leaders of all other resource cores. Additional resources are provided by the ICTR, which will help ensure optimal study design, implementation, and interpretation of results, and Fast Forward, a translationally-focused unit at JHU will facilitate health technology development. This core will play a crucial role in the training of junior investigators engaged in Research Education Component (REC) activities and in pilot/exploratory studies, conduct developmental research as needed and will newly engage community advisory boards to maximize research relevance and potential to increase health equity. RC3 will continue to accelerate the pace of translation of the important biological findings being generated in this OAIC into frailty-related clinical studies that promote the maintenance of independence in older adults.

Information Dissemination Core (IDC)

Leader 1:   Jeremy Walston, MD   jwalston@jhmi.edu

To improve the reach and use of the evidence-based knowledge on frailty that emanates from JHU OAIC-supported research and elsewhere, we developed a state-of-the art Information Dissemination Core (IDC) with a highly experienced partner: the Johns Hopkins Center for Communication Programs (CCP). CCP has long standing, high-profile expertise and experience in knowledge management (KM) and dissemination science, with clients including USAID, The Bill and Melinda Gates Foundation, and UNICEF. The development of this close partnership between knowledge management experts at CCP and the frailty related content experts who lead this OAIC provided a highly rigorous yet accessible approach to more efficiently and effectively disseminate frailty-related findings and recommendations to a broader audience using cutting edge approaches. We envision that this audience will include researchers, students, clinicians, professional societies and foundations, policymakers, and older adults seeking information on frailty. Indeed, our overarching goal is to have this IDC become a national and international 'go-to' resource for the latest information and resources related to frailty science from this OAIC and as well as other authoritative sources: We seek ultimately to accelerate incorporation of best practices for addressing frailty in health practice and promotion, so as to benefit older adults.

Resource Core 4 (RC4): Technological Assessment and Solutions (RC4)

Leader 1:   Najim Dehak   ndehak3@jh.edu
Leader 2:   Vadim Zipunnikov   vzipunn1@jhu.edu

Advances in the uses of engineered technologies and AI, including electronic mobile digital health (EMDH) technologies in health care, hold great promise for improving the older adult well-being and the care of frail older adults. The overarching goal of the Technological Assessment and Solutions Core (RC4) is to develop a novel ecosystem that promotes the development, testing, implementation, and dissemination of novel technologies and new uses of artificial intelligence for frailty-related purposes. This ecosystem will be created by bringing engineers, bioengineers, Gerontologists, Geriatricians and other clinical investigators together into built infrastructure that facilitates the development and testing of novel approaches to health care in frailty. This core will bridge the existing deep expertise in clinical investigation related to frailty to the deep expertise in EMDH technologies, robotics, and AI that exists at Johns Hopkins. Examples of projects that could be supported by this core include 1) robotic assistance with medication 2) treatment adherence the

development of novel mobility and fall prevention technologies, 3) measurement improvements in frailty diagnostics through technology-assisted measurement of gait, activity, and other functional signals; 4) leveraging AI to build frailty assessments from these signals are also envisioned, and 5) remotely deployed technological interventions and measurement modalities could provide rich opportunities to expand reach to underserved older adults. This resource core, in collaboration with RC1, 2, and 3, proposes to support 2 pilot studies in this proposal. The specific aims of RC4 are: 1) to provide state-of-the-art engineering and technology application expertise to facilitate and support a broad array of translational frailty research; 2) to provide access to relevant technologies, and the necessary infrastructure to study frailty; 3) to facilitate the translation of RC4 frailty-related and focused technologies and uses of AI into intervention- or prevention-focused clinical studies in collaboration with the leadership of other resource cores; 4) to provide training, mentorship, and guidance to a diverse group of the most promising junior investigators who can contribute to frailty research, and to assure that RC4-developed technology are accessible to underserved populations of older adults; 5) To provide access to business development as relevant and local and national visibility for RC4-related science and activities.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications

Thomas Laskow, MD

Assistant Professor / School of Medicine, Division of Geriatric Medicine and Gerontology

<u>Physical Frailty, Inflammation, and Response to Clinical Stressors</u>

2022-2024 /
0 (total)
0 (1st/Sr)

Physical frailty has been associated with adverse outcomes in response to a range of clinical stressors among older adults and prior studies have identified an association between physical frailty and markers of inflammation and dysregulated immune response. Less is known about the significance and convergence of physical frailty and inflammation in the context of clinical stressors, despite the fact that a core aim of identifying a phenotype for physical frailty is to better understand and anticipate adverse outcomes in older adults and clarify the biology that underlies these risks. This study will evaluate the relationship between inflammation and physical function measures such as physical frailty in the setting of older adults undergoing a defined clinical stressor. The study will utilize, biospecimens, measures of physical frailty, and related measures of physical function collected during the currently enrolling SPRING study, a multi-arm prospective study characterizing physical resilience in older adults undergoing one of 3 clinical stressors: total knee replacement, allogeneic bone marrow transplant, or living with advanced chronic kidney disease. The relationship between these physical function and inflammatory measures will be evaluated, both at baseline and at one-year follow up. By clarifying the interplay of frailty and inflammation in the context of real-world clinical stressors, this research could contribute to the care of older adults who experience such stressors, both through better risk stratification and through biologically informed interventions to promote physical resilience.

Qinchuan Wang

Assistant Professor / School of Medicine, Division of Geriatric Medicine and Gerontology

<u>CaMKII oxidation links oxidative stress to inflammation, frailty, and premature death</u>

2022-2024 /
0 (total)
0 (1st/Sr)

Inflammation is a key component of immunity against infections, which is necessary for the survival of organisms. However, inflammation can also cause self-damage, and aging-associated chronic inflammation contributes to frailty, diseases, and death. What sustains chronic inflammation in aging and how chronic inflammation promotes aging are incompletely understood. We hypothesize that the oxidative activation of the a2+/Calmodulin-dependent protein kinase II (ox-CaMKII) promotes chronic inflammation in aging. Our studies will determine the underlying mechanisms by which inflammation becomes harmful during aging and delineate a novel molecular pathway with therapeutic potential. We will use a recently established Drosophila melanogaster model to test our hypothesis that CaMKII oxidation activates age-associated inflammation through the master regulator of inflammation, NF-kB. We will also test two potential downstream pathways by which inflammation causes functional deterioration and premature death.

- Glenn and AFAR Junior Faculty Award, CaMKII as a Cause of Age-Related Sarcopenia. PI: Qinchuan Wang.

Melissa deCardi Hladek PhD, CRNP, FNP-BC

Assistant Professor / Johns Hopkins School of Nursing

<u>Using Human-Centered Design to Adapt CAPABLE as a Prehabilitation Intervention for Adults with Frailty Awaiting Kidney Transplant</u>

2021-2023 /
5 (total)
1 (1st/Sr)

Over 700,000 Americans live with end-stage renal disease (ESRD), disproportionally affecting older adults, minority groups and those with lower socioeconomic status. ESRD is best treated with kidney transplant (KT) which increases life expectancy, functional ability and quality of life. Frailty is associated with higher KT waitlist mortality and worse KT surgical and post-surgical outcomes. As such, frailty is increasingly

being evaluated in pre-surgical settings to plan for post-surgery recovery. There is an urgent need to further understand and intervene on the co-occurrence of frailty and KT. Beyond the need to improve surgical outcomes, there are stark health disparities in patients awaiting KT. Due to medical comorbidities, socio-economic constraints, or incomplete testing, Black and Hispanic individuals are more likely to change from active waitlist status (meaning able to receive a KT at any time) to inactive waitlist status (not currently eligible to receive KT) and are more likely to remain classified as inactive longer. There is an urgent need to further understand this disparity and create interventions to lessen it. Person-environment fit posits that improving a person's lived environment will facilitate optimal individual functioning. CAPABLE is an evidence-based intervention that helps functionally limited, low-income older adults successfully age in their homes with better function and quality of life. It has been tested with in-center hemodialysis patients (N=12) which showed meaningful improvements in function and social network scores. This model, however, has not been applied to KT waitlist populations. We propose adapting CAPABLE as a KT prehabilitation program to accomplish two things: 1) To resolve barriers to being classified as active on the KT waitlist and 2) as a surgical prehabilitation intervention targeting the pre-frail/ frail KT waitlist population. We will accomplish this through a 3-phase human-centered design process, which engages the end users of the intervention throughout the research process to tailor interventions to their needs, behaviors and preferences. This work will form the basis for a future K01 proposal to pilot test the CAPABLE-KT prehab adaptation and R01 level funding to expand into other surgical populations conducting a larger community-based, comparative effectiveness trial. The proposed and subsequent studies will help inform the role of person-environment- focused prehabilitation interventions in surgical outcomes for vulnerable, frail populations.

- K23, NIDDK, Addressing Inactive Kidney Transplant Waitlist Status through Adapting a Tailored Psycho-Social-Environmental Program. PI: Melissa Hladek.

Gizem Keceli, PhD   2021-2023 /
Postdoctoral Fellow / Johns Hopkins School of Medicine, Division of Cardiology   1 (total)
<u>Dissecting the Mechanisms Whereby Tryptophan Metabolites Alter Myocardial</u>   1 (1st/Sr)
<u>Function</u>

Cardiovascular diseases (CVD) are a significant cause of morbidity and mortality in the elderly population and represent an important risk factor for frailty. Furthermore, frail patients have a heightened propensity to suffer from adverse outcomes of CVD. Studies emphasize the role of the altered kynurenine (kyn) pathway in the aging process and reveal its link to frailty. In recent clinical reports, increased levels of kyn and/or its metabolites, formed via degradation of the essential amino acid tryptophan, are associated with heart diseases and atherosclerosis. However, if these metabolites directly affect cardiac function is not known. In my pilot studies, kyn significantly impaired cardiac function. Similarly, in isolated cardiac cells, kyn infusion decreased the shortening ability and increased oxidative stress, an important contributor to many age-related CVD. Accordingly, I hypothesized that activated tryptophan degradation escalates ROS formation, jeopardizing cardiovascular function and prompting abnormal cell growth. In Aim1, I will explore whether kyn or its metabolites impact cardiac function directly by determining the functional parameters and ROS levels in isolated hearts/cells. In Aim2, I will investigate if kyn or its metabolites' accumulation induces abnormal growth of cardiac cells and examine the implicated mechanisms underlying kyn-induced alterations. The short-term goal is to gain insight into the potentially detrimental effects of the activated kynurenine pathway on cardiac function and determine whether, via enhanced ROS production, it drives maladaptive hypertrophy and loss of myocyte function. Overall, these studies will provide a better understanding of the reasons underpinning increased CVD risk in frailty and age-related cardiac dysfunction, thus facilitating new therapies.

Lolita Nidadavolu, M.D., Ph.D.   2021-2023 /
Assistant Professor / Johns Hopkins University School of Medicine   4 (total)
<u>Identifying mechanisms by which circulating-cell free DNA contribute to increased</u> 1 (1st/Sr)
<u>TNFR1 in frailty</u>

Frailty, characterized by vulnerability to physical and psychosocial stressors, is an aging-related syndrome that contributes to increased mortality and is associated with changes in cell and tissue homeostasis (apoptosis, necrosis) and increased inflammation, in particular tumor necrosis factor receptor 1 (TNFR1). Circulating cell-free DNA (ccf-DNA) from genomic and mitochondrial DNA are released as a result of these

cell death processes and the relative size of mitochondrial ccf-DNA fragments is related to different mechanisms of cell death. Our preliminary data shows strong associations between cell necrosis-associated mitochondrial ccf-DNA and serum TNFR1 levels as well as between TNFR1 levels and age-related physical decline. Mitochondrial ccf-DNA fragments are detected by innate immune system DNA sensors such as the cyclic GMP-AMP synthetase-stimulator of interferon genes (cGAS-STING) pathway, which is theorized to lead to upregulation in TNFR1. This proposal hypothesizes that frailty-associated increases in TNFR1 are mediated by higher levels of necrosis-associated mitochondrial ccf-DNA and upregulation in STING signaling. Aim 1 will characterize changes in the cGAS-STING signaling pathway with aging and frailty. Aim 2 will measure changes in robust older adult peripheral monocyte TNFR1 expression following treatment with necrosis-associated mitochondrial ccf-DNA from frail individuals and will examine how cGAS-STING mediates this relationship. The overall goal of this project is to identify innate immune system pathways for future intervention studies that can help attenuate frailty-associated chronic inflammation.

Nicholas R. Rowan, MD   2021-2023 /
Assistant Professor / Johns Hopkins Department of Otolaryngology-Head and Neck   2 (total)
Surgery   0 (1st/Sr)

The implications of olfaction with frailty, a population-based and exploratory investigation

The ability to smell, olfaction, is an understudied sensory function with significant implications in health and aging. Olfactory dysfunction (OD) is incredibly common, afflicting approximately one fourth of the global population, and markedly increases with age. While OD has inherent dangers, such as placing individuals at increased risk of environmental hazards, disruption of this special sense has substantial psychosocial and well-being implications in the aged population. Olfaction has been identified as a bellwether of mortality, and there is mounting evidence that OD is a harbinger of multisystem, physical frailty. Often times overlooked, olfaction may represent a novel physiologic measure of frailty and mechanism to identify impending critical transitions in the continuum of frailty. The inherent neuroplasticity of this special sense also represents a modifiable risk factor and an attractive intervention target for vulnerable aging adults. In an effort to better understand appropriate olfactory screening measures and olfaction-related targets for interventional studies, we aim to utilize a robust, nationally-representative database that includes multiple measures of olfaction and phenotypic frailty assessments. Through this approach, differences between self-reported OD and more detailed psychophysical olfactory assessments will be examined. We will also evaluate validated self-reported metrics and novel psychophysical subdomain scores in a cross-sectional case-control cohort. Intrinsic differences in the underlying neurophysiologic mechanisms of these unique subdomains will provide insight into the underlying pathogenesis of olfactory dysfunction and its relationship to frailty. By employing innovative approaches to characterize olfactory deficits, substantiated by detailed psychophysical assessments, our results will offer mechanistic insight for olfactory loss in older adults and serve as a springboard for future interventional investigations aimed at the mitigation of OD and frailty in this population.

Past Scholars
Alden Gross, PhD, Epidemiology (2014-2016)
Charles H. Brown IV, MD , Anesthesiology and Critical Care Medicine (2014-2016)
Charles H. Brown IV, MD , Anesthesiology and Critical Care Medicine (2014-2016)
Rani Hasan, MD, MHS, Cardiology (2015-2018)
Tae Chung, MD, Physical Medicine and Rehabilitation (2016-2018)
Abdulla Damluji, MD, PhD, Cardiology (2017-2019)
Orla Sheehan, MD, PhD, Geriatric Medicine (2018-2020)
Pei-Hsun Wu, PhD, Institute for NanoBioTechnology (2018-2020)
Bharath Ambale-Venkatesh, PhD, Radiology and Radiological Science (2018-2020)
Reyhan Westbrook, PhD, Geriatric Medicine (2018-2020)
Keenan Walker, PhD, Neorology (2019-2019)
Sabra Lewsey, MD, Division of Cardiology (2020-2021)

Jude Phillip, PhD, Department of Biomedical Engineering (2020-2021)
Jenny Pena Dias, Endocrinology/Medicine (2022-2022)

PILOT/EXPLORATORY PROJECTS (14 Pilot Projects Listed)

1. Project Title: **Pilot Behavioral Intervention to Address Pain and Frailty in Older African-American Women**

Leader: **Janiece Taylor, PhD, RN, Mary Catherine Beach, PhD; Sarah L. Szanton PhD, ANP, FAAN, Roland J. Thorpe Jr., PhD**

Older African American women are crucial to target for intervention not only because of their heightened frailty prevalence, but because they are at higher risk of pain than other racial/ethnic groups and African American men and have exacerbated relationship and outcomes of frailty and pain. They often experience difficulties communicating with health care providers, moreover, that may interfere with treatment of symptoms related to pain and frailty: Communication intervention has well documented potential to lessen these difficulties and result in better disease management. Specific aims of this study are: 1) To pilot a tailored behavioral activation intervention focused on improving frailty, chronic pain, and depressive symptoms among community dwelling older African American women and collect summary data needed to design a confirmatory intervention trial. Strategies will be non-pharmacologic and aim to improve communication, physical activity and education. 2) To determine a) feasibility and acceptability of the intervention b) if strategies and evaluation techniques were appropriate.

2. Project Title: **Exploratory Study of Metabolomics Energy Signatures in Frailty**

Leader: **Anne Le, MD, Reyhan Westbrook, PhD**

Building on a small PES awarded to Drs. Le and Westbrook that utilized a frail mouse model previously characterized in RC-2, altered metabolomics signatures were identified that suggest that TCA cycle processes are a component of dysregulated energy utilization in frailty. Given this background, we hypothesize that specific patterns of altered energy metabolites linked to glucose metabolism through mitochondrial bioenergetics, biosynthesis, and redox homeostasis pathways can help to distinguish frail from non-frail older adults, and that the circulating concentrations of metabolites related to glucose metabolism are measurably different between frail and non-frail older adults. Utilizing research resources from all three resource cores, and Dr. Le's established metabolomics measurement infrastructure (Metabolomics facility) and expertise in energy metabolism measurement, the following specific aims were proposed: 1) To utilize metabolomics measurement to reconstruct the relevant metabolic pathways of glucose metabolism related to bioenergetics, biosynthesis, and redox homeostasis, and determine differences between frail and non-frail participants, and 2) To identify the most promising biomarkers for a frailty-related energetic signature and plan for a future targeted validation study of diagnostic utility and biological discovery.

3. Project Title: **Association between Sleep Deficiency and Frailty: What harms most?**

Leader: **Naresh Punjabi, MD, PhD, Jiawei Bai, PhD**

Epidemiologic surveys show that at least 50% of adults over 65 years in age have sleep-related complaints. Sleep disturbance has been associated with neurohormonal, circadian, and homeostatic alterations: As many such changes have been evidenced by this OAIC and others to also underlie frailty, it reasonable to expect interconnections between sleep quality and frailty. We hypothesize that disordered sleep heightens risk for frailty onset and believe that intervention to improve sleep can prevent or buffer frailty. Prior studies indicate that poor sleep quality is associated with frailty. These predominantly have assessed sleep, however, by either self-report or relatively crude summaries (e.g. time in sleep states) of actigraphy or polysomnography data. This project uses data from the community-based Sleep Heart Health Study (SHHS) to extract power spectral "curves" summarizing the history of the overnight sleep EEG, by functional principal components analysis (fPCA), and identify sleep EEG signatures highly associated with frailty prevalence, incidence and transitions, and vice versa.

4. Project Title: **PCSK9 Links Age and Frailty Inflammation to Endothelial Cell Dysfunction**

Leader: **Thorsten Leucker, MD, PhD, Gary Gerstenblith, MD.**

One of the most significant aspects of aging is the marked increase in mortality and significant lifelong disability due to coronary vascular and cerebrovascular disease respectively. There is heterogeneity in that risk with a significant increase in older individuals with frailty and those with the prediabetes, both of which are increased with age and independently associated with vascular disease. Many preclinical and clinical studies indicate that inflammation is a common predisposing factor but the link between inflammation and vascular disease in older adults and particularly in those with frailty and pre-diabetes is not well characterized. Decreased endothelial cell (EC) production and release of nitric oxide (NO), which has potent anti-atherosclerotic effects is a driver of the development and progression of atherosclerotic vascular disease. Beyond its role in cholesterol homeostasis, proprotein convertase subtilisin/kexin type 9 (PCSK9, is associated with the future risk of cardiovascular diseases. Laboratory studies of isolated ECs demonstrate that inflammatory stimuli increase EC PCSK9 and, in separate experiments, that increased PCSK9 decreases endothelial nitric oxide synthase (eNOS) and NO bioavailability, decreases which indicate EC dysfunction independent of low-density lipoprotein cholesterol (LDL-C). This research will examine whether PCSK9 links proinflammatory stimuli with EC dysfunction by studying in vivo endothelial- dependent vascular function and in vitro basic studies of ECs. A comparison of the in vivo and in vitro results will also provide information regarding the extent to which vascular dysfunction in the older groups is related to systemic, circulating factors and to mitochondrial dysfunction. In addition to association, we will examine causality by using PCSK9 targeted small interfering RNA in the above basic studies. The significance of the research to the field of aging, therefore, is the opportunity it offers to understand whether EC PCSK9 is one mediator of the known cardiovascular risk associated with inflammation in older individuals, which then would provide a target of intervention as PCSK9 antibodies are available for clinical use.

5. Project Title: **Daily physical activity patterns and the modifying role of inflammatory markers in frailty**

Leader: **Amal Wanigatunga, PhD, MPH, Jennifer A. Schrack, PhD, Lawrence J. Appel, MD, MPH, Dr. Robert H. Christenson, PhD**

Frailty is a common medical syndrome of increased vulnerability in adults aged 70 years and older that is often accompanied by low daily physical activity (PA) and high chronic inflammation. Currently, the method by which low PA is quantified and defined relies on coarse measures of self-reported time spent in a few daily activities, leaving a large knowledge gap regarding the true manifestation of PA decrements in frailty. Moreover, chronic inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) have been linked to components of frailty, including high fatigability and functional decline, making it plausible that degradation of daily PA patterns may be connected to rising circulation of both IL-6 and CRP. This warrants further investigation into inflammation as a possible underlying mechanism connecting detailed measures of PA and the onset and progression of frailty with aging. Findings from such investigation would lay the groundwork towards building the clinical utility of measuring physical activity in non-laboratory, community-dwelling settings to detect and intervene on trajectories towards frailty and accelerated aging in ever-expanding older adult populations. The proposed research aims to examine (1) whether total daily PA and patterns of daily PA accumulation differ by frailty status (non-frail, pre-frail, and frail), and (2) whether chronic inflammation modifies this association. We hypothesize that free-living PA patterns are deteriorated and diminished in those who exhibit pre-frail and frail phenotypes, compared to non-frail individuals. Further, we hypothesize that these sophisticated measures of PA are sensitive to rising chronic inflammation (IL-6 and CRP) typically present in frail older adults. The proposed research provides an exciting opportunity to use cutting-edge methods to extract unique patterns of PA accumulation from objectively measured PA and assess whether greater deterioration in these PA patterns are seen with higher inflammation and frailty states.

6. Project Title:	Effects of Neurotoxic Kynurenines on Peripheral Nerve Regeneration
Leader:	Tae Chung, MD

Age-related muscle weakness is a critical component of frailty in older adults, and independently predicts morbidity and mortality in late life. Over the past decades, various changes in aging neuromuscular system, such as partial denervation at neuromuscular junction (NMJ), reducing number of motor neurons, and fiber type switching, have been described, but the underlying molecular pathway that links the degeneration of neuromuscular system to overall reduction of morbidity/mortality with aging has not been elucidated to date. In a recent metabolomics study, we have identified alterations in the kynurenine pathway in frail older animal and human subjects. We also found that those kynurenine intermediates strongly correlate to the markers of frailty and chronic inflammation. Kynurenine pathway is a major pathway for tryptophan degradation that eventually leads to NAD synthesis, and interestingly, a few intermediates in the kynurenine pathway are known to be potently neurotoxic, and involved in some age-related neurodegenerative diseases, such as Alzheimer and Parkinson diseases. In addition, kynurenine pathway has been known to play a critical role in immune tolerance and cancer surveillance6, suggesting that alteration of kynurenine pathway may contribute to the immune senescence and increased morbidity/mortality in late life. Taken together, we hypothesized that alteration in kynurenine pathway is the major underlying pathway of age-related muscle weakness, eventually leading to increased morbidity/mortality in late life. To further investigate the influence of kynurenine pathway in frailty and aging, we have utilized a genetically altered mouse, Quinolinate phosphoribosyl transferase (QPRT) knock-out (KO), known to have elevated levels of the potent neurotoxic kynurenine metabolites, quinolinic acid (QUIN), in the nerve tissues and serum. In an NIA K08-funded proposal, we

have been longitudinally tracking the neuromuscular functions of QPRT KO vs wild type mice over the entire lifespan. Our preliminary results have shown that QPRT KO mice have greater degree of NMJ denervation and reduced peak isometric strength as compared to the background-matching wild type mice after middle age. Additionally, QPRT KO mice also showed premature signs of frailty, such as weight loss, reduced lean mass, and poor glucose tolerance after middle age. The above results suggest that increased QUIN is related to degeneration of both motor neuron and skeletal muscle, leading to frailty phenotype. To further investigate the casual relationship between QUIN and neuromuscular dysfunction, we propose the following pilot experiments, using kynurenine inhibitors, JM6 that is known to reduce the levels of QUIN by inhibiting upstream enzyme, kynurenine 3-monooxygenase (KMO). Specific Aims: Aim1: To investigate the toxicity of QUIN on peripheral nerve and skeletal muscle regeneration Hypothesis: Regeneration of both nerve and muscle will be delayed in QPRT KO mice due to neuromyotoxicity of QUIN Subaim1: to compare the speed of nerve regeneration between QPRT KO and wild type mice after ligation of tibial nerve Subaim2: to compare the speed of muscle regeneration between QPRT KO and wild type mice after cardiotoxin injection to gastrocnemius muscle. Aim2: To determine if JM6 may facilitate the regeneration of peripheral nerve axon and skeletal muscle in QPRT KO mice Hypothesis: JM6 will facilitate the regeneration of peripheral nerve and skeletal muscle in QPRT KO mice Subaim1: compare the speed of nerve regeneration between QPRT KO and QPRT KO with JM6 after ligation of tibial nerve Subaim2: to compare the speed of muscle regeneration between QPRT KO and QPRT KO with JM6 after cardiotoxin injection to gastrocnemius muscle. The results from the current study will be used as preliminary data for NIH R01 application and justification for chronic administration of JM6 to prevent frailty phenotype in QPRT KO mice. In the future studies, we will manipulate kynurenine pathway at different points both genetically and pharmacologically, to identify the optimal target for the prevention of age-related muscle weakness, frailty, and eventually prolongation of lifespan.

7. Project Title: **The Effects of Tryptophan Degradation Pathway Manipulation on Metabolism, Healthspan and Lifespan in Mice**

Leader: **Reyhan Westbrook, PhD**

Chronically activated inflammatory pathways are strong predictors of age-related morbidity including disability, physical frailty, mild cognitive impairment1 and morality2. Despite this, the underlying molecular mechanisms that connect chronic inflammation (CI) to these common conditions are poorly characterized. We have recently identified metabolites in the tryptophan degradation pathway (TDP), known as kynurenines, as potential mediators of the effects of CI on functional decline in a mouse model and in older human subjects. Using targeted metabolomics, we showed that kynurenines correlate strongly with inflammation and decreased physical function in both mice and humans, and that the neurotoxic & cytotoxic metabolite 3-hydroxykynurenine (3HK) is elevated in the blood of frail older adults. Inflammatory cytokines activate indolamine 2,3 dioxygenase (IDO) which converts tryptophan to kynurenine, and kynurenine monooxygenase (KMO) which converts kynurenine to 3HK, thus cytokines increase the production of potentially deleterious kynurenines. We postulate that CI raises 3HK to toxic levels causing damage to tissues, including nerves and muscles, leading to accelerated decline in physical function and decreased lifespan. TDP blockade and reduced dietary tryptophan have increased lifespan in Drosophila and in mice, respectively. In this proposed study, we will elucidate the role kynurenines play in the development of age related functional decline by 1) determining if exogenously increased levels of 3HK lead to impaired physiology,

functional decline and early mortality in C57BL/6 mice, and 2) determining if blocking the TDP using an inhibitor, improves physical function, delays age-related physiological changes, and increases lifespan in both C57BL/6 mice and in a mouse model of CI. To assess effects on healthspan, we will longitudinally measure physiological and physical function including grip strength testing, indirect calorimetry, spontaneous activity monitoring, body composition analysis, muscle contractility analysis and insulin/glucose tolerance testing. To assess kidney toxicity, we will measure blood urea and creatinine levels. We will longitudinally profile the metabolome, measure levels of circulating cytokines, and perform ex vivo neuromuscular junction analysis and senescent cell quantification in these mice. Specific Aims: Aim 1: To determine the effects of treatment with the cytotoxic TDP intermediate, 3-hydroxykynurenine, initiated in adult (10 month old) C57BL/6 mice on lifespan and healthspan. Hypothesis: Increased circulating levels of 3HK accelerate functional decline, pathophysiological metabolic changes, and mortality in C57BL/6 mice. Aim 2: Determine the effects of TDP blockade initiated in adult (10 month old) C57BL/6 mice and in chronically inflamed IL10tm mice on lifespan and healthspan using the IDO inhibitor 1- methyl-D-tryptophan. Hypothesis: Treatment with 1-methyl-D-tryptophan initiated at 10 months can prevent or delay functional decline, pathophysiological metabolic changes, and mortality in C57Bl/6 mice and in chronically inflamed IL10tm mice which have known kynurenine elevation. These approaches will allow us to more fully articulate the impact of kynurenines on function, metabolism, body composition, and inflammation in older mice, and facilitate the future development of translational approaches in human subjects. With this work we will gain insight on the mechanisms of decreased physical function associated with chronic inflammation and aging as well as guide the development of interventions that mitigate the effects of chronic inflammation on functional decline.

8. Project Title: **Analysis of lamin A/C-associated proteins in the frail (IL10-KO) heart.**

Leader: **Kathy Wilson, PhD**

We hypothesize that signaling and gene-regulatory complexes that depend on A-type lamins are functionally perturbed in IL10-KO mice. This hypothesis is based on our mass spectrometry multiplex identification and quantification of proteins that co-immunoprecipitated with lamins A/C from old (21-22 months) IL10-KO vs control mouse hearts, skeletal muscle and brain. This pilot study will focus on the heart data, which revealed two groups of proteins proposed to associate with lamin A/C: Proposed novel partners (proteins not known to associate with lamin A/C). This group of 20 candidates includes two exciting proteins: Perm1 and Fam210A. Perm1 is a ~100 kDa intrinsically disordered ('transformer') protein, highly expressed in heart and skeletal muscle, that regulates genes required for endurance exercise, mitochondrial biogenesis and oxidative capacity in muscle (Cho et al., 2016; Cho et al., 2019), as discovered by our Hopkins collaborator Natasha Kralli. Equally interesting is Fam210A, which is genetically linked to grip strength, sarcopenia and bone fractures (Tanaka et al., 2018; Trajanoska et al., 2018; Tanaka et al., 2020), and is unstudied in the heart. Known or proposed partners for which lamin A/C association significantly decreased in frail hearts (log2-fold changes with p-values

9. Project Title: **Resilience and Multifactorial Stressors Among Older Adults During the COVID-19 Pandemic**

Leader: **Alden Gross, PhD**

The COVID-19 pandemic represents a complex stressor for older adults. Though our understanding of COVID-19 pathogenesis is evolving, evidence is accumulating that both age-related physiologic changes and age-associated multimorbidity drive increased hospitalization, ICU admissions, and death seen among older people with this infection (Verity 2020, Zhang 2020, Garg 2020). In addition to its direct impact via infection, older adults also face indirect stressors related to COVID-19 mitigation strategies. These indirect stressors include increased sedentary activity, stress, and nutritional challenges, and decreased access to medical care (Schrack 2020). Additionally, many older adults, in practicing social distancing, also may face increased loneliness and social isolation--experiences known to increase risk for anxiety and depression (Santini 2020). Against this backdrop, modern gerontological thinking recognizes the importance not only of vulnerability, but also ability to withstand or rebound from stressors when evaluating how older adults respond to COVID-19. By understanding the underpinnings of resilience and frailty, we can better understand the needs, interventions, and targeting strategies that can best support the health of older adults during and after the COVID-19 pandemic. In this study, we propose to characterize the multifaceted COVID-19 stressor in older adults living in the Baltimore area through a quantitative survey and qualitative interviews. We will leverage two existing cohorts to measure key aspects of the complex stressor that older adults are facing during the pandemic including direct stressors and indirect stressors. We will relate these stressors to clinical and psychosocial outcomes including stress levels measured objectively using measurements from salivary cortisol, and explore how resilience and frailty affect these relationships. In qualitative surveys of a subset of participants, we will explore perceptions and experiences of older adults as to how the COVID-19 pandemic may have been a stressor impacting their health, social interactions, finances and care of existing chronic medical conditions; and strategies they use to cope with these stressors. Ultimately, we hope to identify targets for interventions to lessen stressor impacts in this and future crises facing older adults. The proposed specific aims are: Specific Aim 1: To characterize the complex stressor older adults face during the COVID-19 pandemic and identify clinically relevant impacts. We will survey: (a) direct and indirect pandemic effects--direct: COVID-19 exposure, infection, hospitalization; indirect: changes and disruptions to daily life and health care, psychosocial effects and coping, social networks, food/medication access; (b) hypothesized outcomes of stressors: physical function, pain, fatigue, depression and anxiety symptoms, loneliness, health behavior changes, worsening chronic medical conditions, nonCOVID-19-related hospitalizations, frailty status and changes, perceived and objective (via serial home salivary cortisol) stress. Specific Aim 2: To characterize associations of clinical outcomes with (a) COVID-19 stressors and (b) sociodemographic and psychosocial factors hypothesized to partially determine resilience. Specific Aim 3: To explore direct associations of pre-pandemic measures of frailty and resilience with outcomes (Aim 1), and potential effect modification of these by stressor type and intensity. Specific Aim 4: To explore in qualitative interviews the perceptions and experiences of older adults as to how the COVID-19 pandemic may have been a stressor impacting their health, social interactions, finances and care of existing chronic medical conditions; and strategies they use to cope with these stressors. If successful, we will identify targets for interventions to lessen stressor impacts in future crises facing older adults.

10. Project Title: **A Pilot Study to Identify Frail Patients Prior to Surgery and Implement a Novel Social Work- Focused Preoperative Intervention**

   Leader: **Lee Goeddel MD, MPH**

Older patients have increased complications after surgery. Although many older adults fare well postoperatively, frail and vulnerable patients seem to be at highest risk. Multiple studies have demonstrated the association between preoperative frailty assessment and post-operative outcomes. These studies have not assessed the associations between individual components of frailty assessment and outcome to better target intervention. Additionally, the majority of preoperative interventions have focused primarily on physical activity with limited outcome benefit. Psychosocial risk factors have been increasingly associated with poor outcome after surgery in this high-risk population. There is a critical need to identify and develop interventions that can improve outcomes for frail patients undergoing surgery. This OAIC proposal focuses on first identifying patients who might benefit from a novel Social Work intervention (by assessing the association of subcomponents of a commonly utilized assessment of frailty with postoperative outcomes), and secondly, the implementation and evaluation of a novel preoperative Social Work intervention to improve postoperative outcomes. We propose three aims of limited scope. In Aim 1, we will retrospectively analyze the subcomponents of the Edmonton Frailty Score (EFS) and the association with postoperative outcomes in a population of 4100 patients. This information will allow us to identify patients who might benefit from the novel Social Work intervention described in Aim 2. In Aim 2, we will assess the feasibility and barriers to implementing a social work intervention in the Johns Hopkins Center for Perioperative Optimization. Patients are identified for social work assessment and plan with EFS36. For the second half of the study, patients will be evaluated with the Physical Frailty Phenotype Assessment and the EFS to assess the feasibility and additional utility of social work intervention in frail patients. Aim 3 will evaluate the postoperative outcomes of the cohort of patients that undergo the social work intervention compared to historical matched controls from Aim 1.

11. **Project Title:** **Identification of emergent patterns of monocyte morphologies and functional heterogeneity in frail and non-frail adults**

    Leader: **Jude M. Phillip, PhD**

During ageing, physiological changes and dysfunctions propagate, eventually manifesting as diseases later in life. In many older adults (>65 years), chronic low-grade inflammation typically associates with adverse outcomes, and is strongly linked to geriatric syndromes such as frailty. Recent studies have shown that potential sources of inflammation include the accumulation of senescent cells within ageing tissues, and from the age associated increase in cellular and protein fragments that are inadequately cleared from the body, (i.e. circulating cell-free DNA). Furthermore, this increased pro-inflammation phenotype induce deficiencies in immune activity and surveillance, likely contributing to the frailty-associated phenotypes in older adults. To address this, we propose to study frailty-induced changes in blood-derived monocytes from older adults (>65 years). For this proof-of-principle study, we hypothesize that frailty-associated inflammation drives the emergence of defective cellular phenotypes and decreased heterogeneity within circulating monocyte compartments. In this proposal we will focus on two interconnected goals: (a) develop and optimize an image-based platform to identify and classify functional cell morphologies and heterogeneity of circulating monocytes from frail and non-frail older adults (Aim 1A), and (b) develop a computational model based on morphological changes to describe how cytoskeletal signaling pathway activities associate with the resultant morphological phenotypes (Aim 1B). This study will form the framework to guide future confirmatory studies, which will enhance our understanding of frailty-associated monocyte phenotypes, and provide new learning opportunities from transfer-learning

approaches for additional cell types, including other immune subtypes and fibroblasts. Successfully attaining this pilot funding will allow us to generate critical preliminary data needed to pursue external funding through R01/R21 mechanisms from the NIA.

12. Project Title: The Effects of a Proof-of-Concept Sedentary Reduction Program on Metabolism in Prefrail Older Adults

Leader: **Amal Wanigatunga, PhD**

The proposed pilot seeks to enhance a K01 project (K01AG076967; PI: Wanigatunga) that aims to evaluate sedentary behavior reduction interventions in prefrail older adults in two important ways by: 1) adding secondary outcomes of glucose and lipid metabolism biomarkers and 2) testing the feasibility of remotely monitoring physical activity continuously for 2 months in prefrail older adults. The Older Americans Independence Center (OAIC) Pilot Core aims are to: OAIC Aim 1: Assess the dose-response relationship between changes in sedentary time and biomarkers of glucose and lipid metabolism, including glucose, insulin, total cholesterol, low-density lipoprotein (LDL), triglycerides, and high-density lipoprotein (HDL) OAIC Hypothesis 1. Decreased daily sedentary time is associated with decreased levels of blood glucose, insulin, total cholesterol, LDLs, triglycerides and increased HDLs over 2 months. OAIC Aim 2: Determine the dose-response and diurnal relationships between changes in sedentary time and blood glucose continuously monitored over 24 hours for 14 consecutive days using a Libre Pro sensor OAIC Hypothesis 2. Decreased sedentary time is associated with decreased overall glucose and different time-of-day glucose levels (e.g., faster returns to pre-meal glucose levels). OAIC Exploratory Aim 3: Explore the feasibility of a protocol to monitor accelerometry 24 hours/day for 60 consecutive days using a fully remote Actigraph Centrepoint system that provides study staff access to real time monitoring of device wear and activity volume and characteristics

13. Project Title: Investigating changes in monocyte-macrophage phenotype and inflammation in older frail adults

Leader: **Nicola M. Heller, Ph.D., and Franco R. D'Alessio, M.D.**

Frailty in older adults increases risk of morbidity and mortality and it is a good predictor of worse health outcomes. Prevention of frailty is therefore of critical importance in raising life expectancy, quality of life and decreasing healthcare costs. Understanding the dysregulation of the cellular and molecular processes that underpin frailty and identifying hallmark cellular characteristics and biomarkers of those dysregulated processes is key to intervention. Chronic inflammation and impaired healing capacity are features of an aging immune system. Tissue reparative macrophages are essential to resolution of inflammation and tissue repair. We found that macrophages from old mice cannot convert to the tissue reparative phenotype as macrophages from young animals do. Therefore, we hypothesize that impairment of conversion to the tissue reparative macrophage phenotype occurs in old frail adults and correlates with frailty and chronic inflammation. To test this idea, we propose three Specific Aims using previously collected and cryopreserved peripheral blood mononuclear cells from old frail, old robust and young healthy donors. First, we will measure the ability of monocyte-derived macrophages to convert to the tissue reparative phenotype in vitro. We will compare gene and surface marker expression of the tissue reparative phenotype in monocyte-derived macrophages from young healthy, old robust and old frail individuals. Second, we will correlate the amount of expression of the tissue reparative phenotype in vitro

with frailty scores and proinflammatory cytokines in the serum of the same donors in the three groups. Third, we will use scRNA-Seq to explore whether monocytes, the circulating precursors of tissue macrophages, from old frail adults show alterations in abundance or gene expression profiles compared to old robust or young healthy adults. The scRNA-Seq data will also allow us insights into changes in other immune cell populations and gene expression in the cells of the peripheral blood of old frail adults. With these preliminary data, our goal is to apply for a larger National Institute on Aging (NIA) award to investigate more thoroughly the cellular and molecular mechanisms in monocyte-macrophages that contribute to frailty in older adults. Our long-term objective is to find new cellular markers of frailty – monocytemacrophage dysfunction - and then find new approaches to slow or stop worsening of the frail state by targeting immune system dysfunction in older adults.

14. Project Title: **Artificial intelligence-based phenotypic biosignals of frailty**
    Leader: **Najim Dehak, PhD, and Laureano Moro-Velazquez, PhD**

Frailty is a clinical state characterized by dysregulation in multiple physiological systems related to cognitive and motor aspects, resulting in an increased vulnerability to stressors for the frail individual. However, cognitive and motor biosignals remain unexplored to predict frailty onset. Moreover, the relationship between physical frailty and cognition has not been deeply studied. In this proposal, we hypothesize that quantitative phenotypic biosignals (voice, speech, handwriting, eye movement, and gait) can provide digital biomarkers to assess frailty in the elderly population. Consequently, our goal is to enroll a cohort of frail and robust subjects older than 64 years and record phenotypic biosignals as well as clinical data. We will use digital biomarkers extracted from the biosignals and study their relationship with frailty and their relationship with the cognitive state of the participants. The rationale behind the use of the proposed biosignals is that they provide a window on motor and cognitive function and are tightly related to multiple physiological mechanisms that drive the frail phenotype. Our first aim will be to determine the correlation between phenotypic biosignals and established frailty scores in the participants. Our second aim will be to study relationships between biosignals and physical frailty in subjects with and without cognitive impairment.

DEVELOPMENT PROJECTS (7 Development Projects Listed)

1. Project Title: **Characterizing Longitudinal Interdependence among Multiple Multi-System Dysregulation (MSD) Biomarkers**

Leader: **Karen Bandeen-Roche, PhD**

Core(s):   Resource Core 1 (RC1): Biostatistics Core (RC1)

MSD has long been hypothesized as a determinant of frailty but rarely has been assessed other than through counts of dysregulated systems taken cross-sectionally. This DP lays groundwork for its study as a dynamic process through specific aims to: (1) Characterize longitudinal interdependence among biomarkers of systems thought to underlie frailty; (2) Derive summary measures of longitudinal dysregulation in multiple systems; (3) Validate measures resulting from (2) by assessing their associations with frailty and mortality, and whether they are stronger predictors of frailty than the count measure.

2. Project Title: **Development of an aptamer to selectively target the angiotensin autoantibody**

Leader: **Peter Abadir, MD, Neal Fedarko, PhD**

Core(s):   Resource Core 2 (RC2): Biological Mechanisms Core (RC2)

Prior RC-2 studies have focused on the angiotensin system as a potential contributor to frailty and as a target for intervention development. A recent publication in part supported by RC-1, 2, and 3 described agonistic autoantibodies (aAbs) against the Angiotensin Type 1 Receptor (AT1R) whose serum levels increased in older
adults and were associated with inflammatory cytokines, hypertension, adverse health outcomes and frailty. Aptamers are oligonucleotides that bind their targets with high affinity and specificity and are currently used for in vitro diagnostics, biosensor technologies, and targeted therapies. RNA aptamer agents can be engineered as allosterically modulated ribozymes - where binding to the targeted aAb activates the selfcleaving ribozyme domain and a fluorescence quencher is removed, yielding a fluorescent signal. This DP seeks to develop the lead agents necessary for creating a unique high throughput diagnostic/prognostic quantitative assay.

3. Project Title: **Implementation of preoperative frailty assessment in older surgical populations.**

Leader: **Frederick Sieber, MD**

Core(s):

The data is compelling that assessment of frailty is germane to determining surgical risk. There are two common means of frailty assessments, the phenotypic model and the deficit accumulation model. When assessing for frailty in the same population, phenotypic frailty instruments and deficit accumulation instruments of frailty display some overlap among subjects, but the populations defined are different. To help define the use of each frailty assessment in clinical practice, this proposal will first examine the use of both the phenotype model ("light-touch" Frailty Screen, LTFS) and the deficit accumulation model (Edmonton Frail Scale, EFS) within a surgical clinic to examine the level of agreement between the two assessments. In addition, relationships between individual domains assessed by the EFS and the

frailty phenotype will be determined. Next, outcomes will be compared between the two models in the same surgical population. This comparison will be used to determine the ability of both assessments to predict postoperative outcomes and garnish support for the targeted use of these assessments in the preoperative workflow for patients ? 65 years. In addition, it will guide the development of domain specific interventions that may ultimately influence postoperative outcomes. Once the analysis is completed, we will use the well-defined Johns Hopkins Translating Evidence into Practice (TRIP) model to guide implementation of both assessments into clinical practice/workflow as a routine part of the pre-operative assessment of surgical patients ? 65 years of age across the John Hopkins Health System. This development grant will include incorporation of EHR documentation and dashboard creation for ease of analysis.

4. Project Title: **Effects of Kynurenine Pathway Manipulation on the Metabolome of Drosophila**

Leader: **Mariann Gabrawy, PhD & Reyhan Westbrook, PhD**

Core(s):

Chronic inflammation is associated with physical frailty and functional decline in older adults; however, the molecular mechanisms of this linkage are not understood. Through findings from translational studies on both aged and chronically inflamed mice, as well as on aged and frail older adults, we have identified metabolites of the kynurenine pathway (KP) as potential mediators of systemic damage caused by chronic inflammation. Tryptophan metabolism is an important precursor to several bioactive metabolites including serotonin and NAD+. Tryptophan metabolism is highly conserved throughout nature and fluxes of this pathway are linked to longevity in numerous species. In humans, overproduction of downstream kynurenines such as 3-hydroxykynurenine (3-HK) and 3-hydroxyanthranillic acid (3-HAA) is linked to diseases such as cardiovascular disease, neurodegenerative disease, and frailty while blockade of the KP increases life span of Drosophila melanogaster. We used line DGRP_229 to elucidate the role of altered levels of kynurenines on physical performance and life span. Our results show that flies treated with 3-HK or 3-HAA have reduced climbing speed, endurance, and life span. Flies treated with a combination of ?-methyltryptophan (?-MT) plus nicotinamide (NAM) or nicotinamide riboside (NR) have greater speed, endurance, and life span than those treated with each metabolite alone. Motor neuron density is commensurate with the above treatments. We conclude that promotion of the KP accelerates functional decline and reduces life span while blockade of the KP, with NAD+ supplementation, attenuates the effect of age on functional decline and increases life span in an age-specific, synergistic manner. We have demonstrated, for the first time, that a combination of blocking the KP while supplementing its product, NAD+ (?-MT+NAM or ?-MT+NR), can increase life span and preserve physical function in Drosophila. Our work provides the foundation for future studies in mice and in humans. In order to understand the etiological linkages between KP manipulations and the resulting changes in physical function and life span, it is necessary to understand how our treatments affected the levels of 1) KP metabolites and 2) other molecular pathways including those involved in energy metabolism.

5. Project Title: **Improving Data Infrastructure and Care Planning for Patients Enrolled in the Program for All-Inclusive Care for the Elderly (PACE)**

Leader: **Qian-Li Xue, PhD**

Core(s):

The goal of this project is to improve communication within the Program for All-Inclusive Care for the Elderly (PACE) care team and between the care team and patient/caregiver by developing and testing a data integration and reporting system that can be used to facilitate personalized care planning, coordination, management, and communication, with the ultimate goal of improving health and quality of life of PACE patients and their informal caregivers. Hypotheses and specific aims: 1. To build a SQL database that serves as a data warehouse for integrating data from EPIC and PACE. 2. To develop a one-page report template that provides a user-friendly summary of clinical data routinely used by PACE for care-planning and communication. 3. To create a streamlined and color-coded care plan document that better communicates care priorities, as well as distinguish patient/caregiver-initiated vs. provider-initiated tasks. 4. To conduct questionnaire-based surveys with the PACE care team and patient/caregiver dyads to assess user experience of the new data report and documentation system.

6. **Project Title:**   **High-throughput screening of mitochondrial function**
   Leader: **Dan Arking, PhD**
   Core(s):

Mitochondria, which are found in 10s to 1000s of copies per cell, are maternally inherited ancient bacterial symbionts that have maintained their own DNA (mtDNA). mtDNA contains 37 genes, including 13 that code for proteins, 2 for rRNAs, and 22 for tRNAs, while the remaining ~1500 genes required for mitochondrial (MT) function are encoded in the nuclear genome. Given the critical role of mitochondria in energy production via the oxidation phosphorylation (OXPHOS) pathway, decline in MT function has long been hypothesized to underlie multiple biological changes that increase vulnerability to chronic disease, and ultimately, to mortality. We and others have demonstrated that mtDNA copy number (mtDNA-CN) measured in peripheral blood cells, which is associated with MT enzyme activity and ATP production, declines longitudinally with age and is associated with general health among the elderly, including frailty susceptibility. Multiple mechanisms contribute to aging-related MT functional decline, including declines in energy (ATP) production, increased free radical production, altered rate of apoptosis and mitophagy, and altered fusion/fission. While mtDNA-CN has proven useful in implicating a role for mitochondria in various aging-related diseases, this measure is a relatively crude estimator of mitochondrial function, as it only captures the number of mtDNA molecules, which does not allow for direct measurement of mitochondrial function. Moreover, it does not distinguish between changes in the function of specific electron transport chain complexes, ROS production, or OXPHOS capacity. To make additional progress in the field, there is an urgent need for high-throughput mitochondrial functional assays that can identify changes in OXPHOS capacity, mitochondrial mass, and ROS, and that could be applied to both patient samples and used in cell culture to rapidly screen for changes in mitochondrial function in response to genetic and/or chemical perturbations.

7. **Project Title:**   **Development of a novel technology for the sustained delivery of valsartan and senolytics to frail older adults with chronic wounds**
   Leader: **Efrosini Kokkoli**
   Core(s):

Non-healing, chronic wounds are a manifestation of multimorbidity and frailty that significantly diminish quality of life with increased risk of infection, amputation, and death, and require long-term treatment at high costs. The angiotensin system is a major hormonal system that contributes to the chronicity of diabetic wounds by keeping them stalled in the inflammatory phase and unable to progress to the proliferative or remodeling phases of healing. We recently demonstrated that a daily, topical reformulation of valsartan cream, an angiotensin receptor blocker, significantly accelerated healing in aged diabetic mice and pigs and regenerated skin of superior quality. Despite these impressive results, two major potential areas of improvement to this novel therapy remain: First, there remains a need to develop an extended release formulation that will maintain the level of local, active valsartan in the wound bed and reduce the frequency of necessary applications. Second, because senescent cells are a significant component of chronic wound base matrix, there remains great potential to target senescent cells in the wound base that could further accelerate chronic wound healing in older, frail adults. Based on these needs, we have devised a plan to develop and evaluate a combination treatment for chronic wounds that consists of a fast release of senolytic agents (dasatinib + quercetin) combined with a thermosensitive and biodegradable valsartan-loaded hydrogel. This is further supported by prior findings related to wound healing with topical valsartan, the recent development of a novel thermosensitive and biodegradable polymeric hydrogel that can be used as a tunable multi-drug delivery system, and our own new feasibility data that shows that an early prototype of this novel hydrogel showed an extended release of valsartan for 2 weeks. We propose the following Specific Aims to engineer a desperately needed solution for chronic wounds. In Aim 1, we will synthesize and characterize a thermosensitive and biodegradable hydrogel that encapsulates nanoemulsions loaded with dasatinib and quercetin senolytics, and valsartan. We will evaluate thermosensitivity and degradation of the hydrogel in the presence of the drugs, and the release profile of the drugs from the hydrogel. In Aim 2, we will evaluate hydrogels loaded with different drugs in an aged mouse model and focus on collecting safety and efficacy data.

RESEARCH (19 Projects Listed)

1. Project Title: **Frailty, Post-Transplant Delirium, and Neurocognitive Underpinnings of Alzheimers**

Leader(s):   **CHU, NADIA MIKHAIL**
JOHNS HOPKINS UNIVERSITY
NIH K01AG064040 / (2020 - 2025)

Core(s):

PROJECT SUMMARY Kidney transplantation (KT) is a growing treatment for older adults with end-stage renal disease (ESRD). Even after careful pre-operative cognitive screening, post-KT incidence of Alzheimer's disease and related dementias (ADRD) is high. Presence of diagnosed ADRD increases the risk of graft loss, and more than doubles post-KT mortality risk; thus, understanding post-KT ADRD is of great clinical significance. Prior studies have suggested that ADRD may be a down-stream corollary of post-operative delirium, an acute decline and fluctuation in behaviors related to attentional capacity that is often preventable in older surgical patients. In fact, our preliminary data from medical claims suggested that older KT recipients with post-KT delirium were 5-fold more likely to be diagnosed with downstream ADRD. Therefore, we assessed 72 KT recipients initially free of cognitive impairment for delirium using the Delirium Rating Scale (DRS-98) and Confusion Assessment Method (CAM), and found that 93% experienced post-KT sub-syndromal delirium symptoms, 64% had moderate delirium, and 15% had severe delirium. The relationship between delirium components (severity, duration, subtypes) and domain-specific cognitive decline is understudied, but could lend insight into neurocognitive underpinnings of the potential delirium-ADRD link. Frailty (low physiologic reserve), comorbidity may be common substrates linking delirium and ADRD, but few underlying mechanisms have been identified. We hypothesize that post-KT delirium, as a marker of cognitive reserve, interfaces with frailty and KT-specific health-related stressors to accelerate cognitive decline and ADRD progression. Older KT recipients are an ideal population to clarify this association; they have a high prevalence of comorbidities and frailty and are screened to be free of dementia prior to KT. We will leverage an ongoing, prospective R01-funded study of frailty and aging in KT recipients. In this K01, we will add novel CAM measures that will be reviewed by a new delirium consensus panel and establish a consensus committee to identify ADRD cases for 500 older (age=50) KT recipients in this cohort. I will work closely with my highly supportive, multidisciplinary advisory team to meet my training goals and accomplish my aims: 1) To assess whether post-KT delirium incidence is associated with steeper global and domain-specific cognitive decline and increased ADRD risk among older KT recipients; 2) To test whether delirium duration, CAM severity, and sub-type are associated with steeper global and domain-specific cognitive decline and increased ADRD risk among older KT recipients; 3) To assess whether post-KT delirium mediates the relationship between pre- and peri-KT factors and ADRD risk. Our findings will help clarify the role of post-operative delirium in cognitive decline and ADRD risk among the highly susceptible surgical population of older KT recipients, and will lend clues into potential underlying mechanisms of the delirium-ADRD relationship.

2. Project Title: **Effects of Genetic and Pharmacological Kynurenine Pathway Suppression on Healthspan, Lifespan, and Cellular Changes Associated with Aging in Mice**

Leader(s):   **WESTBROOK, REYHAN M.**
JOHNS HOPKINS UNIVERSITY
NIH K01AG076873 / (2022 - 2027)

Core(s):

Title: Impact of Genetic and Pharmacological Kynurenine Pathway Suppression on Healthspan, Lifespan and Cellular Changes Associated With Aging in Mice PROJECT SUMMARY/ASTRACT (30 LINES OF TEXT) Through findings from translational studies on both aged and chronically inflamed mice, as well as on aged and frail older adults, we have identified metabolites of the kynurenine pathway (KP) as potential mediators of systemic damage caused by chronic inflammation. We recently identified that KP metabolites including kynurenine, kynurenic acid, 3-hydroxykynurenine and quinolinic acid were significantly elevated in the serum of older mice and robust and frail older adults, and that this was linked to functional decline and neurodegeneration. The family of molecules known as `kynurenines' are derived from the amino acid tryptophan and are precursors for the important electron carrier and coenzyme molecule NAD+. Kynurenines possess unique bioactive properties and some have pathological potential. For example quinolinic acid (QA) and 3-hydroxykynurenine (3-HK) are neuro- and cytotoxic and induce oxidative stress while kynurenine (KYN) and kynurenic acid (KA) are ligands for the aryl

hydrocarbon receptor (AhR), whose signaling activity is linked to immunosuppression, senescence and impaired autophagy. Conversely, genetically inhibiting the KP extends lifespan in C. elegans and Drosophila, and pharmacological KP blockade increases lifespan in Drosophila. Reduced dietary tryptophan extends lifespan in rodents, but it is unknown if genetic or pharmacological KP blockade improves healthspan or extends lifespan in mice. In this study, we aim to evaluate the hypothesis that genetically and pharmacologically suppressing levels of KP metabolites can delay functional decline, pathophysiological metabolic changes, mortality and cellular changes associated with aging in mice. To understand the effects of KP suppression on aging, we will determine the effect of suppressing the oxidative stress inducing kynurenines, 3-HK and QA, using kynurenine 3-monooxygenase knock out mice (KMO -/-, Aim 1). We will also determine the effect of suppressing both oxidative stress inducing kynurenines, 3-HK and QA, as well as AhR agonist kynurenines, KYN and KA using the indolamine 2,3 dioxygenase knockout mouse (Ido -/-, Aim 2). We will then determine if pharmacological suppression of toxic kynurenines and AhR ligands can delay aging in mice using 1-methyltryptophan (Aim 3). Additionally, we will determine if pairing all of these KP suppression strategies with NAD+ supplementation will synergistically benefit healthspan, lifespan and characteristics of aging in mice. These studies will inform on the role of the KP in functional decline and aging and the therapeutic potential of KP suppression as an anti-aging intervention.

3. Project Title: The START trial: a proof-of-concept sedentary reduction program for prefrail older adults
Leader(s):   WANIGATUNGA, AMAL ASIRI
JOHNS HOPKINS UNIVERSITY
NIH K01AG076967 / (2022 - 2027)

Core(s):
PROJECT SUMMARY Frailty is a syndromic state of vulnerability that puts adults aged =65 years at heightened risk of adverse health outcomes. An estimated 50% of older Americans are prefrail a pre-clinical stage of frailty that might be more amenable to intervention efforts than frailty. Increasing physical activity is a promising intervention to better manage/help reverse the multisystem dysregulation that drives frailty and sequalae. However, initiating and maintaining habitual physical activity is difficult for sedentary older adults, particularly those encumbered by health challenges. The 2018 US Physical Activity Guidelines recommends that all adults perform =150 minutes/week of physical activity and reduce sedentary behaviors. Yet, traditional approaches to increase physical activity do little to address sedentary behavior reduction, especially for older adults. Lower sedentary behavior is associated with improved biological and psychosocial health independent of meeting physical activity guidelines. Thus, there remains a critical need to implement and evaluate a structured way to reduce sedentary behavior as a potential pathway for habitual physical activity engagement. Using novel objectively measured physical activity metrics, our research group has shown that daily sedentary time, either in total or accrued in a prolonged manner, is associated with frailty. Our observation evidence shows that: 1) daily, non- exercise physical activity declines and becomes more fragmented with age (less continuous activity with longer sedentary bouts), 2) higher daily sedentary time and activity fragmentation are both associated with higher frailty incidence, and 3) sedentary time is positively associated with frailty-related markers of inflammation. We propose a pilot study in which we randomize 60 prefrail community-dwelling older adults to receive one of two interventions, each designed to gradually reduce sedentary time: 1) continuously to form a 30-minute walking bout, or 2) in a bouted manner to form three 10-minute walking bouts. Project goals are to: a) explore the effectiveness within and between interventions to decrease objectively measured sedentary time over 2 months; b) assess decreased sedentary time s association with i) patient-reported outcomes and ii) frailty- related inflammatory markers. The primary outcome is accelerometer-determined sedentary time. Secondary outcomes include activity fragmentation, patient-reported outcomes, and inflammatory markers. With a transdisciplinary mentoring panel, my career development plan builds on my expertise in aging and physical activity epidemiology to gain proficiency in: 1) developing and implementing clinical trials for older adults, 2) designing interventions to improve health behaviors, 3) conducting frailty and inflammation related research and 4) gaining competencies to become an effective PI and leader. This project utilizes the infrastructure of the Johns Hopkins Institute for Clinical and Translational Research (ICTR) and Beacham Center for Geriatric Medicine which have strong records of supporting early-stage faculty. This award will facilitate my transition to an independent investigator and will also provide informative data for R21 and R01 applications.

4. Project Title: Alteration in the hypothalamic-pituitary-gonadal axis and frailty in aging men with HIV
Leader(s):   PENA DIAS, JENNY

JOHNS HOPKINS UNIVERSITY
NIH K01AG079680 / (2022 - 2026)

Core(s):

PROJECT SUMMARY/ABSTRACT People with human immunodeficiency virus (HIV), (PWH), are at increased risk of frailty, which increases the risk of adverse age-related outcomes, including falls, hospitalization and mortality. The mechanisms of frailty are not completely understood, particularly among PWH. The objectives of this proposal are to study the extent to which free testosterone and sex hormone binging globulin (SHBG) concentrations are associated with frailty and inflammation in men with HIV. We hypothesize that free testosterone and SHBG are key biomarkers for identifying PWH at the highest risk of frailty and who may benefit from intervention with anabolic agents. Our specific aims are to: 1) Determine the association of circulating free testosterone and SHBG with incident frailty using state-of-the-art hormone measurements among men with HIV, 2) Determine the association of diurnal variation in free testosterone with HIV serostatus in men and its association with systemic inflammation, 3) Determine the association of novel SHBG glycans with frailty among men with HIV. In Aim 1, we will measure serum free testosterone with state-of-the-art methods and SHBG in men with HIV who are part of the Multicenter AIDS Cohort Study (MACS), an ongoing prospective study since 1984 studying the natural and treated histories of HIV-1 infection in homosexual and bisexual men. We will determine the associations of these hormones with incident frailty, collected at semi-annual visits since 2007. In Aim 2, we will select men with and without HIV that have collected blood samples in AM and PM to assess diurnal variation in free testosterone and systemic inflammation [Interleukin 6 (IL6) and soluble TNF-alpha receptors II (sTNFRII)]. In Aim 3, we will study novel SHBG glycoforms in men with HIV, the identification and quantification of SHBG glycoforms will be performed by capillary electrophoresis and lectin microarray. The proposed research aims to provide new insights to the contribution of free testosterone and SHBG in frailty and its relationship with systemic inflammation. The goals during the award period include gaining advanced expertise in biostatistical methods, design and conduct epidemiological studies, as well as hands-on experience in the measurement of glycoforms from plasma proteins and interpretation of glycomic data through mentored research, tailored didactic coursework, and supervised performance of relevant laboratory techniques. Long-term goals include developing a career as an independent investigator in translational epidemiology and developing new approaches to treating and preventing age-related outcomes such as frailty in PWH.

5. Project Title: ALTERATION OF KYNURENINE PATHWAY IN AGE-ASSOCIATED MUSCLE WEAKNESS
Leader(s):   CHUNG, TAE HWAN
THE JOHNS HOPKINS UNIVERSITY
NIH K08AG058483 / (2018 - 2023)

Core(s):

PROJECT SUMMARY Decline in skeletal muscle function with aging is a major determinant of disability and morbidity in late life.However, the neurobiology of such decline in skeletal muscle function in normal aging is poorly understood.The proposed K08 project is a critical step towards to understanding the underlying mechanism of age-relateddecline of skeletal muscle function. This study uniquely focuses on the intersection between kynureninemetabolic pathway, motor neuron, neuromuscular junction (NMJ), and skeletal muscle function. Kynureninepathway is a major route to the synthesis of Nicotinamide adenine dinucleotide (NAD), a critical coenzyme thatbalances redox status of all living cells. Many intermediate metabolites of kynurenine pathway are known to bepotent neurotoxins, and involved in various age-related neurodegenerative diseases. The preliminary studiesof this project showed alterations of kynurenine pathway in aging peripheral neuromuscular system. Herein, itis hypothesized that age-related alterations in kynurenine pathway contributes to neurodegeneration in spinalmotor neurons, eventually causing age-associated muscle weakness. Aim1 propose to identify key alterationsin the kynurenine pathway in the aging spinal motor neurons, using mass spectrometry, PCR, and Westernblot techniques. Aim2 propose to determine the neurotoxicity of kynurenine pathway in aging neuromuscularsystem both in vitro and in vivo models. Finally, Aim3 tests the effects of pharmacological inhibition of akynurenine metabolite synthesis. The findings from this study will likely identify molecular targets for age-associated muscle weakness, and used for future translational study. The proposal will take place in the Johns Hopkins School of Medicine under the mentorship of JeremyWalston, MD, Ahmet Hoke, MD, PhD, and Robert Schwarcz, PhD. An integrated career development andmentoring plan has been also proposed to ensure Dr. Chung s successful transition to independence. Thetraining goals are focused on development of Dr. Chung s expertise in kynurenine neurobiology, variousmolecular techniques in neuroscience research, and translational gerontology. The strength of the proposalcomes from the collaboration between all of his mentors who have world-renowned expertise in aging frailty(Dr. Walston), peripheral neurodegeneration (Dr. Hoke), and kynurenine neurobiology (Dr. Schwarcz).

6. Project Title: **A Meal Delivery and Exercise Intervention to Increase Resilience in Homebound Older Adults**

Leader(s):   **LEE, JESSICA LAN**
UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON
NIH K23AG072042 / (2021 - 2026)

Core(s):

PROJECT SUMMARY/ABSTRACT Homebound older adults are often functionally dependent and at risk for placement in institutions such as nursing homes. The majority of older adults would prefer to age in place in their homes so research is needed to identify interventions that can help them maintain their autonomy. Frailty is an age-related syndrome highly predictive of functional decline and mortality, which is very prevalent in our preliminary studies of homebound older adults (56% frail, 44% prefrail, none were robust) and mainly driven by slow walking speed (88%). Because the homebound population is difficult to reach, there have been few studies and no clinical trials in this population. In our pilot randomized controlled trial of an exercise program administered by Meals on Wheels (MOW), 9 participants (5 treatment, 4 control) completed the 12-week study which showed that gait speed and total frailty score improved in the treatment group. The improvement in gait speed is particularly exciting given its prevalence in homebound older adults. In addition, there were no adverse events and the participants enjoyed the exercises as well as the convenience of the meal deliveries. To further evaluate the clinical changes seen in our trial, we assessed potential novel frailty biomarkers. These biomarkers could help identify frailty earlier than may be seen clinically and provide valuable information about the effects of frailty interventions. Inflammatory biomarkers such as interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-a) have been associated with frailty status but not correlated with treatments. We preliminarily tested heat shock protein (HSP) 70, which induces muscle wasting in cancer cachexia, as well as macrophage inflammatory protein-1 (MIP-1), and soluble interleukin-6 receptor (sIL-6R) to see if they could be more specific frailty biomarkers. Our exercise group had decreased HSP70, MIP-1 , and sIL-6R when compared to the control group over 12 weeks. Thus we have 2 aims: 1) evaluate the effects of a home-based exercise program administered through MOW on gait speed and frailty status in frail/prefrail homebound older adults, and 2) assess the association between novel serum biomarkers (HSP70, MIP-1 , sIL-6R) and established but non-specific frailty biomarkers (IL-6, CRP, TNF-a) in frail/prefrail homebound older adults before and after the exercise intervention. Data from this project will be the catalyst for an R01 or equivalent award involving multi-pronged frailty interventions, targeting mechanistic and clinical pathways, with the goal of helping homebound older adults age in place. This career award would also provide training and mentorship for Dr. Jessica Lee to develop into a physician-scientist with independent funding. UTHealth has provided her with a supportive environment, individualized career development plan, and expert mentors with long-standing experience in geriatrics, clinical trials, exercise interventions, biomarkers, and biostatistics. As the medical director of a home-based primary care service, her goal is to become an expert in interventions to improve resilience in her homebound patients.

7. Project Title: **Addressing Inactive Kidney Transplant Waitlist Status through Adapting a Tailored Psycho-Social-Environmental Program**

Leader(s):   **HLADEK, MELISSA**
JOHNS HOPKINS UNIVERSITY
NIH K23DK133677 / (2023 - 2028)

Core(s):

PROJECT SUMMARY/ ABSTRACT Kidney transplantation (KT) is a growing treatment for older adults with end-stage renal disease (ESRD), but there is vast heterogeneity in KT outcomes. Older adults are more likely to be listed as inactive (on the waitlist but ineligible for KT), which is associated with increased waitlist mortality and worse post-surgical outcomes. Those awaiting KT also experience depressive symptoms, pain, loss of physical function, and social isolation, which can contribute to waitlist mortality and decrease chances of KT. As of April 2022, 94,249 people were awaiting KT with an estimated 44% currently inactive. There is a critical need for enhanced models of care to improve inactive waitlist outcomes. The purpose of this study is to adapt and pilot test the evidence-based Community Aging in Place- Advancing Better Living for Elders (CAPABLE) intervention to address barriers for KT waitlist activation which involve symptom burden, self-management, social support, health literacy, patient activation and home function. CAPABLE equips older adults to age in their homes using person-directed priorities and a strengths-based tailored approach by a nurse, occupational therapist and handy worker (PI: Szanton, co-primary mentor). CAPABLE improves function, pain, depressive symptoms, and quality

of life while decreasing hospitalizations and nursing home admissions. CAPABLE also improves healthcare engagement and self-efficacy which are key components to remaining active on the KT waitlist. Our adapted CAPABLE Transplant model will extend services to include options for internet access, training, patient portal usage and patient-directed online social engagement to address the noted isolation. We hypothesize that decreasing patient and clinician reported barriers will decrease time inactive on the KT waitlist status. We plan to examine CAPABLE-Transplant among those with inactive KT waitlist status in a two-phase developmental study leveraging partnership with the JHU Comprehensive Transplant Center and an ongoing, prospective NIA R01-funded cohort study of individuals awaiting KT for recruitment (PI: McAdams-DeMarco, co-primary mentor) through the following aims: (1) To develop an adaptation of CAPABLE targeting those currently KT inactive, (2) To iteratively refine the CAPABLE -Transplant prototype for those currently KT inactive and, (3) To pilot test the CAPABLE-Transplant intervention in a 30 person 1:1 randomized waitlist control trial delivered over 16 weeks with outcomes (e.g. waitlist status, symptom burden, social networks) evaluated at 0,16, and 32 weeks post-randomization to test feasibility, acceptability, fidelity of CAPABLE-Transplant and estimate preliminary effects sizes for a future efficacy trial. To our knowledge, there are no other home-based programs that address patient-directed goals and the home environment among those inactive awaiting KT. This work will form the basis for a future R01 to expand to other KT centers and/or into other transplant populations conducting a larger community-based, efficacy trial.

8. Project Title: Frailty and Resiliency in Older Adults with Acute Myocardial Infarction

Leader(s):   DAMLUJI, ABDULLA AL
INOVA HEALTH CARE SERVICES
NIH K23HL153771 / (2020 - 2025)

Core(s):

The purpose of this research is to support the development of Dr. Abdulla Damluji into an independent investigator focused on studying geriatric syndromes during cardiovascular intervention. The K23 award will allow the development of a fundamental skillset including: the design and methods for analysis of interventions, understanding and proper application of frailty and resiliency assessments, designing pilot prospective studies, and enhancing knowledge of geriatrics and gerontology. Skills will be obtained through coursework, workshops, seminars, scientific meetings and mentored research. The overall goals are: 1) identify a simple universal bedside frailty test for clinical decision-making and 2) become an NIH-investigator prepared to conduct a clinical trial aimed to evaluate the comparative effectiveness of different treatments of acute myocardial infarction (AMI) in a heterogenous population of older adults living with frailty and lack of resiliency. Two thirds of all patients with cardiovascular disease (CVD) are older than 60 years of age, and >85% of patients over age 85 years live with some form of CVD. Of those older patients admitted with acute AMI, a majority experience frailty, a syndrome of decreased physiologic reserve and vulnerability to stressors. Moreover, some of these frail patients lack physical resiliency, the ability to rebound back and recover from a major health crisis. Critical gaps in knowledge in cardiovascular care for older adults, particularly those with frailty and lack of resiliency, have been identified. These gaps need to be addressed in order to provide the best possible care to a growing older patient population. This proposal examines the hypothesis that frailty and resiliency influence the treatment choice and health outcome after AMI. Aim1 evaluates the prevalence of frailty in U.S. among older AMI patients by treatment [percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery, or guideline-directed medical therapy (GDMT)] using the validated claims-based frailty index. Aim 2 examines the role of frailty in treatment response to PCI and CABG. Aim 3 validates the diagnostic accuracy of a bedside 4-item frailty scale and assesses whether this diagnostic tool, used in combination with resiliency measurements, can predict health outcomes at 1-year follow-up. The institutional environments at both the Inova Heart and Vascular Institute (IHVI) and Johns Hopkins University (JHU) are ideal for conducting cardiovascular outcomes research. The mentorship consists of leaders with expertise directly relevant to the career goals of the applicant: Christopher M O Connor, MD (IHVI; expert in experimental design); Dr Wayne Batchelor (IHVI: interventional cardiologist); Jodi B Segal, MD, MPH (JHU: internist/epidemiologist; expertise in clinical effectiveness), and Gary Gerstenblith (JHU: geriatric cardiology). Resources at IHVI include bioinformatics laboratory, grant management office, and a state-of-the-art research office. At JHU, resources include the Bloomberg School of Public Health, Graduate Training Program in Clinical Investigation, JHU Pepper Center Biostatistical and Research Education Cores, and the Welch Medical Library.

9. Project Title: THE JOHNS HOPKINS ALZHEIMER'S DISEASE RESOURCE CENTER FOR MINORITY AGING RESEARCH

Leader(s):   REBOK, GEORGE W.; THORPE, ROLAND J ;

THE JOHNS HOPKINS UNIVERSITY
NIH P30AG059298 / (2018 - 2023)

Core(s):

The Schools of Medicine, Nursing, and Public Health of the Johns Hopkins University areproposing a new Alzheimer's-related Resources Center for Minority Aging Research (AD-RCMAR) in response to RFA-AG-18-002. The aims of this application are to: (1) mentor early-stage investigators from underrepresented backgrounds in minority aging and health disparitiesresearch, with a focus on Alzheimer's disease and related disorders (ADRD), using a life courseperspective encompassing biological, behavioral, and community factors contributing tocognitive impairment and dementia in older minority adults; (2) conduct epidemiological,preventive, and intervention research that addresses ADRD in later life within a multi-levelframework that encompasses individuals, families, social networks, and communities; and 3)engage communities and health care providers especially family caregivers, primary carepractices, communities of faith, and community organizations as our partners in recognizingdementia and developing interventions with the potential to prevent cognitive decline andreduce ADRD dementia risk and disparities in minority older adults. The Johns Hopkins AD-RCMAR consists of: (1) an Administrative Core whose function is to provide governance and anadministrative structure, to support research, to foster interactions between Cores and otherCenters, and to ensure RCMAR Scientists develop mentoring relationships across the affiliateddepartments, schools, the intramural program at NIA in Baltimore, and nationally; (2) aResearch Education Component to foster diverse junior investigators and mid-careerinvestigators transitioning into ADRD-relevant research through support for individual pilotprojects, career mentoring, scholar-to-scholar interactions, and role modeling; (3) a Community-Liaison and Recruitment Core to ensure the relevance of the ADRD research and to increaseknowledge of engagement of community members in the research enterprise with the creationof a Community Resource Institute as a venue for community-investigator interaction; and (4) anAnalysis Core as a foundation for methodological and statistical mentoring, including educationand mentoring in mixed-methods research. An Executive Committee includes communityrepresentatives and a Scientific Advisory Panel consists of distinguished investigators withrelevant expertise in minority aging, disparities, and ADRD. A pilot project program supportedby all Cores to facilitate the development of RCMAR Scientists includes three initial pilotprojects focusing on recruitment of minority populations for ADRD research, early diagnoses ofdementia, and intervention development related to ADRD-related driving disparities.

10. Project Title: Utilizing Technology and AI Approaches to Facilitate Independence and Resilience in Older Adults

Leader(s):   **CHELLAPPA, RAMA ; ABADIR, PETER M.; HAGER, GREGORY DONALD; WALSTON, JEREMY D;**
JOHNS HOPKINS UNIVERSITY
NIH P30AG073104 / (2021 - 2026)

Core(s):

The overarching goal of this application is to build an Artificial Intelligence (AI) and Technology Collaboratory (AITC) ecosystem that will serve as a national resource to promote the development and implementation of novel AI and technology approaches to improve care and health outcomes for older Americans. The specific aims are: 1) To engage AI and geriatric/gerontology investigators from across the country and to identify, validate, test, and develop new AI and technologies relevant to improving the health and wellbeing of older adults through crucial pilot study mechanisms; 2) To serve as a national resource center that stimulates and leads the development and implementation of effective novel AI and technology approaches and products that will promote the health, wellbeing and independence of all older Americans; 3) To support the engagement of stakeholders in AI research; 4) To build an ecosystem of overlapping innovation and business, academic, and communities- of-practice networks ; and 5) To provide highest quality expertise, support, and infrastructure needed to disseminate technical and policy guidelines and best practices for effectively incorporating AI approaches and technology for older Americans, in partnership with private industry, angel investors, venture capital firms, and healthcare systems. This AITC is directed by a multi-PI interdisciplinary team led by two world-class experienced investigators who have long worked successfully in the fields of AI and technology development areas partnered with investigators who have long and successfully worked at the translational interface that connects real-world medical, cognitive, and functional declines that impact older adults with medical and technological solutions. Each of these investigators has a complementary skill set and a long track records of organizing transdisciplinary teams and consortiums of investigators around core themes. This interdisciplinary, accomplished, and highly visible leadership team will work together to develop vision for the next generation of AI in aging science and to build a scientifically and culturally diverse community of AI scholars and trainees around Aging. To achieve our goals, we designed the JHU AITC to have robust scientific and technological expertise that are described in eight core components. This infrastructure will support the

implementation of stakeholder input and the identification of relevant technologies and investigators locally and nationally through a vetting and feasibility testing process of both technology and data processes. It will include a pilot testing phase and related oversight process. We have also established a key partnership with the Iowa office of Rural Health and Veterans Rural Health Resource Centers Leadership and with organizations within Johns Hopkins University that focus on improvements in the health and well-being of older adults in underserved urban communities. Connections with key academic, industry partners have also been established to accelerate the development of relevant technologies into products. This team is dedicated to developing the next AI scientific advances and disseminating resulting strategies into practice and policy that will maximize health, well-being, and independence for older adults.

11. Project Title: DOES VESTIBULAR LOSS PREDICT FALLS IN PATIENTS WITH ALZHEIMER'S DISEASE?

Leader(s): **AGRAWAL, YURI**
THE JOHNS HOPKINS UNIVERSITY
NIH R01AG057667 / (2018 - 2023)

Core(s):

Project summaryThis project investigates whether vestibular loss predicts falls in patients with Alzheimer s disease (AD).The proposed research is an observational study of 150 patients with AD to evaluate the associationbetween baseline vestibular function and 2-year incidence of falls. We will also explore whether vestibularfunction is associated with balance and gait function, as well as spatial cognitive function, as potentialmechanisms by which vestibular function contributes to fall risk. Specifically, Aim 1 is to determinewhether vestibular loss predicts falls in patients with mild-moderate AD. We hypothesize that poorervestibular function at baseline predicts a higher 2-year incidence of falls. Additionally, we hypothesize thatthe attributable risk of falls associated with vestibular loss will be substantial enough (>~10%) to warrantfurther investigation of vestibular therapy as a clinically significant modifier of fall risk. Aim 2 is to evaluatewhether vestibular loss in AD predicts impaired static and dynamic balance, measured using the BergBalance Scale (BBS) and the Timed-Up-and-Go (TUG) test. We hypothesize that greater reduction investibular function over the 2-year follow-up period predicts greater decline in BBS and TUG performance.Aim 3 is to evaluate whether vestibular loss in AD predicts impaired spatial cognitive skills. We willadminister cognitive tests of spatial cognition (including the Money Road Map test, the Card Rotationstest, the Visual Form Discrimination test and the Clock Drawing test), and we will also query participantsand caregivers about difficulty with driving, losing objects, getting lost and wandering behaviors asfunctional manifestations of impaired spatial cognition in AD patients. We hypothesize that greaterreduction in vestibular function over the 2-year follow-up period predicts greater decline in spatial cognitivetest scores, and a higher incidence of functional spatial cognitive impairment. Moreover, we hypothesizethat impaired balance measures (from Aim 2) and impaired spatial cognitive skills will both be independentmediators of the association between vestibular loss and incident falls. To accomplish these aims, we willleverage well-established resources at Johns Hopkins including the Johns Hopkins Alzheimer s DiseaseResearch Center and the Memory and Alzheimer s Treatment Center. Falls are a major source ofmorbidity in AD and current interventions are not uniformly effective. If our observational studiesdemonstrate that vestibular loss is associated with poorer balance and spatial cognition and incident falls,these results will inform the design of interventional trials to prevent falls in AD patients.

12. Project Title: FRAILTY, HIV INFECTION, INJECTION DRUG USE AND THE INFLAMMATORY-MICROBIOME

Leader(s): **PIGGOTT, DAMANI**
THE JOHNS HOPKINS UNIVERSITY
NIH R01AG060825 / (2018 - 2023)

Core(s):

PROJECT SUMMARY/ABSTRACTWith effective antiretroviral therapy (ART), life expectancy for HIV-infected persons has markedly improved, yetmarked deficits in survival remain for HIV-infected persons with a history of injecting drugs (PWID). Disparitiesamong PWID have been attributed in part to a shifting spectrum of disease to aging-associated conditionsdriven by persistent inflammation even with ART. Frailty is an important aging-related state of vulnerability tostress, with an increased burden in HIV infection, strongly associated with heightened inflammation, andpredictive of premature mortality and aging-related morbidity among PWID. Injecting drugs itself can increasethe severity of inflammation in HIV. The human gut microbial ecosystem (gut microbiome) critically regulatesinflammation and

immunity. Alterations in the gut microbiome (gut dysbiosis) together with associateddisruptions of gut structure and immune integrity constitute an inflammatory-microbiome signature (gutdysbiosis, increased gut permeability, translocation of microbial products, immune activation, heightenedinflammation) linked to adverse aging-associated inflammatory conditions and disease. Proposed is asystematic investigation of the role of HIV infection and injection drug use (IDU) in defining the inflammatory-microbiome signature and determination of the relationship of this signature to frailty. Through assessments ofthe fecal and mucosal microbiome in the AIDS Linked to the IntraVenous Experience (ALIVE) cohort of HIV-infected and epidemiologically comparable HIV-uninfected PWID, we will determine how HIV infection andactive IDU alter microbiome composition and function and the relationship of these changes to inflammationand frailty progression over time. Using a germ free murine model, we will further define the frail humanmicrobial communities and gene products that precipitate inflammation. These studies will facilitate elucidationof gut microbial determinants of frailty among HIV-infected PWID and could significantly inform microbiotamodulation strategies to reduce frailty-associated inflammation beyond ART. Understanding the role of the gutmicrobiome in relation to HIV, injection drug use, and frailty remains a critical next step to reducing the markeddisparities in clinical outcomes among HIV-infected PWID.

13. Project Title: CONTRIBUTION OF SENSORIMOTOR FUNCTION TO RISK AND PATHOGENIC MECHANISMS OF ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

Leader(s): **SCHRACK, JENNIFER ANN; AGRAWAL, YURI ; LIN, FRANK R ;**
THE JOHNS HOPKINS UNIVERSITY
NIH R01AG061786 / (2019 - 2023)

Core(s):

PROJECT SUMMARYAlzheimer's disease (AD) is the most common cause of dementia. Underlying pathological and physiologicalchanges related to the onset and progression of AD are believed to emerge several years prior to clinicalmanifestations. Sensory impairments, gait abnormalities, and motor slowing may precede the diagnosis of ADby a decade or more, presenting the exciting possibility that changes in sensorimotor functioning may act asearly noninvasive biomarkers for AD. Previous work by our group has identified links between cognitiveperformance and sensory impairment and gait speed and variability, making them potential preclinical markersof early AD pathology. We propose to use up to 10 years of existing longitudinal data, and ongoing/new datacollection in approximately 1,000 older adults in the Baltimore Longitudinal Study of Aging (BLSA), to examinethe roles of sensory function, gait speed and variability, and free-living measures of daily physical activity (PA)as precursors to cognitive impairment. We will also determine the link between sensorimotor measures andbiomarkers of AD pathology, including A deposition using [11C]-Pittsburgh compound B positron emissiontomography, brain atrophy using structural magnetic resonance imaging (MRI), Tau and pTau from cerebrospinalfluid, and cognitive performance. We will further utilize the rich data resources of the BLSA to develop aparsimonius prediction model for risk of progression to MCI/AD, and validate its performance in theAtherosclerosis Risk in Communities (ARIC) study. A better understanding of the associations amongsensorimotor changes, subclinical AD pathology, and cognitive performance may elucidate a high-risk phenotypethat is associated with increased risk of poor cognitive outcomes over time and increase our understanding ofthe complex associations among declines in sensory, physical, and cognitive functioning with age. To this end,future intervention studies of AD prevention might screen for sensorimotor impairments as a high-risk phenotypereflective of increased risk for developing AD, which could serve as surrogate outcomes in clinical trials.Moreover, sensorimotor impairments may present feasible and modifiable targets for AD prevention byidentifying critical threshold(s) for implementation of assistive and rehabilitative technologies such as hearingaids, corrective lenses, surgical or pharmacologic procedures to correct hearing and/or vision impairment (e.g.,cataract surgery, cochlear implants), and physical therapy/timing and coordination of movement training tocorrect gait abnormalities.

14. Project Title: MITOCHONDRIAL ENERGETICS, EXERCISE INTOLERANCE AND FATIGABILITY IN OLDER PEOPLE WITH HIV

Leader(s): **WEISS, ROBERT G**
THE JOHNS HOPKINS UNIVERSITY
NIH R01AG063661 / (2019 - 2024)

Core(s):

People living with HIV infection (PLWH) are living longer but with advancing age experienceaccelerated functional decline (decreased strength, slowed gait, reduced exercise tolerance) and increasedfrailty, as compared to non-infected individuals. The syndromes of functional decline and frailty are associatedwith impaired quality of life, increased vulnerability to superimposed stresses, and the likelihood of prematuremorbidity and mortality. The mechanisms underlying this accelerated dysfunction and disability, however, arepoorly understood. The proposed project examines the contribution of altered skeletal muscle (SM)mitochondrial function and high energy phosphate metabolism to the related, but distinct syndromes of fatigue,exercise intolerance, and frailty often present in older PLWH. Considerable pre-clinical data and our pilotclinical studies using a 31P magnetic resonance spectroscopy (MRS) fatigability test during and following lower-extremity exercise suggest an energetic myopathy as a possible basis for the fatigue and decreasedperformance in older PLWH individuals. However the extent, underlying responsible factors, and functionalsignificance of altered SM mitochondrial bioenergetics in this population have not been characterized. Inaddition, two potential mechanisms responsible for altered SM high energy phosphate metabolism in otherpopulations, increased inflammation and SM lipid accumulation, have not been examined and related tomuscle energetics in PLWH and so these too will be examined. The central hypothesis is that impaired SMmitochondrial energy metabolism, initiated by aging and accelerated in the setting of contemporary HIV, is acentral contributor to the geriatric syndromes of fatigue, exercise intolerance, and frailty in older PLWH. Wepropose to use state-of-the art 31P MRS exercise testing, detailed muscle and whole body compositionmeasures, functional assessments during observed and free-living conditions, and biomarkers of inflammationand immune activation in 200 older (age>=60) women and men derived from four local NIH-sponsored cohortsto address these questions. The specific aims are 1) to define the scope of SM metabolic changes in olderwomen and men living with HIV, 2) to probe whether inflammation, skeletal fat and other underlying factors arerelated to the energetic abnormalities in older PLWH and 3) to determine the functional significance of SMenergetic changes in older PLWH by examining the relationships between the energetic changes and exercisetolerance and other functional assessments as well as the frailty phenotype. Fatigue, exercise intolerance, andfrailty are common in older PLWH and the underlying mechanisms remain poorly understood These novel,timely studies will provide new insights and guide future intervention strategies designed to attenuate orreverse mitochondrial and bioenergetic decline and thereby reduce the personal and societal toll of thesegeriatric conditions in older women and men living with HIV.

15. Project Title:
Differential Regulation and Roles of A-type Lamins in Early G1

Leader(s):
REDDY, KAREN LYNN; WILSON, KATHERINE L;
JOHNS HOPKINS UNIVERSITY
NIH R01GM132427 / (2020 - 2024)

Core(s):

Summary Lamins A, C, B1 and B2 form nuclear intermediate filaments as major components of the dynamic genome-associated nucleoskeleton. Lamins associate with nuclear envelope (NE) membrane proteins, together forming nuclear lamina networks. Lamins and key partners (LEM-domain proteins and BANF1) are essential during exit from mitosis to ensure that chromosomes are coalesced, captured and properly organized within the daughter nucleus. During interphase, nuclear lamina networks have fascinating roles in the higher-order architecture of transcriptionally-inactive regions of the genome (heterochromatin). Silent regions of each chromosome, known as Lamina Associated Domains (LADs), are typically located near the NE. There are clear correlations between LAD organization, epigenomic regulation, and the functional three-dimensional (3D) folding of the genome. A-type lamins (encoded by LMNA) have key roles in LAD organization. LMNA gives rise to two major somatic isoforms, lamin A and lamin C, by alternative mRNA splicing. Because the first 566 residues of human lamin A and lamin C are identical, they were long thought to function redundantly. However new reports show lamin A and lamin C form separate filaments, associate differentially with nuclear pore complexes and have distinct metabolic phenotypes. We discovered lamin C is required for LADs to associate with the NE during interphase. Furthermore, lamin C is specifically and strikingly nucleoplasmic during telophase and early-G1, in stark contrast to lamin A at the nascent NE. Although lamin C is not LAD- associated in early-G1, we found lamin C associates with LADs as they return to their tethered positions at the NE. We propose lamin C is required for LAD recruitment to the NE, and will test this hypothesis in cells specifically downregulated for lamin C or lamin A. We can detect distinct yet overlapping proteomes in unsynchronized cells, comprising emerin and LAP2beta at the nuclear membrane, lamins and soluble partners (connectome), and a novel LAD-associated proteome. We hypothesize that lamin C specifically interacts with LADs or LAD-associated proteins during exit from mitosis as a pathway to re-establish the tissue-specific positioning of silent chromatin (LADs) at the NE. Our models predict distinct proteomes for lamin C vs lamin A during mitotic exit, distinct changes in the LAD proteome during mitotic exit, and perturbed LAD organization or LAD recruitment to the NE in cells that lack lamin C during mitotic exit. We will test these models by super- resolution imaging of lamins and LADs in single cells, directed proteomics, genome organization mapping and functional studies in cells downregulated for either lamin C, lamin A or validated proteins identified in this work. This work is expected to fill

major gaps in understanding how genome architecture is established after mitosis, and functional differences between lamin A and lamin C that may also be relevant to the mechanisms of diseases linked to LMNA.

16. Project Title: Cerebral Autoregulation in the Cardiac Surgery Intensive Care Unit: Associations with Postoperative Delirium, Cognitive Change, and Biomarkers of Brain Injury

Leader(s):   **BROWN, CHARLES HUGH**
JOHNS HOPKINS UNIVERSITY
NIH RF1AG072387 / (2021 - 2024)

Core(s):

PROJECT SUMMARY/ABSTRACT Delirium occurs in up to 50% of patients after cardiac surgery and is associated with cognitive decline and Alzheimer s disease and related dementias (ADRD). However, the underlying mechanisms for these complications are elusive. Further, the extent to which events in the early postoperative period increase risk for delirium, cognitive decline, and ADRD is unclear. The goal of this proposal is to examine cerebrovascular contributions to delirium / cognitive decline, with a focus on cerebral perfusion in the cardiac surgery intensive care unit (ICU). Given the wide variations in blood pressure in the ICU, coupled with the high prevalence of cerebrovascular disease, cerebral malperfusion in the ICU may contribute to delirium and cognitive decline. Current practice of targeting empiric mean arterial pressure (MAP) goals in the perioperative period may be inadequate for individual patients. Our group has championed a more personalized method based on cerebral autoregulation monitoring. Through the process of cerebral autoregulation, the brain is regulated to maintain a constant cerebral blood flow across a range of MAP. However, when MAP exceeds limits of autoregulation or when autoregulation is impaired, compensatory mechanisms fail and inadequate or excessive cerebral blood flow results. Our work in the cardiac surgery operating room has shown several results that emphasize the importance of individualizing blood pressure goals. First, the MAPs at the limits of autoregulation vary widely in patients, and both impaired autoregulation and MAP outside the limits of autoregulation are associated with organ injury. Second, in a recent trial, targeting MAP to be >lower limit of autoregulation during cardio- pulmonary bypass vs. usual care reduced delirium by 28% and improved memory scores at 1- and 12-months. To date, the majority of research has been conducted in the operating room during cardiopulmonary bypass. However, our preliminary data suggests that the early phase of ICU care may be equally important. In a small pilot study, we found that in the ICU, the extent of MAP outside the limits of autoregulation, as well as impaired autoregulation, were associated with delirium. Importantly, cognitive change was not assessed in this pilot and mechanisms for these findings are unclear. These results motivate the proposed observational study, which will examine whether (a) MAP outside the limits of autoregulation and (b) impaired autoregulation in the ICU are associated with delirium after cardiac surgery (Aim 1) and cognitive change from baseline at 1- and 12- months (Aim 2). In an exploratory mechanistic aim (Aim 3), we will characterize whether perioperative brain injury mediates or baseline neurodegeneration moderates the association of cerebral autoregulation characteristics and delirium and cognitive decline. The results of this study will more precisely characterize the role of cerebral malperfusion in the ICU with delirium and will identify mechanisms through which brain injury occurs. Promising results would also support a trial to target MAP in the ICU based on these methods. Although the cohort is only followed for one year, these results may also provide insight into potential mechanisms for longer-term cognitive decline and ADRD.

17. Project Title: VALIDATION OF NUCLEAR MORPHOLOGY AS A BIOMARKER OF AGING AND AGING-RELATED PHENOTYPES

Leader(s):   **WIRTZ, DENIS**
THE JOHNS HOPKINS UNIVERSITY
NIH U01AG060903 / (2018 - 2023)

Core(s):

AbstractAlterations in the nuclear protein lamin and associated structures in the nucleus have beenidentified as a source of nuclear morphology changes that markedly impact overall cellularfunction. These changes in nuclear morphology are thought to drive molecular changes thatinfluence a wide range of aging-related phenotypes and chronic disease states. Importantly, wehave recently used high-throughput measurements of nuclear morphology to identify outstandingbiomarkers of chronological age. We hypothesize that these age-related changes in nuclearmorphology are highly correlated with chronological age in healthy individuals, and that a specificage-related biological change in lamin underlies this phenomenon. Building on our priordevelopment of these high-throughput and accurate measures of nuclear

morphology, we proposehere to further develop this biological discovery and technology as a valid and reliable biomarkerof aging-related biological mechanisms. We hypothesize that changes in nuclear morphology canbe rapidly measured and that age-related alterations correlate with aging-related phenotypes anddisease states independently of chronological age, consistent with a measure of cellular biologicalage. To test these hypotheses and move results toward clinical utility, we have assembled a highlysynergistic, interdisciplinary team propose the following specific aims:Aim 1. Using our validated single-cell technologies, we will develop a mechanistic understandingof how descriptors of nuclear morphology in human dermal fibroblasts and B-lymphocytes arerobust biomarkers of aging in healthy individuals. Aim 2. Establish the accuracy and precisionwith which our proposed biomarkers identify chronological age for individuals with varyingdemographic, behavioral, and health characteristics. Aim 3. We will examine the strength withwhich morphological biomarkers discriminate individuals with adverse phenotypes and outcomesof aging, and at risk for the development of these, from healthy older adults, above and beyondchronological age.

18. Project Title: Leveraging an ongoing longitudinal study of influenza vaccination to define immune signatures of response and risk of infection in older adults >75

Leader(s): LENG, SEAN XIAO; BREAM, JAY H.;
JOHNS HOPKINS UNIVERSITY
NIH U01AI165826 / (2021 - 2026)

Core(s):

Project summary Seasonal influenza (flu) remains a serious public health threat with the highest burden of severe disease and complications affecting older adults, particularly those over age 75. In addition to vaccine itself, responses to vaccination and vaccine effectiveness in older adults are likely influenced by comorbidity (e.g., frailty), immune senescent remodeling (i.e., immunosenescence and inflammaging), repeated annual vaccination, intra-seasonal immune waning, and virus strain variations both in vaccine formula and in circulation. Since 2014, we have established a study cohort in community-dwelling older adults >75. The cohort has accumulated 815 person-seasons with comprehensive demographic, clinical, functional and laboratory data, as well as banked pre- and post-vaccination serum, plasma, and peripheral blood mononuclear cell (PBMC) samples. We also identified 15 breakthrough flu infection cases with banked post-infection serum, plasma and PBMC samples. Importantly, 20 subjects participated in all 7 seasons, 36 in 6 seasons, 31 in 5 seasons, 16 in 4 seasons, and 165 in 3 seasons or less. Here, we propose to leverage this unique cohort and employ cutting edge immunologic research tools to develop state-of-the-art immune signatures reflecting both general immune status (distribution and function of immune cell subsets through high-dimensional flow analysis and RNA-Seq; cytokine profiling) and influenza-specific immunity (breadth and depth of flu-specific T cell repertoire; distribution/function of homotypic/heterotypic anti-flu T cells through flow analysis and scRNA-Seq; deep serological profiling of strain-specific and cross-reactive flu antibodies). Our objective is to characterize immune signatures and their intra- and inter-seasonal changes over time as determinants of vaccine responses and risk of breakthrough infection in older adults >75. Our specific aims are: 1) Characterize seasonal baseline (pre-existing) immune signatures as determinants of vaccine response and how they change over time. We will not only determine inter-season longitudinal trajectory, but also identify specific baseline immune signatures predict responses to vaccination; 2) Characterize seasonal immune signature responses to vaccination as determinants of risk of breakthrough infection and how they change over time. We will evaluate and compare differences and similarities of immune signature responses elicited by vaccination vs natural infection to explore immune mechanisms of vulnerability; and 3) Characterize intra-seasonal waning of immune signature responses to vaccination and its change across seasons through monthly blood sampling until the end of each flu season across multiple seasons. Upon completion, the proposed studies will advance our understanding of immune signatures as key immunologic mechanisms for vaccine responses and risk of breakthrough infection in a typical geriatric population. Ultimately, these studies will help define correlates of protection and develop more effective immunization strategies including a universal vaccine for this highly vulnerable subset of older adults.

19. Project Title: SEX AND AGE DIFFERENCES IN IMMUNITY TO INFLUENZA (SADII)

Leader(s): KLEIN, SABRA L.
THE JOHNS HOPKINS UNIVERSITY
NIH U54AG062333 / (2018 - 2023)

Core(s):

SEX AND AGE DIFFERENCES IN IMMUNITY TO INFLUENZA (SADII) SUMMARYThe NIH Office of Research on Women s Health (ORWH) should support a Specialized Center of ResearchExcellence (SCORE) on sex differences in influenza immunity because despite having antivirals and vaccines,influenza remains a significant public health threat, causing approximately 100,000 hospitalizations, 30,000deaths, and approximately $7 billion in lost productivity in the United States, alone. Sex and age are emergingas two host variables that significantly impact the pathogenesis of influenza virus infection and responses toinfluenza vaccines. The Sex and Age Differences in Immunity to Influenza (SADII, pronounced sade) SCOREwill leverage the internationally recognized research, resources, and educational opportunities at JohnsHopkins University to transform women s health and impact the development of and policy decisions aboutinfluenza vaccine programs, including universal influenza vaccines. The overarching hypothesis being testedthrough the SADII SCORE Research Projects is that female-biased vaccine-induced immunity to influenzaviruses is age-dependent and reflects both hormonal and genetic differences between the sexes that impactimmune responses (i.e., both effector and memory) to influenza vaccine antigens. SADII will bring togetherinvestigators focused on 1) seasonal influenza vaccination in an existing age and sex stratified humanpopulation; 2) animal models that can test hypotheses and mechanisms of action that are inferred from studiesin human populations; and 3) the contributions of age, frailty, sex, and gender to vaccine outcomes usingquantitative and qualitative statistical models. By using the combined expertise in our research groups, SADIIis uniquely positioned to identify the biological basis behind sex and age differences in immune responses toinfluenza vaccination and disseminate those findings to the broader research, clinical, and public healthcommunities. The overarching mission of the SADII SCORE will be achieved through the following SpecificAims: 1) To provide leadership and oversight of the SADII SCORE and collaboration with other entities atJohns Hopkins and elsewhere to develop a translational research program focused on sex and age differencesin immunology and infectious diseases; 2) To systematically evaluate sex differences in vaccine-inducedimmune responses across the life course using translational approaches involving human studies andmechanistic animal models; and 3) To meet the career enhancement needs of diverse translational scientistsstudying sex differences at Johns Hopkins and beyond. We are prepared to transform women s health, sex,and gender research into a signature initiative at Johns Hopkins and in the fields of microbiology andimmunology.

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Citations: 57 | AltScore: 11.75

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    Ijaz N, Buta B, Xue QL, Mohess DT, Bushan A, Tran H, Batchelor W, deFilippi CR, Walston JD, Bandeen-Roche K, Forman DE, Resar JR, O'Connor CM, Gerstenblith G, Damluji AA
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Roth DL, Bentley JP, Mukaz DK, Haley WE, Walston JD, Bandeen-Roche K
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Sezgin D, O'Donovan M, Woo J, Bandeen-Roche K, Liotta G, Fairhall N, Rodr?guez-Laso A, Ap?stolo J, Clarnette R, Holland C, Roller-Wirnsberger R, Illario M, Ma?as LR, Vollenbroek-Hutten M, Dogu BB, Balci C, Pernas FO, Paul C, Ahern E, Romero-Ortuno R, Molloy W, Cooney MT, O'Shea D, Cooke J, Lang D, Hendry A, Kennelly S, Rockwood K, Clegg A, Liew A, O'Caoimh R
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Sinha SS, Rosner CM, Tehrani BN, Maini A, Truesdell AG, Lee SB, Bagchi P, Cameron J, Damluji AA, Desai M, Desai SS, Epps KC, deFilippi C, Flanagan MC, Genovese L, Moukhachen H, Park JJ, Psotka MA, Raja A, Shah P, Sherwood MW, Singh R, Tang D, Young KD, Welch T, O'Connor CM, Batchelor WB
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Citations: 28 | AltScore: 32.2

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Tehrani BN, Damluji AA, Batchelor WB
Curr Cardiol Rev, 2022, 18(2): 15-30
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Citations: 150 | AltScore: 3

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Vohra V, Leland EM, Schlosser RJ, Kamath V, Rowan NR
Nutrients, 2022 Mar 15, 14(6):
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Westbrook R, Abadir PM
J Gerontol A Biol Sci Med Sci, 2022 Dec 29, 77(12): 2343-2345
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Westbrook R, Zhang C, Yang H, Tian J, Guo S, Xue QL, Walston J, Le A, Abadir PM
J Gerontol A Biol Sci Med Sci, 2022 Dec 29, 77(12): 2367-2372
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Citations: 25 | AltScore: NA

EXTERNAL ADVISORY BOARD MEMBERS

Harvey J. Cohen, M.D.
Walter Kempner Professor of Medicine, Director Emeritus, Center for the Study of Aging and Human Development, Chair Emeritus, Department of Medicine, Duke University Medical Center
Serving since 2003 (20 years)

Luigi Ferrucci, M.D., Ph.D.
Scientific Director, Senior Investigator, Longitudinal Studies Section, National Institute on Aging, National Institutes of Health
Serving since 2003 (20 years)

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Serving since 2008 (15 years)

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Howard Bergman, M.D.
Assistant Dean, International Affairs, Faculty of Medicine and Health Sciences, Professor of Family Medicine, Medicine and Oncology and the Institute for Health and Social Policy, McGill University
Serving since 2013 (10 years)

RECOGNITION AND AWARDS (2022-2023)

Nicholas Rowan (2023)

- Johns Hopkins University Center for AIDS Research (JHU CFAR), Developmental Core Award.

Qinchuan Wang (2023)

- Glenn and AFAR Junior Faculty Award, CaMKII as a Cause of Age-Related Sarcopenia.

MINORITY RESEARCH

General Brief Description of Minority Activities:

Janiece Taylor, PhD: Pilot Study. "Pilot Behavioral Intervention to Address Pain and Frailty in Older African-American Women."

Karen Bandeen-Roche, PhD: RC1 Development Project: includes analyses of frailty measurement variance by race in the National Health and Aging Trends Study.

Janiece Taylor, PhD, and Karen Bandeen-Roche, PhD: Small Pilot Study: "Focus groups to study racial differences in the frailty phenotype measure."

Minority Trainee(s):

- Janiece Taylor, PhD, Assistant Professor
  Janiece Taylor, PhD: Pilot Study. "Pilot Behavioral Intervention to Address Pain and Frailty in Older African-American Women."
- Jude Phillip, PhD, Assistant Professor
  Jude M. Phillip is an Assistant Professor of Biomedical Engineering, with a secondary appointment in Chemical & Biomolecular Engineering and a core member in the Institute for Nanobiotechnology (INBT) at Johns Hopkins University. His lab studies biological ageing dynamics in the context of health and disease. He combines fundamental engineering approaches with translational ageing and oncology research to develop strategies and technologies to probe ageing and identify mechanisms to modify ageing trajectories to drive heathy ageing.
- Melissa Hladek, Assistant Professor
  Using Human-Centered Design to Adapt CAPABLE as a Prehabilitation Intervention for Adults with Frailty Awaiting Kidney Transplant.
- Reyhan Westbrook, PhD, Instructor
  Division of Geriatric Medicine and Gerontology
- Sabra Lewsey, MD, Assistant Professor
  Advanced Heart Failure and Transplant Cardiology, Cardiomyopathy, Congestive Heart Failure (CHF), Heart Failure

No minority grant information specified.

UNIVERSITY OF MARYLAND
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Program Administrator

CENTER DESCRIPTION

The mission of the UM-OAIC is to address the process by which function is lost, and the multiple factors that affect the onset and progression of disability. Building on these important perspectives, the UMOAIC focuses on the restoration of function (i.e., enablement) in order to improve function in those with impairments, and prevent or delay further progression in those who are already disabled. This is accomplished by 1) conducting research that examines the mechanisms underlying the functional impairments associated with chronic diseases in older people, such as stroke, hip fracture, obesity, Type-2 diabetes, osteoarthritis, Parkinson's disease, and vascular disease; 2) designing novel, efficacious rehabilitation interventions that produce clinically relevant outcomes and study the mechanisms underlying these interventions; 3) translating interventions found to be efficacious in UM-OAIC clinical laboratories and other clinical centers for implementation and rigorous evaluation outside the clinic (e.g., home, senior center, gym); 4) supporting pilot and exploratory studies (PESs), UM-OAIC REC Scholar research, development projects (DPs), and externally funded projects (EP) that are consistent with the UM-OAIC theme; and 5) supporting the development of junior faculty and REC Scholars from multiple disciplines as they pursue careers as independent, academic scientists with expertise in the study of older persons with disabling diseases through mentor-based, didactic and experiential training in bench-to-bedside-to-community translational research.

The UM-OAIC has three resource cores (RC): Biostatistics and Informatics (RC1); Applied Physiology and Mechanisms (RC-2); and Rehabilitation Science and Technologies (RC-3), that serve as resources for the conduct of innovative exercise and activity-based rehabilitation research. An enhanced Research Education Core (REC) will provide didactic and experiential, and leadership training under the guidance of an interdisciplinary mentoring teams to prepare the next generation of scientists committed to careers in aging research. A Pilot and Exploratory Studies Core (PESC) supports the development and execution of pilot and REC Scholar projects. Center aims will be accomplished by: 1) advancing our understanding of the mechanisms by which exercise and activity-based and multi-modal rehabilitation interventions directed a specific impairments affect multiple body systems; 2) developing and testing interventions to restore function and minimize disability following acute disabling events and to prevent declines related to serious chronic diseases; and 3) training the next generation of investigators who will further the understanding of the aging process and develop interventions that help promote health and independence in older adults with disabling medical conditions.

CORES

Leadership and Administrative Core (LAC)

<u>Leader 1:</u>   Jay Magaziner, PhD, MS Hyg.   jmagazin@som.umaryland.edu

<u>Leader 2:</u>   Leslie I. Katzel, MD   lkatzel@som.umaryland.edu

<u>Leader 3:</u>   Alice Ryan, PhD   aryan@som.umaryland.edu

The Leadership and Administrative Core (LAC) ensures that the UM-OAIC provides support for conducting novel research and training the next generation of scientists pursuing research careers in aging and oversight to the five UM-OAIC cores. Core leaders also foster maximal outreach and interaction with the rest of the University of Maryland, Baltimore (UMB) inter-professional campus, other OAICs, and research programs elsewhere pursuing work on areas relevant to the UM-OAIC's enablement theme. The LAC will receive input and guidance, and discuss program operations in the Core Leadership Executive Committee (CLEC) meeting of core leaders; the UM-OAIC Research and Education Advisory Panel (REAP) charged with reviewing proposed Development and Pilot Exploratory Studies and progress of Scholars; a Community Advisory Board (CAB) that will provide input on issues that are most relevant for enabling function in older persons with disabling conditions in different communities and on the merit of research that is being proposed and conducted in the UM-OAIC; an Internal Advisory Committee (IAC) that evaluates UM-OAIC progress and accomplishments, and provides advice on ways to extend research on aging to other university centers and departments; and an External Advisory Board (EAB) that will provide guidance to the program and report progress annually to the NIA. In addition, the LAC receives advice from an Internal Data and Safety Monitoring Board (I-DSMB) that will review the conduct of clinical protocols to ensure patient safety and progress of projects, and an External Data and Safety Monitoring Board (E-DSMB) that will provide another layer of review by experienced, impartial scientists that will monitor study progress and data quality and safety, and report to the NIA annually.

Research Education Component (REC)

<u>Leader 1:</u>   Mary-Claire Roghmann, MD, MS   mroghman@som.umaryland.edu

<u>Leader 2:</u>   Jack Guralnik, MD, PhD, MPH   jguralnik@som.umaryland.edu

The purpose of the Research Education Core (REC) is to support the development of junior faculty from multiple disciplines as they pursue careers as scientists with a focus on the restoration of function among older adults with impairments and on the prevention or delay of progression in those who are already disabled. The REC supports Scholars and affiliated faculty (who are former Scholars or junior faculty with career development awards related to our mission) in mentor-based research training and other career development activities in a supportive research environment. The REC will achieve the above with the following aims: 1) Recruit and retain REC Scholars and affiliated faculty committed to research careers congruent with the UM-OAIC mission; 2) train REC Scholars and affiliated faculty through mentored research projects and individualized training plans which use the resources of the UM-OAIC, the national OAIC network and other NIA supported programs; 3) Develop a Leadership Academy which will teach leadership skills and provide leadership experience for promising junior and mid-level scientists with demonstrated commitment and expertise to become the next leaders, in the UM-OAIC and nationally, in research aimed at improving function in older adults and 4) evaluate the UM-OAIC Research Education Core with the help of experts in the University of Maryland Baltimore (UMB) Faculty Center for

Teaching and Learning and in the Research Education Advisory Panel (REAP).

Pilot and Exploratory Studies Core (PESC)

<u>Leader 1:</u>   Stephen Seliger, MD, MS   sseliger@som.umaryland.edu

<u>Leader 2:</u>   Marc Hochberg, MD, MPH, MACP, MACR   mhochber@som.umaryland.edu

The purpose of the UM-OAIC Pilot and Exploratory Studies Core (PESC) is to provide critical initial funding for pilot and exploratory studies that are consistent with the UM-OAICs overall goal of advancing the study of enablement in older adults by: 1) identifying the deficits associated with specific disabling conditions; 2) investigating the mechanisms and pathophysiology responsible for these deficits; and 3) developing exercise, other activity-based interventions, and multi-modal rehabilitation strategies that target these mechanisms and deficits; 4) testing them in clinical laboratories/centers under carefully controlled conditions; and 5) adapting them for implementation and further testing in home and other settings outside the medical center. To meet this objective, the PESC will attract junior investigators (and established investigators new to aging research) across a broad range of disciplines to study rehabilitation and recovery in older adults and in relevant pre-clinical models, stimulate new studies in aging-related rehabilitation research through targeted funding, encourage new interdisciplinary collaborations, and translate efficacious therapies across the spectrum from bench to clinical laboratory to community practice. This will advance the UM-OAIC research goal of expanding therapies in the broadest context of rehabilitation that emphasizes restorative and preventive medicine to promote the recovery and enablement of older adults with disabling conditions.

Applied Physiology and Tissue Mechanisms

<u>Leader 1:</u>   Alice Ryan, PhD   aryan@som.umaryland.edu

<u>Leader 2:</u>   Leslie I. Katzel, MD   lkatzel@som.umaryland.edu

<u>Leader 3:</u>   Chris Ward, PhD   ward@som.umaryland.edu

RC-2 provides UM-OAIC investigators comprehensive support for quantified physical activity, functional and metabolic phenotyping, and blood and tissue bioassays to advance clinical research. Research performed by UM-OAIC investigators demonstrates that various modes of exercise, and/or rehabilitation training, improve cardiovascular fitness, muscle endurance, strength, neuromotor control, and body composition in older people with chronic disease and disability such as those with stroke, peripheral arterial disease (PAD), congestive heart failure, obesity, diabetes, hip fracture, an intensive care unit stay, HIV and cancer. Collectively, these works inform our overarching hypothesis that exercise, activity-based, and multi-modal rehabilitation can improve multiple physiological systems in older mobility-limited individuals which in turn can improve functional performance, reduce cardiometabolic disease risk, and prevent further functional decline. To achieve this goal, RC2 implements specific aims that: 1) advance research focused on the mechanisms of functional decline in older persons with disability and the mitigation of decline with exercise or activity-based or multi-modal rehabilitation and 2) provide mentoring and training to REC Scholars, affiliated faculty, and UM-OAIC researchers in the performance of aging research relevant to exercise and rehabilitation-based restoration of function and the prevention of functional declines in older people with chronic disabling diseases.

Biostatistics and Informatics

<u>Leader 1:</u>   John D. Sorkin, MD, PhD   jsorkin@som.umaryland.edu

<u>Leader 2:</u>   Michael Terrin, MD, MPH   mterrin@som.umaryland.edu

Leader 3:   Laurence Magder, PhD   lmagder@som.umaryland.edu

The goal of the Biostatistics and Informatics Core (RC-1) plays a central role in UM-OAIC research helping investigators design, conduct, and report results of research studies. RC-1 plays a key role in the coordination and integration of UM-OAIC. Our informatics infrastructure facilitates UM-OAIC operation and oversight by tracking study progress, recording and reporting adverse events, monitoring core requests and use, and providing reports to PIs and Core leaders. RC-1 participates in REC organized education efforts and participates in other research training initiatives at the university. This core has 2 two major goals: 1) to support the conduct of studies that promote the independence of older adults with disabling conditions; 2) train the next generation of investigators who will conduct studies that promote health and independence in older adults. One-on-one training will take place as we help Scholars and other investigators design, execute, analyze and publish their results and as we participate in Research Design Studios, Project Initiation Support Groups and Research Working Groups. In addition, the RC-1 will help investigators find and enroll participants for their research projects, we are expanding our recruitment efforts by adding an investigator experienced in recruiting older persons. Finally, the core will also develop biostatistical methods and informatics resources that facilitate funded and supported projects of the UM-OAIC.

Rehabilitation Science and Technologies Core

Leader 1:   Li-Qun (Larry) Zhang, PhD   l-zhang@som.umaryland.edu

Leader 2:   Kelly Westlake, PhD, MSc, PT   kwestlake@som.umaryland.edu

Rehabilitation Science and Technologies Resource Core 3 (RC-3), aims to improve our ability to prevent and reverse these declines. We build on this core's strengths in rehabilitation medicine and physical therapy with a focus on gait, balance and mobility research, by expanding to mechanistic studies of motor learning and activity-dependent plasticity. Incorporation of new bioengineering capacity has expanded the resources and mentoring needed by UM-OAIC investigators to design, test, and translate novel rehabilitative technologies and engineering-informed approaches into new services and products. Technology transfer processes and academic-private partnerships are introduced to accelerate translation into community practice and into products with public health impact. The central hypothesis of RC-3 is that rehabilitation science-based therapeutics that leverage activity-dependent plasticity and neuromotor learning (including balance, mobility training, and bioengineering-modelled rehabilitation robotics and other technologies) will improve recovery and enhance function in older adults with functional limitations and disability and will be accomplished through the following aims: Specific Aim 1. To support investigations of sensory, motor, and cognitive mechanisms that underlie loss of functional independence and improvements produced by preventative or rehabilitative interventions. This will be accomplished by providing a repertoire of rehabilitation assessment and training of sensory, motor and cognitive function, development of assistive technologies, assessments of neuroplasticity, and tests of neurocognitive function. Specific Aim 2. To mentor and support REC Scholars and UM-OAIC researchers in the design, development and implementation of sensory, motor, and cognitive rehabilitation studies. These studies may involve implementation of technologies and examining underlying sensory, motor, and cognitive mechanisms to reduce and prevent functional declines in older persons with or at risk for functional limitations . Specific Aim 3. To facilitate translation of UM-OAIC discoveries across the mechanistic, rehabilitation engineering, applied clinical testing, and technology transfer phases into evidence-based clinical assessments and interventions using novel products and tools for precision rehabilitation.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications

Stephanie Jo, MD, PhD
Assistant Professor / Department of Diagnostic Radiology and Nuclear Medicine, UMSOM

2023-2025 / 18 (total) 7 (1st/Sr)

<u>Identification of high-risk prognostic factors of osteoarthritis based on single nucleotide polymorphism and MRI morphometry utilizing the Osteoarthritis Initiative database</u>

Hypothesis: OA susceptibility SNPs along with semiquantitative and quantitative knee MRI features of OA can predict future knee arthroplasty and severity of pain. Specific aims: Specific aim 1: Identify SNPs associated with semiquantitative and quantitative OA features on knee MRI: Current studies have identified OA susceptibility SNPs based on clinical diagnosis and radiographs. This study will utilize MRI features, which are more specific and sensitive for early OA and OA severity, for SNP association. Specific aim 2: Develop models to predict future knee arthroplasty and pain score based on SNPs and semiquantitative and quantitative OA features on MRI: OA susceptibility SNPs are not part of OA assessment in the current clinical setting, and evaluating 100+ SNPs may not be practical. Also, no studies have yet evaluated the additional predictive value of SNPs and MRI features of OA over the clinical symptoms and signs. This aim will develop OA prediction models with SNP genotype and MRI phenotype for clinical use.

Sui-Seng Tee, PhD
Assistant Professor / Department of Diagnostic Radiology and Nuclear Medicine, UMSOM

2023-2025 / 11 (total) 5 (1st/Sr)

<u>Metabolic Imaging as a Biomarker of Muscle Aging</u>

Metabolic imaging using hyperpolarized magnetic resonance imaging (HP-MRI) is based on injecting non-radioactive, carbon-13 (13C) labeled metabolites as contrast agents, allowing quantification of metabolic flux7. Uniquely, this technique uses non-ionizing radiation, allowing longitudinal imaging. Therefore, this grant breaks new ground in proposing to track metabolic flux in muscles over time, while the organism ages. Indeed, altered metabolism is a hallmark of aging8 and altered muscle metabolism is closely linked with age-related functional decline9. Our overarching hypothesis is HP-MRI detects alterations in glycolytic and mitochondrial metabolism that can be used as predictive and prognostic biomarkers. To this end, we propose 2 aims: Specific Aim 1: Longitudinal Muscle Imaging of Aging in Mice 1.1: Metabolic Imaging of Sarcopenia in a mouse model of physiological aging 1.2: Compare imaging with gold-standard body composition measures, frailty index and histology Specific Aim 2: Metabolic Imaging of Exercise Regimens in Mice 2.1: Compare high-intensity intermittent training (HIIT) with moderate intensity continuous training (MICT) using metabolic imaging 2.2: Validation of metabolic Imaging

- OAIC Coordinating Center: Early Career Faculty Flexible, High Value Award. Tee (PI). 07/2022-06/2023. $5,000

Jeanine Ursitti, PhD
Assistant Professor / Department of Orthopaedics

2021-2024 / 9 (total) 2 (1st/Sr)

<u>Cell Mechanics as a Biomarker of Osteosarcopenia"</u>

Abstract: Previous work has identified increased cytoskeletal stiffness, driven by increased levels of microtubules post-translationally modified by detyrosination, as a common predictor of biological dysfunction across bone, skeletal muscle, and cardiac tissue. Our new preliminary evidence in aging mice (17-78 weeks) finds increasing microtubule detyrosination in muscle and bone and increased stiffness/mechanics in the muscle fiber. The goal of this pilot project is to determine whether microtubule dependent cytoskeletal stiffness is a novel biomarker of biological aging. Here we will extend our measures of cell mechanics (in isolated intact skeletal muscle fibers) and tubulin biochemistry (in skeletal muscle and bone), to circulating peripheral blood mononuclear cells (PBMCs), to test our hypothesis that the level of

microtubule detyrosination, and microtubule dependent cytoskeletal stiffness, are biomarkers of biological age. Hypothesis/Aims: We hypothesize that age-related changes in microtubule (MT) structure and post-translational modifications in Peripheral Blood Mononuclear Cells (PBMCs) will track with changes in skeletal muscle fibers, bone osteocytes, and perhaps other tissues, making it a predictive, easily assessable biomarker. We further hypothesize that the cellular stiffness of PBMCs will track with deTyrosinated MTs (deTyr-MTs) in aging skeletal muscle. We have two specific aims: Aim 1: Define age dependent changes in cytoskeletal structure and properties across disparate tissues and blood monocytes. Aim 2. Determine age-related changes in PBMC mechanics as a biomarker of aging and treatment efficacy.

- OAIC Coordinating Center: Early Career Faculty Flexible, High Value Award. Ursitti (PI). 07/2021-06/2022. $5,000

Andrea Levine, MD 2022-2024 /
Assistant Professor / Department of Medicine 28 (total)
<u>The Longevity of ARDS Inflammatory Subphenotypes and Their Role in Predicting</u> 9 (1st/Sr)
<u>Functional Recovery in Older Adults</u>
Abstract: Acute Respiratory Distress Syndrome (ARDS) is a life-threatening illness of severe hypoxemia. A hyper- and hypo-inflammatory subphenotype exist with a differential treatment effect. We aim to describe the longevity of the subphenotypes determine whether these subphenotypes can predict functional recovery in older adult patients. Hypothesis/Aims: Subphenotype longevity: To determine whether the ARDS subphenotype established on hospital admission is sustained during the inpatient hospitalization and post-acute recovery phase. Approach: We will utilize a parsimonious combination of validated plasma biomarkers (IL-8, HCO-3, and Protein C) to determine whether ARDS subphenotypes established at admission are maintained through the duration of the inpatient hospitalization and at post-acute follow-up three months after discharge in older adult patients. Aim 2: Correlation with longitudinal functional recovery: To determine whether ARDS subphenotype predicts the trajectory of functional recovery in older survivors of ARDS. Approach: In a pilot study, survivors of ARDS will be followed at three months after hospital discharge and assessed for pulmonary recovery via spirometry, neurocognitive function using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), psychiatric status using the Hospital Anxiety and Depression Survey (HADS) and PCL-5 and neuromuscular function using a six-minute walk test and short physical performance battery (SPPB). We will determine whether the inflammatory subphenotype assigned at hospital discharge predicts functional recovery at three-months after hospital discharge.

- UM-OAIC Pilot Award: The Longevity of ARDS Inflammatory Subphenotypes and Their Role in Predicting Functional Recovery in Older Adults. Levine (PI). 07/2021-06/2024. $46,350
- NIH Loan Repayment Program: The Longevity of ARDS Inflammatory Subphenotypes and Their Role in Predicting Functional Recovery in Older Adults. Levine (PI). 07/2022-06/2024. $100,000

Past Scholars
F. Rainer von Coelln, Dr. med, Department of Neurology, University of Maryland School of Medicine (2017-2020)
Tasneem Khambaty, PhD, Department of Psychology, University of Maryland Baltimore County (2018-2021)
Sarasijhaa Desikan, MD, Department of Surgery, University of Maryland School of Medicine (2020-2022)
Jason Falvey, PT, DPT, PhD, Department of Physical Therapy and Rehabilitation Science (2021-2021)

PILOT/EXPLORATORY PROJECTS (14 Pilot Projects Listed)

1. Project Title: **Relations of Glucose Variability with Cognitive Function and Functional Status among Older Adults at Risk for Diabetes**

Leader: **Tasneem Khambaty, PhD**

Abstract: Type 2 diabetes (T2DM) is an independent risk factor for dementia and less severe forms of cognitive dysfunction and may compromise functional status. Metrics derived from continuous glucose monitoring (CGM) technology – i.e., glucose variability – may facilitate the detection of impaired glycemia much earlier than the conventional glycemic metrics. We propose a robust characterization of intra- and inter-day variability in glucose regulation and a deeper understanding of the extent to which this variability influences cognitive aging and functional decline in persons at risk for diabetes. Understanding this early aging trajectory is an important step towards discerning the mechanisms underlying various aspects of glycemia and neurocognition. Hypotheses: Our central hypothesis is that even before diabetes onset, glucose variability will be associated with worse cognitive function and lower functional status among older adults. Our specific aims are to examine the association of glucose variability derived from CGMS over a 10-day self-monitoring period with cognitive function, and functional status among individuals with prediabetes, aged 50 or older.

2. Project Title: **Home Exercise (HEX) for Homebound Older Adults**

Leader: **Alyssa Stookey, PhD**

Abstract: Little is known about the feasibility and utility of pragmatic home-based exercise in older homebound adults with severe mobility disability. We propose a feasibility study to design and implement a pragmatic 12-week home exercise program (HEX) intervention program to improve physical functioning and quality of life in homebound older adults with mobility disability.

Hypothesis: Our general hypothesis is HEX will prove feasible and effective in maintaining and restoring physical functioning and perceived quality of life. Aim #1: We will work with providers and patients to develop a feasible and pragmatic, multi-component home exercise program targeting mobility, strength, and performance of task-oriented ADLs. Aim #2: Perform a small study to better assess feasibility and determine the effect(s) of the home-based intervention created in Aim 1 on functional outcomes and QOL(at baseline, 6 weeks, and 12 weeks) in older, homebound adults.

3. Project Title: **Mobile Sensor Investigation of Gait Variability and Hip abductors**

Leader: **Odessa Addison, DPT, PhD**

Abstract: Our work suggests that dysfunction of the hip abductors may contribute to balance and mobility limitations resulting in increased fall risk. We have previously shown that gait variability, defined as fluctuations between gait cycles, are an important assessment of mobility and balance function and related to muscle composition of the hip abductor muscles. Gait variability is traditionally assessed via a short 25-foot walk way. However, this distance is too short to account for the impact of fatigue. We propose examining changes in gait variability over a six-minute walk distance may allow for an earlier detection of fall risk by exposing impairments that occur under conditions of fatigue that would otherwise go undetected. The

overall aim of our work is to study the use of technology-based assessments and interventions which impact enablement of older adults. Hypothesis/Aims: Aim 1: Examine changes in gait variability between the early and late phase of the six-minute walk. Aim 2: Compare how gait variability in the early and late phases of the six-minute walk relates to muscle size and composition of the hip abductors. Aim 3: Examine how changes in the hip abductors after a 12-week intervention relates to changes in gait variability during the early and late phases of the six-minute walk.

4. Project Title: **Neural Mechanisms of Motor Recovery with Technology Assisted Training for Post-stroke Hemiparesis**

Leader: **Robynne Braun, MD, PhD**

Abstract: Arm weakness persists chronically in 40% of stroke survivors and accounts for at least half of the decline in quality of life after stroke. Our preliminary work indicates that technology-assisted-training can provide clinically meaningful improvements in arm function for approximately 30% of patients with chronic post-stroke-hemiparesis. The goals of this proposal are: 1) to investigate brain network activity changes that occur during technology-assisted-training and 2) to determine the baseline residual brain network connectivity required for patients to respond to technology-assisted-training, The results of this study will lead to establishment of a personalized medicine algorithm for technology-assisted-training to the patients most likely to respond to it, shifting the delivery of therapy for chronic stroke-induced arm weakness towards individualized, evidence-based care. Hypothesis/Aims: Aim 1: Define cortical connectivity dynamics during technology-assisted-training. Hypothesis: Technology- assisted- training induced increases in cortical connectivity between bilateral primary motor areas and angular gyrus and parietal operculum will positively correlate with improvement in technology-assisted-assessments. Approach: Near infrared spectroscopy brain imaging will be used to measure cortical activity in motor and non-motor cortical areas real-time during 9 sessions of technology-assisted-training over 3 weeks in a cohort of 10 patients with chronic post-stroke-hemiparesis. The relationships between cortical connectivity and measures of movement and proprioception will be analyzed and compared between stroke survivors and 10 healthy controls. Aim 2: Identify baseline brain network connectivity predictors of technology-assisted-training impairment reductions. Hypothesis (a): Baseline connectivity of angular gyrus and parietal operculum to sensorimotor networks will predict reductions in impairment induced by technology-assisted-training. Approach: We have brain MRI baseline network functional connectivity data on 66 patients with chronic post-stroke hemiparesis who have undergone 3 months (~36 sessions) of technology-assisted-training of the upper extremity. This aim will analyze baseline brain functional connectivity prior to the onset of training to find correlates of training induced impairment reduction.

5. Project Title: **Ryanodine Receptors as Novel Targets in Chronotropic Incompetence in the Aging Heart**

Leader: **B. Maura Greiser, PhD**

Abstract: Chronotropic incompetence is the hallmark of the aging heart. This means that the heart's pacemaker, the sino-atrial node (SAN), fails to produce a heart rate that is fast enough to match circulatory demand. This results in reduced left ventricular output over time in the aging heart compared to younger hearts. Hypothesis/Aims: The goal of this Pilot Project is to provide foundational evidence linking RyR2 dysfunction to chronotropic incompetence. We further want to test whether aging-mediated RyR2 dysfunction in SAN cells can be partially reversed by a) pharmaceutical agents that stabilize RyR2 function and b) by reducing the levels of intracellular reactive oxygen species (ROS).

6. Project Title: **Persistence of Depression and Pain and Functional Outcomes in Knee Osteoarthritis**

Leader: **Alan Rathbun, PhD, MPH**

Hypothesis/Aims: Aim 1: To assess how the persistence of depressive symptoms cumulatively affect functional outcomes among persons with or at risk for symptomatic knee OA. Hypothesis: Greater persistence of depressive symptoms is associated with worse function over time in a dose-dependent manner. Aim 2: To determine whether dynamic fluctuations in knee pain mediate the association between persistent depression and functional outcomes. Hypothesis: Higher pain severity will be associated with a stronger indirect (mediated) effect of depressive symptoms on functional outcomes.

7. Project Title: **Cell Mechanics as a Biomarker of Osteosarcopenia**

Leader: **Jeanine Ursitti, PhD**

Abstract: Previous work has identified increased cytoskeletal stiffness, driven by increased levels of microtubules post-translationally modified by detyrosination, as a common predictor of biological dysfunction across bone, skeletal muscle, and cardiac tissue. Our new preliminary evidence in aging mice (17-78 weeks) finds increasing microtubule detyrosination in muscle and bone and increased stiffness/mechanics in the muscle fiber. The goal of this pilot project is to determine whether microtubule dependent cytoskeletal stiffness is a novel biomarker of biological aging. Here we will extend our measures of cell mechanics (in isolated intact skeletal muscle fibers) and tubulin biochemistry (in skeletal muscle and bone), to circulating peripheral blood mononuclear cells (PBMCs), to test our hypothesis that the level of microtubule detyrosination, and microtubule dependent cytoskeletal stiffness, are biomarkers of biological age. Hypothesis/Aims: We hypothesize that age-related changes in microtubule (MT) structure and post-translational modifications in Peripheral Blood Mononuclear Cells (PBMCs) will track with changes in skeletal muscle fibers, bone osteocytes, and perhaps other tissues, making it a predictive, easily assessable biomarker. We further hypothesize that the cellular stiffness of PBMCs will track with deTyrosinated MTs (deTyr-MTs) in aging skeletal muscle. We have two specific aims: Aim 1: Define age dependent changes in cytoskeletal structure and properties across disparate tissues and blood monocytes. Aim 2. Determine age-related changes in PBMC mechanics as a biomarker of aging and treatment efficacy.

8. Project Title: **The Longevity of ARDS Inflammatory Subphenotypes and Their Role in Predicting Functional Recovery in Older Adults**

Leader: **Andrea Levine, MD**

Hypothesis/Aims: Subphenotype longevity: To determine whether the ARDS subphenotype established on hospital admission is sustained during the inpatient hospitalization and post-acute recovery phase. Approach: We will utilize a parsimonious combination of validated plasma biomarkers (IL-8, HCO-3, and Protein C) to determine whether ARDS subphenotypes established at admission are maintained through the duration of the inpatient hospitalization and at post-acute follow-up three months after discharge in older adult patients. Aim 2: Correlation with longitudinal functional recovery: To determine whether ARDS subphenotype predicts the trajectory of functional recovery in older survivors of ARDS. Approach: In a pilot study, survivors of ARDS will be followed at three months after hospital discharge and assessed for pulmonary recovery via spirometry, neurocognitive function using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), psychiatric status using the Hospital Anxiety and Depression Survey (HADS) and PCL-5 and neuromuscular function using a six-minute walk test and short physical performance battery (SPPB). We will determine whether the inflammatory subphenotype assigned at hospital discharge predicts functional recovery at three-months after hospital discharge.

9. Project Title: **The Effects of Neuromuscular Activity and Muscle Structure on Stepping Performance in older Adults**

Leader: **Marcel Lanza, PhD**

Abstract: This pilot project seeks to understand the effects that age has on the time to transfer weight, torque production, and neuromuscular control during the weight transfer for different step directions and whether a step direction is more impaired. The results of this project may provide insight into the direction most likely to result in a fall among older adults. Hypothesis/Aims: The aims of this project are: 1) to determine the age associated changes in the control of the weight transfer of the lateral, forward, and backward steps by comparing older to younger adults; 2) to determine the age associated changes in the hip abductors and adductors rate of torque development and rate of activation of the lateral, forward, and backward steps between young and older adults; 3) to determine the age associated changes in the hip abductors and adductors muscle structure and association with the weight transfer.

10. Project Title: **A Combination Therapy with a Brain-Selective Estrogen and Physical Exercise to Halt or Slow the Progression of Cognitive Decline**

Leader: **Jacek Mamczarz, PhD**

Abstract: The mice are treated continuously with DHED, a brain selective precursor for estrogen synthesis, for 3 months with subcutaneously implanted Alzet pumps, while exercising groups have free access to running wheels. Time spent exercising and distance is monitored over the course of the experiment. Muscle strength and bone density is evaluated every 4 weeks. After 1.5 months on the treatment/exercising, mice are subjected to a battery of tests evaluating motor coordination/motor learning and cognitive behavior. Hypothesis/Aims: We hypothesize that a combination therapy with DHED and physical exercise will provide better outcome in naturally aged female mice than these therapies alone, improving neuromuscular and cognitive functions.

11. Project Title: **Retinal Blood Flow and its Evolution with Aging**

Leader: **Osamah Saeedi, MD, MS**

Abstract: We are investigating objective and quantitative retinal vascular biomarkers of functional performance, specifically cognition, and mobility in older adults. We anticipate that participants with lower cognitive and balance scores will have significantly lower vessel density, retinal blood flow velocity, and vasomotion. Hypothesis/Aims: Specific Aim 1: Quantitively investigate the relationship between cognitive and mobility performance with retinal microvascular metrics: Aim 1A: Correlate cognitive and mobility performance with retinal vessel density and flow rate using in vivo measures of ocular blood flow: optical coherence tomography angiography (OCTA) and laser speckle contrast imaging (LSCI). We hypothesize that participants with lower cognitive and balance scores will have significantly lower vessel density and retinal blood flow velocity as measured by OCTA and LSCI respectively. Aim 1B: Correlate cognitive and mobility performance with vasomotion using in vivo erythrocyte mediated angiography (EMA). We hypothesize that vasomotion, as quantified by vascular erythrocyte pausing in the optic disc and the macula, will be significantly impaired in participants with lower cognitive and balance scores. Specific Aim 2: Confirm the validity of these vascular biomarkers in comparison with the systemic microvasculature using in vivo nailfold video capillaroscopy (NVC). We hypothesize that the retinal vascular parameters will demonstrate greater diagnostic accuracy in differentiating participants according to their cognitive and balance performance levels.

12. Project Title: Exercise Capacity Improvement in Heart Failure with Preserved Ejection Fraction and Pulmonary Hypertension (PH-HFpEF) after SGLT2 Inhibitor (Empagliflozin) Initiation

Leader: Steven Cassady, MD

We propose a pilot study to evaluate use of SGLT2 inhibitors on functional outcomes in a cohort of patients with HFpEF and pulmonary hypertension determined by echocardiography. Our primary outcome will be the change in peak VO2 achieved by patients during maximal cardiopulmonary exercise testing (CPET) from within 20 days of drug initiation to 90 days after drug initiation. Secondary outcomes will include CPET-derived measures of ventilatory efficiency as well as changes in performance on the Short Physical Performance Battery and six-minute walk testing. Through the establishment of improved functional outcomes in this specific patient population, we hope to demonstrate sufficient benefit to encourage wider prescribing of SGLT2 inhibitors in PH-HFpEF and to generate promising data for larger scale studies in this population. Additionally, this study would also function to provide blood samples to be used for future investigation of the metabolic effects of SGLT2 inhibitor use in this group.

13. Project Title: Time-restricted eating to entrain circadian rhythm, increase physiological responsiveness, and prevent stressor-induced frailty

Leader: Amber Kleckner, PhD

Frailty affects more than 5.4 million people over the age of 65 in the United States alone (>10%) and is one of the main reasons older adults lose independence. Frailty, or the reduction of physiological reserve, does not progress linearly; its pathogenesis often accelerates in response to a "stressor event," for example cancer and its treatment. Specifically, a diagnosis with prostate cancer and androgen deprivation therapy (ADT) treatment are associated with accelerated frailty. While the body is resilient to everyday stressors, large-scale, enduring stressors can accumulate and cause the body to have difficulty predicting energy supply and

demand. The result is that stress-induced energy costs compete with cellular growth, maintenance, and repair, i.e., frailty. Treatments for frailty are intensive (e.g., resistance exercise) and often unsuccessful, and there are critical needs to 1) develop effective interventions to prevent and treat frailty, and 2) identify physiological precursors to frailty so that we can provide timely intervention(s) to prevent progression to the frail state. We theorize that entrainment of circadian rhythm, or the body's internal body clock, will improve the body's ability to predict energy supply and demand, and therefore enable the body to allocate more resources to anabolic processes and promote resilience to toxicities caused by ADT. Time-restricted eating (TRE) entails consuming food within a defined, consistent window every day. It has emerged as a powerful intervention to entrain circadian rhythm and regulate metabolic homeostasis. We hypothesize that, by entraining circadian rhythm, TRE can enhance physiological regulation and prevent stressor-induced frailty. To test this hypothesis, we will recruit 30 patients over 55 years old undergoing ADT therapy for prostate cancer. Participants will be randomized 1:1 to a 12-week TRE intervention or a time- and attention-matched nutrition control intervention; both groups will be under the supervision of a licensed clinical nutritionist with expertise in the cancer population to ensure adequate nutrient intake. At baseline and post-intervention, we will assess frailty using Fried's Frailty Index and a novel set of five physiological responsiveness measures: a) lying-to-standing blood pressure, b) heart rate variability, c) oral glucose tolerance test, d) 24-hour circadian cortisol rhythm, and e) usual vs. fast gait speed. These data will allow us to test the feasibility of TRE among patients with prostate cancer during ADT treatment and optimize measures of reduced physiological reserve with the ultimate goal of optimizing an intervention to prevent the progression of frailty.

14. **Project Title:**   **Using Deep Learning to Measure Quantitative Imaging Biomarkers of Body Composition on MRI of the Knee in Older Adults With or At-Risk for Knee Osteoarthritis**

Leader: **Paul Yi, MD**

Osteoarthritis (OA) of the knee is a leading cause of disability in older adults and a driver of healthcare spending. Preventing the incidence and progression of knee OA would have tremendous impact on both the health of older adults and the healthcare system. Prior work has shown that body composition biomarkers derived from thigh MRIs, such as muscle cross-sectional area, are associated with progression of knee OA, suggesting they can be used to initiate neuromuscular stimulation and strength training to prevent the progression of knee OA. Unfortu-nately, thigh MRIs are impractical for real-world monitoring because they are not routinely obtained in clinical practice. In contrast, knee MRIs are routinely obtained. Therefore, development of analogous quantitative bi-omarkers of body composition on knee MRI could facilitate evaluation for potentially modifiable risk factors for knee OA as part of routine clinical care. This project proposes to use deep learning (DL), a state-of-the-art set of artificial intelligence (AI) machine learning techniques, to develop an automated tool for measuring quantitative imaging biomarkers of body composition on knee MRIs in older adults with or at-risk of knee OA. We will use knee MRIs from the NIH Osteoarthritis Initiative (OAI) dataset to train and test a DL algorithm for segmentation of muscle, fat, and bone in images of the distal thigh and proximal calf – these segmentations will be used to quan-tify imaging biomarkers, such as tissue cross-sectional area and intramuscular fat. This tool will allow for auto-mated measurement of these biomarkers that would otherwise be practically infeasible and time-consuming, and which could be used in the future to identify older adults

at-risk of knee OA progression and tailor treatment reg-imens to prevent the onset and/or progression of this debilitating disease.

DEVELOPMENT PROJECTS (0 Development Projects Listed)

No development projects.

RESEARCH (16 Projects Listed)

1. Project Title: **Rehabilitation Interventions Based on Accurate Assessments with Combined Home-Hospital Rehabilitation.**

Leader(s):   **Zhang, Li-Qun**
          UNIVERSITY OF MARYLAND BALTIMORE
          National Institute on Disability and Rehabilitation Research (NIDILRR) 90REMM0001 / (2020 - 2025)

Core(s):

The mission of this RERC is to champion innovative technologies/approaches for assessment-based rehabilitation with combined hospital-home rehabilitation that will improve therapeutic outcomes among individuals with neurologic disorders and older adults with disabilities. This RERC develops and tests devices and techniques to increase the volume and effectiveness of impairment-specific therapies. Stroke and other neurologic disorders often involve considerable sensorimotor impairments with complex pathological changes: these impairments involve multiple muscle groups, multiple joints, and thus many variables are involved. These impairments negatively affect mobility and manipulation in a large population of patients. Due to this complexity, it is often not feasible to assess complicated impairment accurately through current clinical examinations. Furthermore, the vast majority of therapies focus on in-clinic, one-on-one treatments with therapists, and there is a need for combining technology-enabled home therapies and accurate impairment assessments to augment clinic-based treatment. This RERC develops and tests devices and techniques that may increase the volume and effectiveness of impairment-specific therapies. Many rehabilitation technologies including rehabilitation robots have been developed and applied to rehabilitation successfully. However, there is a lack of combined accurate assessment and treatment protocols and devices that evaluate and treat specific impairments. The RERC objectives are to assess closely related impairments post-stroke or associated with older adults with high fall risks, including sensorimotor impairments across multi-joints, impaired balance and gait post-stroke, and reduced balance and increased risk of falls associated with aging. Outcomes include accurate assessments of mobility and manipulation impairments and improvements following combined hospital and home rehabilitation, ranging from muscles to joint, from single to multiple joints, from hand to arm, and from balance control to stepping. The project develops novel products, including assessment tools, wearable rehabilitation robots, multi-joint arm/hand robots, and sliding-stepping robots.

2. Project Title: **PREVENTING DIABETIC FOOT ULCERS THROUGH MANIPULATING THE SKIN MICROBIOTA**

Leader(s):   **ROGHMANN, MARY-CLAIRE**
          BALTIMORE VA MEDICAL CENTER
          VA I01CX001601 / (2018 - 2023)

Core(s):

Diabetes is common in the Veterans Health Administration (VHA) patient population with a prevalence of 24% making it a priority clinical issue for Veterans. Between 10 and 25% of people with diabetes will develop a foot ulcer during their lifetime. Diabetic foot ulcers are a leading cause of hospitalization, as well as the primary cause of lower limb amputations. About 5% of patients with a foot ulcer require an amputation each year, typically due to the development of infection at the site of the foot ulcer. Because foot ulcers are a leading cause of disability in people with diabetes, more effective prevention is needed. The role of the skin microbiota on the development of chronic foot ulcers after minor trauma is unknown. Prior work has shown that the feet of diabetic Veterans had a higher load of S. aureus compared with non-diabetic veterans. Our preliminary data suggest that there are higher loads of S. aureus and total bacteria on the feet of diabetic Veterans at high risk for future foot ulcer compared to diabetic Veterans at low risk of a future foot ulcer. If so, manipulating the skin microbiota of the feet could reduce the risk of foot complications. Thus, we propose the following aims to test our central hypotheses that the skin microbiota is part of the causal pathway in the development of chronic ulcers. Using a randomized, double-blind clinical trial, 200 adults with diabetes and a prior foot ulcer will be randomly assigned to chlorhexidine or placebo wipes for daily foot care over one year. Specific Aim 1A: To determine if chlorhexidine reduces the recurrence of foot complications including chronic foot ulcer, foot infection or foot amputation. We hypothesize that the chlorhexidine group will have a lower incidence of chronic foot ulcer or foot infection or foot amputation than the placebo group. Specific Aim 1B: To determine if chlorhexidine increases antibiotic resistance among ESKAPE [and diabetic foot infection] pathogens. We hypothesize that a) the chlorhexidine group will not be colonized with E. cloacae, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa and

E. faecium (ESKAPE) [and diabetic foot infection] pathogens with a higher MIC tochlorhexidine than the placebo group and b) the chlorhexidine group will not be colonized with ESKAPE [anddiabetic foot infection] pathogens with a higher MIC to key antibiotics than the placebo group. We expect to gain: 1) an assessment of the feasibility of chlorhexidine as a daily intervention to preventrecurrent foot ulcers in Veterans with diabetes, and 2) an understanding of the risk of antimicrobial resistancewith long term chlorhexidine use. Our long term goal is to test whether interventions which manipulate the skinmicrobiota prevent foot ulcers in a larger (adequately powered for a clinically relevant endpoint) clinical trial inorder to reduce the risk of amputation associated with diabetic foot ulcers.

3. Project Title: CONTINUOUS GLUCOSE MONITORING IN INSULIN TREATED HOSPITALIZED VETERANS WITH DM2 AT HIGHER RISK FOR HYPOGLYCEMIA

Leader(s): SPANAKIS, ILIAS
BALTIMORE VA MEDICAL CENTER
VA I01CX001825 / (2018 - 2023)

Core(s):

More than 25% of patients admitted to general wards/non Intensive Care Unit (non-ICU) setting have a historyof Diabetes Mellitus (DM); and as for 2012, $125 billion dollars were costs associated with hospitalization ofdiabetics in the United States (US). Up to 30% of the hospitalized diabetics develop hypoglycemia, a conditionthat is associated with higher hospital charges, prolonged length of stay, and increased morbidity and mortality.Reducing hypoglycemic events in the inpatient setting has led hospitals to develop hypoglycemia preventionpolicies; policies which are however limited by the infrequent Point of Care (POC) capillary blood glucose testingin the general wards. Continuous Glucose Monitoring (CGM) devices represent additional ways to monitorblood glucose levels. Only a limited number of studies have examined the use of CGM devices in the non-ICUsetting. In all these studies, CGM use was found to be superior compared to POC in hypoglycemia detection.However, as the results of CGM were blinded (alarms were turned off) for both the investigators and theparticipants, interventions to prevent hypoglycemia were not performed. Additionally, one major limitation ofCGM technology is that CGM receiver/monitor needs to be located in the patient's room, due to BluetoothTechnology signal-strength restrictions, necessitating nurses to enter frequently the patient's room in order tocheck CGM glucose values. In the current award application, we describe the development of an innovativesystem that allows CGM glucose values to be transmitted from the patients' bedside to a monitoring device thatis located at a central nursing station- a system that we call Glucose Telemetry System (GTS).We propose the conduction of a prospective randomized clinical trial that will examine whether GTS combinedwith a hypoglycemia prevention protocol, can decrease hypoglycemia in the medical wards without resulting inhyperglycemia- resulting to better clinical outcomes. Specifically we hypothesize that: (1) Veterans who will berandomized to GTS will have less hypoglycemia than Veterans randomized to control group (standard of care);(2) Veterans who will be randomized to GTS will not experience more frequent hyperglycemia, as a result ofthe frequent application of the hypoglycemia prevention protocol, compared to Veterans randomized to thecontrol group; and (3) GTS use will reduce the frequency of hypoglycemia induced seizures during theirhospitalization decreasing length of stay and inpatient mortality. We will study 244 Veterans with DM2 whoare at a higher risk for hypoglycemia. Consenting Veterans will be stratified in two groups based on the numberof risk factors of hypoglycemia (=2 risk factors, =3 risk factors); and then further randomized in a 1:1randomization scheme (122 Veterans randomized to GTS and 122 randomized Veterans to standard of care-POC blood glucose monitoring). For the participants of the control group, retrospective CGM devices will beused in order to compare glycemic outcomes between the two groups. Our primary outcome is difference inhypoglycemic event rate between the two groups. Other outcomes of interest are times spent in hypoglycemia,normoglycemia, hyperglycemia and severe hyperglycemia, length of stay, seizure activity related tohypoglycemia and inpatient mortality.Discovering novel ways to monitor glucose values in the hospital setting could have a significant impact inpreventing hypoglycemia in the inpatient setting- a condition that is associated with adverse clinical outcomes.We believe that our proposal is highly innovative. The trial may lead to future wider use of CGM in hospitalizedpatients with DM who are at a higher risk for hypoglycemia, similar to the way that we use cardiac telemetry forpatients who are at an increased risk for developing arrhythmias.

4. Project Title: PROMOTION OF SUCCESSFUL WEIGHT MANAGEMENT IN OVERWEIGHT AND OBESE VETERANS

Leader(s): RYAN, ALICE S.; ORTMEYER, HEIDI K ; SERRA, MONICA C ;
BALTIMORE VA MEDICAL CENTER

VA I01CX001965 / (2020 - 2025)

Core(s):

Over 70% of Veterans who receive health care at the VA are overweight or obese, and obesity rates of Veterans receiving care at the VA are higher compared to non-Veterans and Veterans who do not use the VA. Obesity contributes to loss of mobility which is a significant determinant of morbidity and loss of independence. Obesity also is associated with elevated cardiometabolic risk factors, including lipid profile, insulin resistance, hypertension, and inflammation. Though weight loss of as little as 3% improves physical functioning and reduces type 2 diabetes and cardiovascular risk factors, most subjects are unsuccessful at long-term weight maintenance, regaining almost half the weight lost within the following two years and return to baseline weight within the next 3-5 years. This clinical trial takes on the challenge of maintaining weight reduction by altering energy balance and possibly skeletal muscle substrate oxidation to mitigate weight regain in overweight and obese older Veterans with mobility limitations. The objective of this award proposal is to test in a randomized clinical trial the effectiveness of an intensive weight management program with and without intermittent fasting (IF) to combat weight regain and the obesity crisis in our Veterans. IF refers to short periods of intense energy restriction. We propose to enroll a total of 200 overweight and obese Veterans with mobility impairments into a 12 weeks weight loss program that incorporates a low calorie Heart Healthy (HH) diet and exercise at the Baltimore and Atlanta VAMCs. Following weight loss (WL), Veterans will be randomized to weight maintenance (WM: continuation of HH and exercise guidelines) program or weight maintenance with intermittent fasting (WM+IF) for 24 weeks. Our central hypothesis is that IF will provide the stimulus for prevention of weight regain at 36 weeks and will improve cardiometabolic and functional health factors. Further, we hypothesize that the ability to appropriately modify fuel utilization through skeletal muscle fatty acid oxidation enzymes is an important factor in weight maintenance and weight regain. This CSR&D Clinical Trial Merit Award introduces an innovative practice of IF to prevent weight relapse after clinically significant weight reduction and could provide evidence-based recommendations to promote this type of intervention in the Veteran population.

5. Project Title: EFFECTS OF 12-WEEKS OF HIGH-INTENSITY RESISTANCE AEROBIC CIRCUIT EXERCISE TRAINING ON EPIGENETIC AGING AND INFLAMMATION IN OLDER HIV-INFECTED VETERANS

Leader(s): OURSLER, KRISANN K; MARCONI, VINCENT CHARLES ; RYAN, ALICE S. ;
SALEM VA MEDICAL CENTER
VA I01RX002790 / (2019 - 2023)

Core(s):

The Veterans Health Administration (VHA) is the largest U.S. HIV health provider with 64% of these Veterans 50+ years of age. HIV infection in the setting of antiretroviral therapy represents a chronic disease with an advanced aging phenotype manifested as increased cardiovascular disease, sarcopenia, and frailty, primarily driven by systemic inflammation. We found a 42% reduction in VO2peak in older HIV+ adults that significantly improved with high-intensity aerobic (AEX) and resistance training (RT). Yet, durable strategies for high-intensity exercise in older adults remain a challenge and limited data are available in older HIV+ adults. There is an urgent need to address these knowledge gaps in order to prevent widespread disability in HIV+ Veterans. Our objective is to provide a high-intensity exercise program for older Veterans that can be widely disseminated and attenuates processes underlying aging. Epigenetic changes with increased age encapsulate the putative effects of biological aging and lifestyle factors. DNA methylation (DNAm) patterns are frequently modified in genes encoding pro-inflammatory cytokines, but can be reversed with exercise training. DNA methylation age (DNAm Age) is an epigenetic biomarker that is expressed in years and provides a concrete benchmark of advanced aging. We found that HIV+ adults have DNAm Age 11 years greater than age- matched adults without HIV. Further, in adults without HIV, increased DNAm Age is associated with physical inactivity, weakness and frailty. Our preliminary data in the Veterans Aging Cohort Study (VACS) show that DNAm Age correlates with the VACS Index, a measure of frailty in HIV+ adults. However, the impact of exercise training on DNAm Age has yet to be determined in any patient population. We propose to adapt our center-based high-intensity AEX+RT intervention in older HIV+ Veterans into a video telehealth (VTEL) delivered functional (no stationary equipment) exercise program that leverages epigenetic outcomes to demonstrate anti-aging effects of exercise. The overarching hypothesis is that VTEL high-intensity functional circuit exercise in older HIV+ Veterans will improve the advanced aging phenotype and attenuate DNAm epigenetic processes underlying aging. Our experimental approach includes a 12-week VTEL exercise intervention in 80 older HIV+ Veterans who are randomized to exercise or standard of care sedentary control groups. AIM 1 will determine the effect of VTEL exercise on VO2peak, sarcopenia, and frailty as phenotypic outcomes of advanced aging in HIV. AIM 2 will investigate the effect of VTEL exercise on DNAm Age as a biomarker of advanced aging. AIM 3 will determine the effect of VTEL exercise on DNA

methylation of specific genes encoding specific pro-inflammatory cytokines in leukocytes. This approach will advance our understanding of effective and feasible exercise strategies to prevent and minimize disability in patient populations with advanced aging. Findings will provide an innovative approach to functional exercise in all older adults. DNAm Age could be used as a personalized benchmark for an individual s benefit from exercise to promote sustainable behavior change. Findings will also provide epigenetic risk profiles that can be used to generate a personalized exercise prescription, an important next step in the next decade of precision medicine. The proposal leverages our exercise training experience in HIV and VTEL, availability of 3,000 HIV+ Veterans at Atlanta and Baltimore VAMCs, and the VHA VTEL infrastructure. The capacity to disseminate VTEL exercise with minimal cost using existing infrastructure will facilitate large-scale dissemination and national impact. Deliverables include improved clinical outcomes and substantial cost savings from reduced hospitalization and institutionalization rates.

6. Project Title: A BALANCED REACH TRAINING PLATFORM TO ADDRESS BALANCE DISORDERS IN OLDER AND NEUROLOGICALLY DISABLED VETERANS

Leader(s): BARTON, JOSEPH EDWARD; HAFER-MACKO, CHARLENE E ; BALTIMORE VA MEDICAL CENTER
VA I01RX003096 / (2020 - 2024)

Core(s):

Falls are by far the leading cause of accidental injury and death in older adults. The Veteran population is more severely affected by falls since it is significantly older than the overall population (45% over 65 years of age vs. 13%); and Veterans would benefit substantially more from an accurate diagnosis and treatment of fall propensity. Despite its importance, much is still unknown about the manner in which balance control is compromised by age and disease. Therapeutic interventions for people who are at risk of falling have proven to be of limited utility. Engineering methods are well suited to study and evaluate balance; but have to date been applied to overly simplified scenarios that lack the complexity to probe the musculoskeletal and neurophysiological bases for balance and falls. The long term objective of this research, which began with a VA Rehabilitation Research & Development (RR&D) Career Development Award (CDA-2), is to develop improved directives and protocols for the diagnosis and treatment of balance-related posture and movement coordination problems. This proposal significantly advances engineering methods to address existing gaps in the diagnosis and treatment of balance impairments through the development of a Balanced Reach Training Protocol (BRTP). The BRTP continuously challenges subjects to perform reaching tasks at the limits of their balance for an extended period of time, and increases these limits as subjects demonstrate improved performance. The goal of this tool is to quantitatively assess and improve at-risk individuals' ability to maintain balance when disturbed by volitional movements of the body and its parts an important class of balance disturbances integral to many activities of daily living that can precipitate falls. The BRTP focuses on performance at and just beyond the limits of balance, unlike most such tests and training protocols that do not challenge subjects in this way. The BRTP's most immediate and salient metric is the limiting boundary of standing reach; and we hypothesize that expanding this boundary, as the BRTP is designed to do, will improve balance and make individuals more resistant to falls (in the context of expected balance disturbances). Confirmation of this hypothesis could provide a new perspective on existing training protocols' modest success rates, and direction for the design of new protocols with the potential to significantly improve these rates. [Though the BRTP is a training platform, we also believe that the performance metrics and analytical results produced by it can form the basis for new diagnostic measures that more reliably and precisely quantify and explain balance performance problems; and track changes in them over time.] Such diagnostic and treatment protocols would be particularly beneficial to the VA Health Care System, as it would lead to improvements in: patient throughput, quality of care, and treatment costs. Though this proposal targets the aging Veteran population, the BRTP is a general tool that can aid in the diagnosis and treatment of balance disorders arising from conditions other than aging. These include obesity, diabetes (which often leads to lower extremity muscle degeneration and peripheral neuropathy), sarcopenia, vestibular disorders, and neurological disorders such as stroke. Veterans whose balance has been compromised by Traumatic Brain Injury (TBI) (whether combat-related or not) may also benefit from the BRTP.

7. Project Title: A FEASIBILITY AND PILOT STUDY OF COMBINED TREATMENT PROTOCOL USING AEROBIC EXERCISE AND DULOXETINE IN OLDER ADULTS WITH SYMPTOMATIC KNEE OSTEOARTHRITIS AND COMORBID DEPRESSION

Leader(s): RATHBUN, ALAN MICHAEL

UNIVERSITY OF MARYLAND BALTIMORE
NIH K01AG064041 / (2019 - 2024)

Core(s):

Symptomatic knee osteoarthritis (OA) affects 10% of men and 13% of women 60 years or older, anddepressive symptoms are common, estimated to be prevalent in one-fifth of these patients. Depressivesymptoms worsen knee OA disease severity and are a barrier to pain management and engagement inphysical activity. Clinical care guidelines recommend depression treatment in older adults with knee OA butprovide no direction on how to simultaneously manage both conditions, and patients are often not treated fortheir depressive symptoms and receive interventions only for their chronic physical illness. This issue isexacerbated by the routine exclusion of individuals with chronic physical diseases and comorbid depressionfrom clinical trials and lack of protocols designed for these patients. Recent research advocates the use oftreatments that benefit both conditions simultaneously, or combined treatment using two interventions inparallel that are designed to work together, such that approaches enhance efficacy beyond that of an individualtherapy with a single disease target. Treatment guidelines advise exercise programs to manage pain anddisability and improve psychosocial health in those with knee OA, but compliance to physical activity protocolsis low in persons with chronic pain and disability and is only made worse by comorbid depression. Adherenceis critical to the efficacy of depression treatments using exercise training, and no such exercise program hasever been designed for and tested in OA patients with co-occurring depressive symptoms in a way to enhancecompliance. Duloxetine is the only antidepressant medication indicated for pain management in knee OApatients that has demonstrated efficacy and tolerability when treating depression in older adults, and therefore,is a viable pharmacological complement to exercise training. There are no protocols that combine treatmentsusing interventions that affect symptoms of both knee OA and depression, and a strategy focused on co-management of the two conditions could be disseminated to and implemented by generalist medicalpractitioners. Thus, the research goal of this K01 application is to evaluate the feasibility of and then pilot test aprotocol comprised of aerobic exercise training plus duloxetine for the treatment of symptomatic knee OA andcomorbid depression. The proposed research will be implemented with a period of close mentoring and careerdevelopment activities focused on learning 1) methods for qualitative data collection and analysis that can beused to understand patients perspectives and experiences and 2) strategies for the implementation andevaluation of interventions in clinical research. This proposal is aligned with the NIA Strategic Directions forResearch on Aging emphasizing older adults with multiple chronic conditions that complicate clinical care andis intended to lead to a research program that uses observational epidemiology evaluating the relationshipsand mechanisms between musculoskeletal disorders and comorbid depression in older adults to inform thedevelopment of protocols that are designed to manage symptoms of both the primary condition and sequalae.

8. Project Title: Gerofit - A Program Promoting Exercise and Health for Older Veterans

Leader(s):   **KATZEL, LESLIE I**
BALTIMORE VA MEDICAL CENTER
VA N/A / (2018 - NA)

Core(s):

Gerofit is a supervised exercise program for older Veterans that was developed at the VA Medical Center in Durham, North Carolina, in 1986. As a part of Gerofit, veterans are given a personal exercise program based on their physical profile and goals. Veterans are welcome to remain in the program as long as they wish. Gerofit can include individual and group based exercises such as Tai Chi, line dancing, balance, core coordination, and strengthening classes. The exercise program may include treadmills, elliptical machines, stair climbers, bicycles and a variety of strengthening machines. Guidance in carrying out the exercise program is provided by trained exercise staff such as a nurse or physical therapist. Participants in the program have demonstrated improved health, physical function and well-being. They have shown improvements in blood pressure, diabetes management, symptom management, well-being, quality of life, physical function, overall fitness, and longevity.

9. Project Title: Comparative effectiveness of pulmonary embolism prevention after hip and knee replacement (PEPPER): balancing safety and effectiveness

Leader(s):   **PELLEGRINI, VINCENT**
DARTMOUTH-HITCHCOCK MEDICAL CENTER

PCORI PCS-1402-09328 / (2016 - 2024)

Core(s):

Nearly 1 million total hip (THR) and knee (TKR) replacements are performed each year in the United States, and comprise the largest single type of operation paid for by Medicare. Because disturbing the bone marrow cavity turns on the blood clotting system in humans, these operations are often complicated by formation of blood clots in the veins of the leg (deep vein thrombosis, DVT). Sometimes, these blood clots detach from the leg veins and travel to the lungs (pulmonary embolism, PE), where they interfere with the normal pumping of blood from the heart. When a large clot gets stuck in the lung, it can result in death; this happens in 0.1-0.5 percent of patients after hip or knee replacement, which means between 1,000 and 5,000 deaths each year. The use of blood thinners around the time of operation reduces the risk of pulmonary embolism and related death, but also increases the risk of bleeding from the raw bony surfaces that are created when the joint replacement is done. The ideal balance between use of blood thinners to prevent PE and the risk of bleeding associated with their use is not known. Nearly all surgeons and professional organizations agree that use of blood thinners is beneficial in this setting, but some clinical guidelines recommend the use of very strong blood thinners while others favor weaker blood thinners in order to reduce bleeding risk. These events are so uncommon that no clinical trial is large enough to provide an answer as to whether the strongest of blood thinners, or weaker medicines, are the best to use in this setting. Similarly, information that is available from billing records of large health care insurance companies, such as Medicare, is unable to provide an answer because this information also has shortcomings that limit its usefulness. Since 2012, no study, including the very detailed AHRQ Comparative Effectiveness Review, has been willing to recommend a specific blood thinner as the best to use after hip and knee replacement because there is so little information about the tradeoff between preventing pulmonary embolism and the risk of bleeding that occurs more frequently with the strongest of blood thinners. Objectives: Our purpose is to combine information about effectiveness in preventing blood clots in the lungs and legs, which is important to how patients do after total hip and knee replacement, with the opinions of patients about the safety of the most commonly employed blood thinners with respect to the chance of bleeding problems that each drug might cause after the operation. The patient's preferences for using blood thinners to decrease the risk of blood clots that might result in death will be balanced with the patient's concerns about how bleeding problems related to the blood thinners might reduce the success of the joint replacement by causing pain, stiffness, a need for another operation, or infection that might result in having to remove the joint replacement parts altogether. This work will therefore provide background information to help both patients and their surgeons in deciding which blood thinner would be best to use after hip and knee replacement. We expect that the choice of blood thinner will understandably be different for many patients and their surgeons, depending upon how much of a chance of a poor result after the joint replacement that each patient would be willing to accept in return for lowering the risk of a life-threatening blood clot. Because it is so uncommon for a patient to die from a blood clot in the lung after hip and knee replacement, it takes a very large number of patients to be able to see a real difference in the effects of these drugs on blood clots and bleeding in order to determine which drug is best. In fact, none of the previous studies about this issue have been large enough to see any real differences between drugs with respect to death from blood clots, but there have been differences in bleeding with the stronger blood thinners having as much as three to five times more bleeding problems than aspirin, which is a weak blood thinner that may be equally effective in preventing life-threatening blood clots. Methods: We propose a study that is large enough to compare real differences in rates of life-threatening blood clots between the three most commonly used blood thinners after hip and knee replacement, while also comparing different rates of bleeding with each drug that can make a repeat operation necessary and may ultimately make the joint replacement function less well. Approximately 25,000 patients undergoing elective THR or TKR will be enrolled at 25 centers over 2.5 years at a rate of 400 patients per site per year. The study will encompass four years, with six months startup for IRB approval, six months follow-up per patient, and six months for final data analysis. Together, the study centers account for 33,000 THR and TKR per year; each center will randomize patients to all three groups representative of current practice; aspirin plus pneumatic compression (least bleeding risk regimen), low-intensity warfarin (most popular North American regimen), and rivaroxaban (greatest effectiveness in preventing blood clots). A patient advisory board (PAB) has been established; each member has undergone THR or TKR and some have experienced PE or reoperation for wound complications. The PAB will attach a relative value to each event, the effort spent in its prevention, and its impact on function, risk of reoperation, and loss of the implant. Patient outcomes: Primary effectiveness outcomes will include clinically important PE/DVT resulting in readmission and death from all causes. Safety outcomes will include major bleeding and patient-reported wound and remote bleeding. Patients will attach relative importance to blood clots, bleeding, and death and consider this tradeoff in order to determine the relative risk tolerances for blood clots and bleeding to decide which blood thinner is most appropriate for which patients.

10. Project Title: **A practical intervention to improve patient-centered outcomes after hip fractures among older adults (REGAIN Trial)**

      Leader(s):   **NEUMAN, MARK**

UNIVERSITY OF PENNSLYVANIA
PCORI PCS-1406-18876 / (2015 - 2023)

Core(s):

Hip fractures occur more than 300,000 times each year among older US adults; the vast majority of patients undergo surgery that requires anesthesia. One year after fracture, 50 percent of previously independent patients have died or require nursing home placement, and 40 percent of survivors who previously walked independently need help to walk 10 feet. The REGAIN trial (REgional versus General Anesthesia for promoting INdependence after hip fracture) will compare short- and long-term outcomes of two common approaches to anesthesia for hip fracture surgery. We hypothesize that patients treated with spinal (nerve block), versus general anesthesia, will experience fewer complications and less pain during hospitalization; be more likely to regain independence in walking by 60 days after surgery; be more likely to return home by 180 days; have better overall health, less disability, and less pain; and be more satisfied with their care. REGAIN will enroll 1,600 patients from 18 academic and community hospitals across the United States. Participants will be adults aged 50 and older undergoing surgery for hip fractures, who could walk independently before fracture, and who are eligible for spinal and general anesthesia. Patients will be centrally randomized to receive either spinal or general anesthesia. We received extensive input into the overall study question, the outcomes to be studied, and methods for outcome assessment from our lead patient partner (the Center for Advocacy for the Rights and Interests of the Elderly); stakeholders, including the Gerontological Society of America; and a community patient and caregiver advisory group. Patients and stakeholders also drafted key sections of the proposal, and we received additional input from leading medical professional societies in orthopedic surgery and anesthesia, and from major health care payers. By comparing two universally available, basic anesthetic approaches, the REGAIN trial will directly and immediately affect patient decision making, care, and outcomes for the more than 300,000 US patients who need surgery to treat hip fractures each year, as well as the more than 8.5 million older US adults who face decisions about anesthesia for other major surgeries each year.

11. Project Title: HIP MUSCLE POWER, LATERAL BALANCE FUNCTION, AND FALLS IN AGING
Leader(s):   GRAY, VICKI L.
UNIVERSITY OF MARYLAND BALTIMORE
NIH R01AG060051 / (2018 - 2023)

Core(s):

Project Summary/Abstract Falls and their consequences are among the major problems in the medical care of older individuals.The long-term goal of this research is to a mechanistically derived therapeutic intervention to enhance musclepower, weight-shifting capability, and lateral balance to prevent falls. When human balance is challenged,protective stepping is a vital strategy for preventing a fall during activities of daily life. Many older people at riskfor falls have particular difficulties with successfully stepping sideways as a protective response to loss ofbalance in the lateral direction. We propose that age-related declines in lateral balance function throughimpaired weight transfer and protective stepping linked with falls, result from neuromuscular and biomechanicallimitations in hip abductor-adductor (AB-AD) muscle power generation. Moreover, we hypothesize that thesefunctional and neuromotor impairments can be improved with high velocity muscle resistance power training.The specicic aims are: Aim 1. To determine the age-associated changes in neuromuscular and biomechanicalperformance of the hip joint AB-AD musculature by evaluating the isolated maximum torque and powerproduction and neuromuscular activation patterns. Aim 2. To determine the aging changes in neuromotorperformance of the hip AB-AD musculature during the pre-step weight transfer phase of waist-pull induced sidestepping and voluntary reaction time stepping. Aim 3. To establish a first line of evidence showing thathypothesized aging deficits in sidestepping caused by neuromotor impairments in hip AB-AD muscle powerproduction may be reversible, we will determine the effects of velocity dependent muscle resistance powertraining (3 x/week x 10 weeks) compared with strength training on neuromuscular, biomechanical, andfunctional performance outcomes. Overall, the studies will identify age-related neuromotor mechanisms ofabnormal hip AB-AD muscle power production that impair lateral weight transfer, balance stability, and mobilityfunction. Establishing a first line of support for the superiority of velocity dependent power training overstrength training on muscle performance and protective balance and functional mobility outcomes, will lead to afuture comparative intervention trial to enhance these functions and prevent falls in older adults.

12. Project Title: MECHANISMS OF OSTEOCYTE MECHANO-SIGNALING AND SCLEROSTIN REGULATION

Leader(s):   **STAINS, JOSEPH P.; WARD, CHRISTOPHER WILLIAM ;
UNIVERSITY OF MARYLAND BALTIMORE
NIH R01AR071614 / (2018 - 2023)**

Core(s):

PROJECT SUMMARYOsteoporosis and other diseases of skeletal fragility affect more than 200 million people worldwide andcontributes to ~9 million factures annually. Preventing bone loss and/or restoring lost bone mass in patients isof vital importance to limiting the personal and economic impact of diseases of skeletal fragility. A key target inthe stimulation of new bone formation is the protein sclerostin, an antagonist of the Wnt/beta-catenin signalingcascade, which is produced by bone embedded osteocytes. Numerous osteoanabolic cues, includingmechanical load, reduce expression of the sclerostin leading to de-repression of osteoblastogenesis andstimulation of de novo bone formation. However, key mechanistic details of how osteocytes sense mechanicalload, transduce these load signals to biologic effectors, the identity of these biological effectors and howsclerostin bioavailability is regulated are unclear. Our preliminary data have uncovered a number of novelmediators of how osteocytes sense and respond to mechanical cues. Specifically, we show that microtubule-dependent cytoskeletal stiffness regulates mechano-activated Ca2+ influx. Furthermore, we implicate TRPV4as a major mechano-dependent Ca2+ influx pathway that drives Ca2+ dependent activation ofcalcium/calmodulin-dependent kinase II (CamKII) to reduce sclerostin bioavailability in the osteocyte. In thepresent grant, we will use in vitro, ex vivo and in vivo models to determine the contribution of MT density andcytoskeletal crosslinking to osteocyte mechanosensing, define the contribution and mechanisms of osteocyteTRPV4 channel opening in response to mechanical stress and elucidate the mechanisms by which FFSS-dependent CamKII activation regulates sclerostin degradation and Sost gene transcription. This work will morefully explain the biological regulation of sclerostin, will mechanistically link several gaps in the knowledge ofhow osteocytes sense and respond to mechanical load, and will reveal novel targets to improve or preservebone mass in aging and disease.

13. Project Title: **ADVANCING GERIATRICS INFRASTRUCTURE & NETWORK GROWTH (AGING) INITIATIVE**

Leader(s):   **GURWITZ, JERRY H
UNIV OF MASSACHUSETTS MED SCH WORCESTER
NIH R33AG057806 / (2018 - 2023)**

Core(s):

PROJECT SUMMARY / ABSTRACTThe Health Care Systems Research Network (HCSRN)-Older Americans Independence Centers (OAICs)AGING (Advancing Geriatrics Infrastructure and Network Growth) Initiative, funded under an R24 grantmechanism (R24 AG045050), was initiated in 2014 to foster collaborations between HCSRN and OAIC (akaPepper Centers) investigators in order to advance an interdisciplinary research agenda focused on advancingthe science of multiple chronic conditions (MCCs) in older adults. The AGING Initiative is a highly productive,collaborative, transdisciplinary endeavor involving scientists from 18 HCSRN research centers, embeddedwithin healthcare delivery systems caring for nearly 2 million persons aged 65 and older, in partnership withinvestigators from 15 premier, university-based centers established by the National Institute on Aging (theOAICs). Under the R24, efforts relevant to advancing MCCs science have centered around: (1) characterizingand sharing unique data resources; (2) supporting innovative, collaborative pilot projects; (3) mentoring newand early-stage investigators; and (4) disseminating research methods and findings. This collaboration hasidentified several understudied, high priority research domains, as well as an urgent need for formal careerdevelopment support for new and early-stage scientists committed to aging research on etiology, prevention,and treatment, relevant to the care of older persons with MCCs. The overarching aim of our expanded R33program, conceived and developed by the R24 HCSRN-OAICs AGING Initiative Steering Committee, and itsWorkgroups and External Advisory Committee, is to elaborate on the successful programs and infrastructure ofthe R24, while taking our AGING Initiative in new, more ambitious directions. We will create new coreresources, career development opportunities, and funding opportunities, aligning patients' interests with thoseof scientists. Our specific aims are: (1) to expand on and further develop innovative methods related tomeasurement and analytics, observational research, and pragmatic clinical trial design and implementation, toinform the development and testing of novel interventions that improve the care and outcomes of older personswith MCCs; (2) to foster the career development and success of new and early-stage investigators, includingunderrepresented minorities, and create a nation-wide cohort of MCCs scholars, who are prepared to establishproductive collaborations early in their careers to catalyze an expansion of interdisciplinary research relevant tothe science of MCCs; (3) to create a new core function as part of an elaborated infrastructure that promotespatient-centered research by engaging patients and care partners in all stages of the research process; and(4) to fund a series of P-2-R (Pilot-to-R award) grants that will advance the R33 research priorities relevantto the science of

MCCs. The P-2-R grants will serve to promote the development and implementation oflarger, multi-disciplinary, multi-site studies laying a foundation upon which to continue to grow the AGINGInitiative.

14. Project Title: RESEARCH TRAINING IN THE EPIDEMIOLOGY OF AGING.
Leader(s):   MAGAZINER, JAY
UNIVERSITY OF MARYLAND BALTIMORE
NIH T32AG000262 / (1998 - 2023)

Core(s):

AbstractThe aging of the United States population highlights the need for increased interdisciplinary research on diseasesand disabilities that affect older persons. The objective of years 21 25 of this successful program is to continuetraining 5 pre- and 2 postdoctoral fellows to conduct independent and original research in the epidemiology ofaging, with an emphasis on the prevention of late life disability and functional decline and the maximization offunction in those with existing disabilities and disabling conditions. The program emphasizes four broadsubstantive areas in which program faculty have gerontologic research experience and are conducting ongoingprojects: musculoskeletal epidemiology; neuroepidemiology; genetic epidemiology; and pharmacoepidemiology.The program prepares trainees to: 1) contribute to an interdisciplinary research team under the supervision of aprimary mentor expert in the epidemiology of aging and secondary mentors expert in epidemiology methodsand/or biostatistics, gerontology and content areas relevant to trainee research; 2) develop a research question,articulate hypotheses, and design and perform an epidemiologic study to address hypotheses; 3) become expertin at least one substantive area relevant to functional decline and the maximization of function in those withdisabilities and disabling conditions; 4) demonstrate excellence in conducting independent, innovative research;5) gain experience presenting research results; 6) master a core curriculum in epidemiology and biostatistics; 7)be knowledgeable about basic biological and psychosocial processes of aging; 8) master principles ofresponsible conduct of research; and 9) be prepared for transition to a research career in academia,government, industry or non-profit sector using capabilities in the epidemiology of aging.The program is located within the Department of Epidemiology and Public Health (EPH) of the University ofMaryland School of Medicine. Major program strengths include: 1) availability of core epidemiology of agingfaculty, and faculty expert in gerontology, epidemiology, biostatistics, and substantive areas that are focus ofprogram; 2) interdisciplinary training and research opportunities in aging and related areas; 3) graduate trainingopportunities including advanced coursework through the Doctoral Programs in Epidemiology and HumanGenetics, Gerontology, and Pharmaceutical Health Services Research; and 4) ability to capitalize onBaltimore/Washington corridor to leverage resources across multiple domains (academia, government, industry,and non-profit). We expect the training program, with its team of dedicated faculty, will continue to serve traineesin launching successful careers as leaders in the epidemiology of aging. The program director is recognized forhis leadership nationally and within the University of Maryland; as such, he is in an excellent position to fosterthe development of trainees through participation in interdisciplinary research programs locally and nationally.Leaders of the Doctoral Programs Epidemiology and Human Genetics and in Gerontology will serve as programassociate directors.

15. Project Title: INTERCOLLABORATIVE RADIATION COUNTERMEASURE (INTERACT) CONSORTIUM FOR ADVANCED DEVELOPMENT OF MEDICAL COUNTERMEASURES TO MITIGATE/TREAT ACUTE AND DELAYED RADIATION SYNDROMES
Leader(s):   VUJASKOVIC, ZELJKO
UNIVERSITY OF MARYLAND BALTIMORE
NIH U19AI150574 / (2020 - 2025)

Core(s):

The Inter-collaborative Radiation Countermeasures (INTERACT) Consortium was assembled for the overall goal of developing safe and effective medical countermeasures (MCM) to mitigate and/or treat the acute, delayed, and long-term consequences of radiation exposure for all subsets of the civilian population in the event of a radiological or nuclear (RadNuc) public health emergency. The biological complexity of multiorgan injury (MOI) and failure associated with acute radiation sickness (ARS) and delayed effects of acute radiation exposure (DEARE) requires a comprehensive, multidisciplinary approach to efficiently identify new targets for therapeutic intervention and to move promising MCMs from the research laboratory to advanced pharmaceutical development and approval under the U.S. Food and Drug Administration s (FDA) Animal Rule (AR) regulatory pathway. INTERACT, a newly formed University of Maryland

School of Medicine (UMSOM)-based Center for Medical Countermeasures against Radiation (CMCR), is a partnership of internationally-recognized investigators from four U.S.-based universities who possess a broad depth of expertise in MCM development, a unique set of animal model platforms, and a common goal of sharing ideas and quality practices to advance the cutting-edge scientific discovery and translational development of MCMs. INTERACT projects are broadly designed around a common theme to promote tissue regeneration through targeting the biological processes involved in cellular degeneration that contribute to the clinical manifestation of ARS/DEARE after prompt exposure to high-doses of total body irradiation (TBI). Candidate MCMs under investigation target key biological mechanisms associated with a radiation-induced accelerated aging process including genomic instability, mitochondrial damage, cellular senescence, and inflammation that leads to the hematopoietic (Project 1) and gastrointestinal subsyndromes of ARS (Projects 2, 3), cutaneous radiation injury (Project 3), and DEARE (Projects 1 and 4). Preliminary datum for each of the MCMs under investigation in Projects 1-4 have shown a significant improvement in survival when administered at least 24 hours post-exposure and strong safety profiles in preclinical, and in some cases clinical trials. To advance MCM development within the framework of the AR regulatory pathway for all subsets of the population, projects are supported by two service cores (Core A- Administrative, Core B- Multispecies Efficacy and Pharmacometric Modeling Core) and two consortium cores (Coordinating Center Core, and the Opportunities Fund Management Core). Core B offers one of, if not the most, comprehensive animal model platforms available for MCM testing within the broader CMCR consortia, and includes rabbit, minipig, and non-human primate models of ARS and/or DEARE. INTERACT is synergistic with other potential Centers by offering capabilities and resources currently unavailable to other sites through data and resource sharing and technology transfer to advance and strengthen the National Institute of Allergy and Infectious Diseases (NIAID)/National Institute of Health (NIH) s mission to ensure the nation s preparedness to respond to a radiological or nuclear incident.

16. Project Title: **Cooling to Help Injured Lungs (CHILL) Phase 2B Randomized Control Trial of Therapeutic Hypothermia in Patients with ARDS**

Leader(s): **HASDAY, JEFFREY J**
UNIVERSITY OF MARYLAND BALTIMORE
Department of Defense W81XWH-20-1-0432 / (2019 - 2024)

Core(s):

Acute respiratory distress syndrome (ARDS) is a disease in which the lungs are injured and no longer are able to support the body s needs for absorbing oxygen and removing carbon dioxide. About 40% of patients with ARDS die. There are no medications available that are effective in patients with ARDS. The objective of the proposed study is to test whether reducing body temperature by 4 F-6 F for 48 hours while giving a paralytic medication to prevent shivering will reduce lung injury in patients with ARDS. The rationale for this study is based on (1) the known effect of cooling to reduce the need for oxygen thereby reducing the work required of the injured lungs and (2) the effect of cooling to inactivate certain molecules that cause the lung injury.

PUBLICATIONS

2023

1. **Association Between Race and Receipt of Home- and Community-Based Rehabilitation After Traumatic Brain Injury Among Older Medicare Beneficiaries.**
   Albrecht JS, Kumar A, Falvey JR
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Citations: 60 | AltScore: NA

41. **Adipose and Skeletal Muscle Expression of Adiponectin and Liver Receptor Homolog-1 With Weight Loss and Aerobic Exercise.**
Ryan AS, Li G
J Endocr Soc, 2022 Aug 1, 6(8): bvac095
https://doi.org/10.1210/jendso/bvac095 | PMID: 35854979 | PMCID: PMC9281870
Citations: 38 | AltScore: 1.75

42. **Predictive Equations Overestimate Resting Metabolic Rate in Survivors of Chronic Stroke.**
Ryan AS, Novitskaya M, Treuth AL
Arch Phys Med Rehabil, 2022 Feb 19, 103(7): 1352-1359
pii: S0003-9993(22)00226-X. https://doi.org/10.1016/j.apmr.2022.01.155 | PMID: 35192798 | PMCID: PMC9246861
Citations: 33 | AltScore: NA

43. **Randomization to Treadmill Training Improves Physical and Metabolic Health in Association With Declines in Oxidative Stress in Stroke.**
Serra MC, Hafer-Macko CE, Robbins R, O'Connor JC, Ryan AS
Arch Phys Med Rehabil, 2022 Nov, 103(11): 2077-2084
https://doi.org/10.1016/j.apmr.2022.06.011 | PMID: 35839921 | PMCID: PMC9637747
Citations: 37 | AltScore: 2

44. **Waste Not, Want Not: Proper Design, Analysis, and Interpretation Are Essential to Advancing Aging Research Across the Translational Science Spectrum.**
Shardell M, Speiser JL
J Gerontol A Biol Sci Med Sci, 2022 Nov 21, 77(11): 2165-2167
https://doi.org/10.1093/gerona/glac036 | PMID: 35588371 | PMCID: PMC9678189
Citations: 15 | AltScore: 0.5

45. **Impact of psychological resilience on walking capacity in older adults following hip fracture.**
Soliman G, Fortinsky RH, Mangione K, Beamer BA, Magder L, Binder EF, Craik R, Gruber-Baldini A, Orwig D, Resnick B, Wakefield DB, Magaziner J
J Am Geriatr Soc, 2022 Jul 20, 70(11): 3087-3095
https://doi.org/10.1111/jgs.17930 | PMID: 35856155 | PMCID: PMC9669123
Citations: 30 | AltScore: 272.75

46. **Reply to Verhoef et al.**
Sorkin JD, Manary M, Smeets PAM, MacFarlane AJ, Astrup A, Prigeon RL, Hogans BB, Odle J, Davis TA, Tucker KL, Duggan CP, Tobias DK
Am J Clin Nutr, 2022 Feb 9, 115(2): 598-600
https://doi.org/10.1093/ajcn/nqab371 | PMID: 35139165 | PMCID: PMC8827123
Citations: 4 | AltScore: NA

47. **Factors Associated With Incidence and Spontaneous Clearance of Molecular-Bacterial Vaginosis: Results From a Longitudinal Frequent-Sampling Observational Study.**

Tamarelle J, Shardell MD, Ravel J, Brotman RM
Sex Transm Dis, 2022 Sep 1, 49(9): 649-656
https://doi.org/10.1097/OLQ.0000000000001662 | PMID: 35969846 | PMCID: PMC9387550
Citations: 30 | AltScore: 0.75

48. **Genetic determinants of telomere length from 109,122 ancestrally diverse whole-genome sequences in TOPMed.**
Taub MA, Conomos MP, Keener R, Iyer KR, Weinstock JS, Yanek LR, Lane J, Miller-Fleming TW, Brody JA, Raffield LM, McHugh CP, Jain D, Gogarten SM, Laurie CA, Keramati A, Arvanitis M, Smith AV, Heavner B, Barwick L, Becker LC, Bis JC, Blangero J, Bleecker ER, Burchard EG, Celed?n JC, Chang YPC, Custer B, Darbar D, de Las Fuentes L, DeMeo DL, Freedman BI, Garrett ME, Gladwin MT, Heckbert SR, Hidalgo BA, Irvin MR, Islam T, Johnson WC, Kaab S, Launer L, Lee J, Liu S, Moscati A, North KE, Peyser PA, Rafaels N, Seidman C, Weeks DE, Wen F, Wheeler MM, Williams LK, Yang IV, Zhao W, Aslibekyan S, Auer PL, Bowden DW, Cade BE, Chen Z, Cho MH, Cupples LA, Curran JE, Daya M, Deka R, Eng C, Fingerlin TE, Guo X, Hou L, Hwang SJ, Johnsen JM, Kenny EE, Levin AM, Liu C, Minster RL, Naseri T, Nouraie M, Reupena MS, Sabino EC, Smith JA, Smith NL, Su JL, Taylor JG, Telen MJ, Tiwari HK, Tracy RP, White MJ, Zhang Y, Wiggins KL, Weiss ST, Vasan RS, Taylor KD, Sinner MF, Silverman EK, Shoemaker MB, Sheu WH, Sciurba F, Schwartz DA, Rotter JI, Roden D, Redline S, Raby BA, Psaty BM, Peralta JM, Palmer ND, Nekhai S, Montgomery CG, Mitchell BD, Meyers DA, McGarvey ST, NHLBI CARE Network, Mak AC, Loos RJ, Kumar R, Kooperberg C, Konkle BA, Kelly S, Kardia SL, Kaplan R, He J, Gui H, Gilliland FD, Gelb BD, Fornage M, Ellinor PT, de Andrade M, Correa A, Chen YI, Boerwinkle E, Barnes KC, Ashley-Koch AE, Arnett DK, NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium, TOPMed Hematology and Hemostasis Working Group, TOPMed Structural Variation Working Group, Laurie CC, Abecasis G, Nickerson DA, Wilson JG, Rich SS, Levy D, Ruczinski I, Aviv A, Blackwell TW, Thornton T, O'Connell J, Cox NJ, Perry JA, Armanios M, Battle A, Pankratz N, Reiner AP, Mathias RA
Cell Genom, 2022 Jan 12, 2(1):
pii: 100084. https://doi.org/10.1016/j.xgen.2021.100084 | PMID: 35530816 | PMCID: PMC9075703
Citations: 88 | AltScore: 4.5

49. **Combining exercise, protein supplementation and electric stimulation to mitigate muscle wasting and improve outcomes for survivors of critical illness-The ExPrES study.**
Verceles AC, Serra M, Davis D, Alon G, Wells CL, Parker E, Sorkin J, Bhatti W, Terrin ML
Heart Lung, 2022 Dec 3, 58: 229-235
pii: S0147-9563(22)00277-1. https://doi.org/10.1016/j.hrtlng.2022.11.013 | PMID: 36473808 | PMCID: PMC9992240
Citations: 57 | AltScore: 27

50. **Exome Array Analysis of 9721 Ischemic Stroke Cases from the SiGN Consortium.**
Xu H, Nguyen K, Gaynor BJ, Ling H, Zhao W, McArdle PF, O'Connor TD, Stine OC, Ryan KA, Lynch M, Smith JA, Faul JD, Hu Y, Haessler JW, Fornage M, Kooperberg C, On Behalf Of The Trans-Omics For Precision Medicine TOPMed Stroke Working Group, Perry JA, Hong CC, Cole JW, Pugh E, Doheny K, Kardia SLR, Weir DR, Kittner SJ, Mitchell BD, SiGN Consortium
Genes (Basel), 2022 Dec 24, 14(1):
https://doi.org/10.3390/genes14010061 | PMID: 36672803 | PMCID: PMC9858999

Citations: 13 | AltScore: NA

51. **Beyond In-Hospital Mortality: Use of Post-Discharge Quality-Metrics Provides A More Complete Picture of Older Adult Trauma Care.**
Zogg CK, Cooper Z, Peduzzi P, Falvey JR, Tinetti ME, Lichtman JH
Ann Surg, 2022 Sep 15, 278(2): e314-e330
https://doi.org/10.1097/SLA.0000000000005707 | PMID: 36111845 | PMCID: PMC10014495
Citations: 45 | AltScore: 4.1

EXTERNAL ADVISORY BOARD MEMBERS

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RECOGNITION AND AWARDS (2022-2023)

Alice Ryan, PhD (2022)

- Federal Advisory Committee Appointment, Veterans Affairs Rehabilitation Research and Development Service

Andrea Levine, MD, MS (2023)

- Educator of the year award in pulmonary and critical care medicine
- Woodward Award for Educator of the Year for the Department of Medicine
- COVID-19 Healthcare Hero award from The Daily Record

Andrea Levine, MD, MS (2022)

- Dean's Alumni Award for Diversity and Inclusion
- Educator of the year award in pulmonary and critical care medicine

Barbara Resnick, PhD, RN, CRNP, FAAN, FAANP (2022)

- University of Maryland Baltimore Distinguished University Professor: highest appointment bestowed on a faculty member at UMB. It is a recognition not just of excellence, but also of impact and significant contribution to the nominee's field, knowledge, profession, and/or practice.

Jason Falvey, PT, DPT, PhD, GCS (2022)

- Jack Walker Award: by the American Physical Therapy Association (APTA) National Honors and Awards program. The Jack Walker Award honors an author or team whose published study in Physical Therapy & Rehabilitation Journal presents novel and innovative research related to patient care and advance clinical science, as it pertains to the physical therapy profession. Dr. Falvey will be recognized and will receive his award, by APTA's Board of Directors, in August at the APTA Honors and Awards Ceremony, held during the APTA House of Delegates.
- New Investigator Award: Health and Aging Foundation/American Geriatrics Society
- Top Platform Presentation in Health Policy and Administration: American Physical Therapy Association Combined Sections Meeting, San Antonio, Texas
- Steven M. Levine Award, awarded to a physical therapist or physical therapist assistant who demonstrates leadership in the APTA at a state and/or national level, advocates for the profession at the state and/or national level, and is a role model for professionalism, American Physical Therapy Association Maryland Chapter

Jeanine Ursitti, PhD (2023)

- Best Poster award at the OAIC National meeting

Shari Waldstein, PhD (2023)

- Martica Hall Outstanding Mentor Award, Academy of Behavioral Medicine Research
- Inducted as Fellow, American Psychosomatic Society

MINORITY RESEARCH

General Brief Description of Minority Activities:
Not defined.

Minority Trainee(s):

- Abdou Simon Senghor , Postdoctoral Fellow, University of Maryland, School of Pharmacy
  Abdou is interested in bioethics and is mentored by Dr. C. Daniel Mullins.
- Alan Rathbun, PhD, MPH, Assistant Professor of Epidemiology and Public Health, University of Maryland School of Medicine
  Dr. Rathbun is a musculoskeletal epidemiologist whose current research career is focused in musculoskeletal disorders, epidemiological theory, research study design, causal inference, and applied biostatistics. He currently has a K01 award and a UM-OAIC pilot award and is collaborating with OAIC investigators on both of these projects.
- Bianka Onwumbiko, PhD Candidate, PhD Student, Psychology Department, University of Maryland Baltimore County
  Ms. Onwumbiko's interests include the role of epigenetic modifications such as DNA methylation in the relations of structural discrimination to racial health disparities. Her master's thesis project will examine the association between neighborhood disorder and DNA methylation based immunosenescence among African American and White women and men. Dr. Shari Waldstein currently serves as her mentor and master's thesis chair.
- Bisola Amodu, Clinical Research Coordinator and Pre-Med student, Department of Neurology, University of Maryland School of Medicine
  She is being mentored by Dr. Robynne Braun for training and education in the conduct of clinical trials and trained in the use of TMS for stroke recovery research.
- Candace Hall , PhD student, University of Maryland, School of Pharmacy
  She is interested in patient-centered research and community-engaged research and is mentored by Dr. C. Daniel Mullins.
- Danielle Beatty Moody, PhD, Assistant Professor of Psychology, University of Maryland Baltimore County
  Dr. Beatty Moody's area of interest includes relations of early life social disadvantage and perceived discrimination to cardiometabolic and brain health endpoints as a function of race, SES, gender and age. Dr. Shari Waldstein is her department mentor and primary mentor for Dr. Moody's current K01. She continues to work on her diversity supplement "Early life social disadvantage, brain, frailty, and physical function: HANDLS" that is funded from NIA through the UM-OAIC.
- Derik Davis, MD, Associate Professor of Diagnostic Radiology and Nuclear Medicine, University of Maryland School of Medicine
  Dr. Davis' current research career is focused in musculoskeletal radiology examining the effects of increased visceral adipose tissue (VAT) and reduced skeletal muscle (SMM) on cardiovascular disease (CVD), diabetes and functional outcomes in older adults. He collaborates with UM-OAIC studies performing radiology imaging and reading with Dr. Alice Ryan. He also has a R03 grant "Shoulder Pain, Rotator Cuff Tear, Coordination, and Mobility in Aging" funded by NIA.
- Derrick Larkins, DPT, PhD Candidate, PhD Student in the Department of Physical Therapy and Rehabilitation Science, University of Maryland, School of Medicine

Dr. Odessa Addison is his primary mentor, and he is interested in muscle quality and injury prevention.

- Frances Alfonzo, PhD Candidate, PhD Student, Psychology Department, University of Maryland Baltimore County
  Ms. Alfonzo's interests include relations of diabetes and pre-diabetes status to neurocognitive function. Her master's thesis project will examine potential interactive relations of prediabetes status and self-identified race to cognitive performance in midlife urban dwelling adults. Dr. Shari Waldstein currently serves as her mentor and master's thesis chair.

- Henry Asante Antwi , PhD Student, University of Maryland, School of Pharmacy
  His interest is patient-centered research and community-engaged research. His mentor is Dr. C. Daniel Mullins.

- Jennifer Kirk, BA, PhD Candidate, Gerontology PhD Student, Department of Epidemiology and Public Health, University of Maryland, School of Medicine
  Her research focus is disparities in bone health among older adults. She is currently conducting analyses using Medicare administrative claims data to estimate the impact of comorbid OSA on healthcare utilization among older adults with depression. Her dissertation title is "Individual, Neighborhood, and Provider-level Factors Associated with Racial and Ethnic Disparities in Osteoporosis Screening and Treatment." Dr. Jennifer Albrecht served as the chair of her dissertation committee and her mentor and Dr. Denise Orwig is her co-mentor.

- Lindsey Mathis, PT, DPT, PhD Student in Department of Physical Therapy and Rehabilitation Science, University of Maryland School of Medicine
  Her area of interest is: Disparities in Disability Outcomes Among Older Adults with Cardiopulmonary Disease. Dr. Jason Falvey serves as her co-primary mentor.

- Marcel Lanza, PhD, Research Associate of Physical Therapy and Rehabilitation Science, University of Maryland School of Medicine
  Dr. Lanza's area of research interest includes falls and stepping recovery and its relationship to muscle. He was recently awarded a UM-OAIC pilot study "The Effects of Neuromuscular Activity and Muscle Structure on Stepping Performance in Older Adults". He is co-mentored by Drs. Odessa Addison, Vicki Gray and Alice Ryan.

- Patrice Forrester , Postdoctoral Fellow, University of Maryland, School of Pharmacy
  Her interest is in patient-centered research and community-engaged research and she is mentored by Dr. C. Daniel Mullins.

- Pedro Rodriquez-Rivera , PhD student; Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland, School of Medicine
  He is planning to use our ABCD dataset to study substance use on brain development and Dr. Linda Chang is the Chair of his PhD thesis committee.

- Peter MacIver, PhD Candidate, PhD Student, Psychology Department, University of Maryland Baltimore County
  Mr. Maciver's interests include disparities in relations of cardiovascular risk factors to cognitive function and MRI-assessed subclinical brain pathology as a function of race and socioeconomic status. His master's thesis examined relations of arterial stiffening (assessed by pulse wave velocity) to cognitive function and associated socio-demographic variation. His dissertation will examine relations of anxiety to cerebral perfusion as a function of race and sex. Dr. Shari Waldstein currently serves as his mentor and dissertation chair.

- Ruth Akinlosotu, PT, MPH, PhD Candidate, PhD student, Predoctoral Scholar, Department of Physical Therapy and Rehabilitation Science, University of Maryland School of Medicine
  She worked with Dr. Rainer von Coelln on the analysis of Dynaport data generated during his

UM-OAIC pilot project. She was a co-author on a poster with Dr. von Coelln during a University of Maryland School of Medicine Center for Research on Aging: Aging Research Symposium and at a recent Department of Neurology Research Day. She is mentored by Dr. Kelly Westlake.

- Shaline Escarfulleri, PhD Candidate, PhD Student, Psychology Department, University of Maryland, Baltimore County
  Ms. Escarfulleri's interests include the role of emotion regulation in the relation of stress exposure and negative affect to cardiometabolic risk factors and neurocognition as a function of socioeconomic status. Her master's thesis project will examine whether the relation of SES to carotid intimal medial thickening is partially mediated by negative affect. Dr. Shari Waldstein currently serves as her mentor and master's thesis chair.

No minority grant information specified.

UNIVERSITY OF MICHIGAN
Claude D. Pepper Older Americans Independence Center

Raymond Yung, M.D.   734-647-9746   ryung@umich.edu
Principal Investigator

Ryan McCleery   734-770-8571   rmccleer@med.umich.edu
Program Administrator

CENTER DESCRIPTION

Funded by the NIA as the nations first Geriatric Research and Training Center in 1989, the University of Michigan (UM) Pepper Center has evolved to meet the objectives of the OAIC program with successful competing renewals as an OAIC in 1994, 1999, 2004, 2009, 2015, and 2020. Thus, our Center is completing its 31st consecutive year of operation in 2020. The overarching goal of the UM Pepper Center is to create, enhance and maintain a cohesive intellectual, technological, and administrative environment to maximize geriatrics research that will promote health and functional independence in older adults. Drawing on the large base of research currently underway in the fields of geriatrics and gerontology at UM, the UM Pepper Center fosters collaborative multidisciplinary research to integrate basic science, clinical science, and health services research relevant to the health care problems of older adults. The UM Pepper Center grant supports important research activities of the UM Geriatrics Center. Founded in 1987, the Geriatrics Center is the umbrella organization for geriatrics research, education, and patient care at the University of Michigan. The specific goals of the UM Pepper Center are:To support research that will improve understanding of how metabolic factors and inflammation interact with age-related diseases and comorbidities to determine key health outcomes related to mobility and functional status.

- To support translational research on the interaction of metabolic factors and inflammation with age-related diseases and comorbidities to improve health outcomes related to mobility and functional status.
- To provide Resource Cores that support and assist investigator-initiated projects related to the UM Pepper Center's research focus.
- Through its Research Education Core (REC), to strengthen the UM environment for training of future academic leaders in geriatrics and aging who can conduct research related to the UM Pepper Center's research focus.
- Through its Pilot and Exploratory Studies Core (PESC), to attract UM junior faculty, as well as selected senior faculty not previously involved in aging research, to develop new research projects related to the UM Pepper Center's research focus.

Faculty from the following UM Schools and Institutes are involved: the Institute of Gerontology, School of Public Health, Institute for Social Research, Medical School, College of Engineering, School of Nursing, School of Social Work, and College of Literature, Science, and the Arts. As of 2018 there were 89 active NIA grants at the UM with over $60 million/year of total costs. The UM OAIC's faculty participant data base includes a total of 239 current UM faculty who have 221 current external grants relevant to the UM Pepper Center's focus totaling over $57 million/year direct costs.

CORES

Leadership and Administrative Core (LAC)

<u>Leader 1:</u>   Raymond Yung, MD   ryung@med.umich.edu

<u>Leader 2:</u>   Lona Mody, MD, MSc   lonamody@umich.edu

A well-defined and effective Leadership Administrative Core (LAC) that supports the rich activities of the OAIC is already in place. The faculty and staff in the LAC have proven leadership and administrative skills. The LAC will foster critical interactions among the OAIC Program Director, the OAIC Core Directors/Co-Directors and the leadership structure of the Institution as a whole. These linkages are fostered by the proven administrative structure, which requires meetings of the OAIC leadership on a regular and ongoing basis, and of key advisory committees: the UM Geriatrics Center's Research Operating Committee (ROC) and the OAIC External Advisory Board (EAB). The ROC, led by two fellowship-trained geriatricians/physician scientists (Yung, Mody) with complementary expertise and research interests, provides strategic planning, coordination and oversight for all OAIC activities. The membership of the ROC includes the LAC Leader and Co-Leader, the former OAIC Director, the ten other OAIC Core Directors/Co-Directors, and Geriatrics Center administrative leaders.

Research Education Component (REC)

<u>Leader 1:</u>   Neil B. Alexander, MD   nalexand@med.umich.edu

<u>Leader 2:</u>   Lillian Min, MD, MSHS   lmin@umich.edu

<u>Leader 3:</u>   Carrie Karvonen-Gutierrez ckarvone@umich.edu

The overarching goal of the UM OAIC Research Education Core (REC) is to recruit, select, support, mentor, and train junior faculty to become independent investigators in aging-related research and academic leaders in geriatrics and gerontology within their respective disciplines. A key additional objective is to train the next generation of investigators about the UM OAIC focus of how metabolic factors and inflammation interact with age-related diseases to determine key health outcomes related to mobility and functional status. The REC continues to draw from a substantial pool of UM junior faculty from a wide range of disciplines across the UM campus who are doing research relevant to the OAIC focus to participate in the proposed REC training activities.

Pilot and Exploratory Studies Core (PESC)

<u>Leader 1:</u>   Lona Mody, MD   lonamody@med.umich.edu

<u>Leader 2:</u>   Mary Janevic, PhD, MPH mjanevic@umich.edu

The goal of the Pilot and Exploratory Studies Core is to provide support for studies that will develop and test new research ideas of high relevance to the Center's overall theme: "To improve understanding of how metabolic factors and inflammation interact with age-related diseases and comorbidities to determine key health outcomes related to mobility and functional status" The PESC will thus fund pilot research studies over a wide range of disciplines, ranging from basic genetics and physiology through behavioral and health services research.

Biomechanics Core (BC)

<u>Leader 1:</u>   James Ashton-Miller, PhD jaam@umich.edu

<u>Leader 2:</u>   Neil Alexander, MD   nalexand@umich.edu

The Biomechanics Core provides an array of techniques and equipment for the precise experimental quantification of physical functioning of healthy and frail elders in order to investigate attributes of the aging phenotype. It also supplies support for theoretical investigations in the form of computer simulation models to analyze the elements of those functional abilities and to establish the major determinants of abilities to perform motor acts in an effective manner. The Core is physically based in the Biomechanics Research Laboratory(link is external) (directed by Dr. Ashton-Miller) and the Mobility Research Center(link is external) (directed by Dr. Alexander). Physical disabilities are epidemic in the elderly. Whatever the underlying pathologies, these disabilities express themselves in biomechanical terms: reduced muscular strengths and rates of developing strengths, limited ranges and speeds of motion, reduced afferent feedback, inappropriate body segment coordination patterns, difficulty with balance and fall arrests, and even impaired pelvic floor and continence system function. The Biomechanics Core will contribute to the development of academic leaders in geriatrics by helping interested faculty and their fellows to analyze a range of geriatric problems through biomechanical research techniques. Thus, it will train them through directed study involving background reviews, hypothesis generation, interdisciplinary pilot research projects, and data analysis and interpretation to examine issues adversely affecting the physical abilities of the elderly.

Core Facility for Aged Rodents (CFAR)

 Leader 1:   Richard Miller, MD, PhD   millerr@umich.edu

The Core Facility for Aged Rodents, CFAR, has been a major feature of the University of Michigan Claude Pepper Center since its inception in 1989. CFAR serves the needs of Pepper Center investigators through four Specific Aims. CFAR will provide advice to all OAIC investigators, from student through faculty levels, in the use of rodents for research into the biology of aging and its role in late life disease. CFAR will support specialized colonies of mice particularly well suited for research on the biology of aging and its relationship to late-life disease. These include (a) genetically heterogeneous mice of the UM-HET3 stock; (b) calorically restricted UM-HET3 mice; and (c) mice of the long-lived Snell dwarf (dw/dw) stock, carrying the Pit1 dw mutation. Mice from these colonies will be provided to faculty members working on Pilot Studies Exploratory Core (PESC) and Research Career Development Core (RCDC) research projects, as well as to Geriatrics Center faculty members who wish to conduct pilot studies on mouse aging supported by other sources of NIA funds. CFAR funds will support the development of new animal models for specific purposes. In the first year, these will include a new four-way cross suitable for studies of late-life hearing loss.

Design, Data, and Biostatistics Core (DDBC)

 Leader 1:   Andrzej Galecki, PhD, MD   agalecki@umich.edu
 Leader 2:   Julie Bynum, M.D., M.Ph.   bynumju@umich.edu

The Design, Data, and Biostatistics Core (DDBC) will provide technical support and training of investigators developing or performing intervention and other geriatric research projects examining the aging phenotype and outcomes research. It will also develop new instruments, methodologies, and data archives to enable future studies. Thus the DDBC will both address techniques for appropriate design and execution of current experiments and set the foundation for future research studies. Building on our experience with the UM Pepper Center, the DDBC will address the needs of OAIC investigators, and especially junior investigators, for assistance in the design of intervention experiments, and the collection, maintenance, analysis, and interpretation of their data.

Human Subjects and Assessment (HSAC)

<u>Leader 1:</u>   Raymond Yung, MD   ryung@med.umich.edu

<u>Leader 2:</u>   Kenneth Langa, MD, PhD   klanga@umich.edu

The Human Subjects and Assessment Core (HSAC) supports activities involving human subjects at the University of Michigan Claude D. Pepper Center. It has four specific aims: HSAC will establish, maintain, and facilitate access to human subjects and related data sets. HSAC will expand, promote and facilitate access to minority human subjects through collaborative linkages with the Wayne State University Institute of Gerontology (WSU IoG). HSAC aims to provide selected efficient physical health measures, which will complement our existing collection of self-reported health, health care utilization, and psychosocial measures in subject selection. HSAC will provide training and consultation to investigators on issues related to (a) recruitment and retention of human subjects, and (b) measurement of quality of life and psychosocial factors closely linked with aging phenotype.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications
Haylie Miller PhD / School of Kinesiology <u>Visuomotor Integration as a Predictor of Mobility and Fall Risk in Autistic Older Adults</u>	2023-2024 / 47 (total) 18 (1st/Sr)

- K01 MH107774 Miller (PI) 07/15/2017–06/14/2023 (currently in NCE) Visuomotor Integration and Attention in Autism Spectrum Disorder
- U54 MD006882 Vishwanatha (PI), Role: sub-award principal investigator, Texas Center for Health Disparities Pilot Program 11/01/2018-12/31/2020 Preliminary Assessment of Visuomotor Profiles in Hispanic Children with Autism

Aleda Leis PhD, MS / School of Public Health <u>Advance uderstanding of the metabolic causes and effects of cardiometabolic disease, with and without obesity, and the implications for primary prevention and disease management in older adults</u>	2023-2024 / 58 (total) 2 (1st/Sr)

- 75D30122C14944 (PI: Martin) 9/1/22 – 8/31/25 Centers for Disease Control and Prevention, Subaward of Vanderbilt University Medical Center Surveillance of Acutely Ill Adults with Respiratory Viruses, including SARS-CoV-2 (IVY5) The objective of this study is to continue the current Influenza and Other Viruses in the Acutely Ill (IVY) vaccine efficacy test-negative design cohort of individuals hospitalized with influenza, COVID-19, and other respiratory diseases in Southeast Michigan. Role: Co-investigator
- 1 U01IP001193-01-00 (PI: Martin) 9/30/22 – 9/29/27 Centers for Disease Control and Prevention Michigan-Ford Initiative to Measure Vaccine Effectiveness (MFIVE): Seasonal Influenza, COVID-19 and Respiratory Virus Vaccines The objective of this study is to continue the current outpatient Michigan-Ford Influenza Vaccine Effectiveness (MFIVE) vaccine efficacy test-negative design cohort in Southeast Michigan. Role: Co-investigator
- NIH R01 AR076994-02 (PI: Whitney) 9/23/21 – 8/31/24 National Institute of Arthritis and Musculoskeletal And Skin Diseases Addressing Knowledge Gaps by Multi-Level Research Design to Optimize Clinical Trial Development in Order to Reduce Fracture Burden for Adults with Neurodevelopmental Disabilities This project will address fundamental knowledge gaps in order to improve clinical care for skeletal fragility and to optimize clinical trial design to reduce the non-trauma fracture burden for adults with neurodevelopmental disabilities
- AOTFHSR21Whitney (PI: Whitney) 7/1/21 – 6/30/23 American Occupational Therapy Foundation The Effect of Rehabilitation Utilization on Risk of Fragility Fracture and its Related Disease, Mortality, and Healthcare Cost Burden for Adults with Cerebral Palsy: Providing Actionable Information to Inform Rehabilitation Efforts This project will examine rehabilitation patterns and their implication in prevention of fragility fractures and associated adverse downstream clinical effects of fracture.
- 1 U19AG063720-01A1 (MPI: Brooks (contact); Karvonen-Gutierrez; Burnett-Bowie; Derby; Hedderson; Janssen; Karlamangla; McConnell; Thurston; Waetjen) 9/30/20 – 8/31/24 National Institute on Aging (NIA), Subaward of University of Pittsburgh The Study of Women's Health Across the Nation (SWAN): The Impact of Midlife and the Menopause Transition on Health and Functioning in Early Old Age This project will build upon the resources of the Study of Women's Health Across the Nation (SWAN) to quantify the impact of ovarian aging, the Menopausal Transition and the midlife on successful aging.
- NIH R01 AR068452-01 (PI: Jepsen) 8/1/18 – 7/31/23 National Institute of Arthritis and Musculoskeletal and Skin Diseases Changes in Periosteal and Endocortical Width Across the Menopausal Transition This proposal seeks to better elucidate the structural changes that underlie loss in strength during the Menopausal Transition by examining relative changes in endocortical

expansion (bone loss) versus periosteal expansion (bone gain).

Emily Briceno, Ph.D.	2021-2023 /
Clinical Assistant Professor / Department of Physical Medicine & Rehabilitation	4 (total)
<u>Measurement of cognition across language and education among Mexican American and non-Hispanic white older adults</u>	2 (1st/Sr)
Joseph Endicott, M.D.	2022-2023 /
Research Investigator / Department of Pathology	3 (total)
<u>Metabolic reprogramming by chaperone-mediated autophagy downstream of the lifespan-extending PTEN transgene</u>	3 (1st/Sr)
David Flood, M.D., M.Sc.	2022-2023 /
Clinical Instructor / Department of Internal Medicine	4 (total)
<u>Cross-national comparisons of disability among older adults with diabetes in 23 countries</u>	2 (1st/Sr)
Victoria Powell, M.D.	2022-2023 /
Clinical Instructor / Division of Geriatric and Palliative Medicine	31 (total)
<u>Recruiting Older Adult Research Participants: Considerations, Sources, and Methods</u>	17 (1st/Sr)

Past Scholars

Marco Cassone, MD, PhD, University of Michigan, Geriatrics & Palliative Medicine (2018-2020)
Jaclynn Hawkins, University of Michigan School of Social Work (2019-2020)
Xiaoling Xiang, University of Michigan School of Social Work (2019-2021)
Jiha Lee, MD, MHS, University of Michigan (2019-2021)
Matthew Pianko, M.D., Department of Internal Medicine (2021-2022)
Michael Smith, PharmD, Department of Pharmacy (2021-2022)

PILOT/EXPLORATORY PROJECTS (12 Pilot Projects Listed)

1. Project Title:	**Viral Infection Burden and Immunosenescence**
Leader:	**Grace Noppert, Ph.D.**

LAC Year 17 (7/1/21-6/30/22) *RAPID PILOT* Adults aged 65+ years account for 45% of hospitalizations and 53% of intensive care admissions due to COVID-19 despite comprising 17% of the U.S. population. The systemic hyperinflammatory response is a key feature observed in many severe cases of COVID-19 and may signal an underlying immunopathology related to substantial T cell stimulation. This immunopathology is likely an indication of advanced immunological age, or immunosenescence. irhe mechanisms underlying the increased risk for severe outcomes, including mortality, from COVID-19 among older adults are still being elucidated. Emerging evidence suggests that viral infections may accelerate the pace of immunosenescence. However, significant questions remain With regards to the role of viral co-infections, differential immune control of viral infections, and the ??pecific changes in the immune compartment induced by viral infections. Our long-term goal is to examine the role of viral infections in driving population-level patterns of immunosenescence. The overall obiective of the current application is to characterize the viral burden resulting from five herpesviruses by examining both seropositivity to each virus as well as antibody level with higher antibody levels reflecting worse immune control of the virus and thus a greater burden to the immune system. Using previously collected human samples from the University of Michigan's Central Biorepository, we will first characterize the viral infection burden to five human herpesesviruses and describe differences by age, race/ethnicity, and gender (Aim 1). We will then estimate whether viral infection burden is associated with advanced immunosenescence in the T cell compartment (Aim 2). At its conclusion, these pilot data will shed further light on the immune parameters most likely to be affected by viral infections. Ultimately, the goal of this work to provide insights into future development of interventions that can address long-term immune consequences older adults are likely to continue to face due to viral infections.

2. Project Title:	**Cross-national comparisons of disability among older adults with diabetes in 23 countries**
Leader:	**David Flood, M.D., M.Sc.**

PESC Year 18 (7/1/22-6/30/23) Diabetes is one of the most critical worldwide health issues for older adults. Research largely from high-income countries has shown that diabetes is associated with an increased risk of disability among older adults. However, there is limited understanding of how prevalence of disability among older adults with diabetes may be similar or different across the world. The objective of this pilot project is to assess cross-national patterns of disability among older adults with diabetes by leveraging the Global Gateway to Aging, an NIA-funded platform of harmonized data from international cohorts aligned with the U.S. Health and Retirement Study. Aim 1 will augment the Gateway to Global Aging platform by developing a harmonized measure of diabetes status in 23 countries that incorporates both questionnaire and blood-based biomarker data. Aim 2 will assess cross-national patterns of disability among older adults using the augmented Gateway to Global Aging dataset developed in Aim 1. This proposal's focus strongly aligns with the Pepper Center's overarching mission and will take advantage of unique expertise at the University of Michigan through interaction with Dr. Kenneth Langa (Human Subjects and Assessment Core) and Dr. Andrzej Galecki (Design, Data, and Biostatistics Core). If funded, this project will assist Dr. Flood's career goal

of developing expertise to conduct independent aging research.

3. Project Title: **Metabolic reprogramming by chaperone-mediated autophagy downstream of the lifespan-extending PTEN transgene**

Leader: **Joseph Endicott, Ph.D.**

PESC Year 18 (7/1/22-6/30/23) Maintaining the balance between glycolysis and oxidative phosphorylation is essential for disease-free aging. Oxidative capacity declines with age across diverse animal models, and compensatory increases in glycolysis have been hypothesized to contribute to a "Warburg transition" which makes aging mammals more susceptible to cancer. Global overexpression (OE) in mice of PTEN, an antagonist of the INS/PI3K/AKT pathway, shifts metabolism to favor oxidative phosphorylation over glycolysis and extends lifespan of male and female mice. Our unpublished work has found: (1) PTEN OE enhances chaperone-mediated autophagy (CMA); (2) In a CMA-dependent manner, PTEN negatively regulates proteins involved in glycolysis (PKLR and TKFC), and proteins that drain mitochondria of TCA cycle metabolites aketoglutarate and citrate to generate cytoplasmic acetyl-coA (IDH1 and ACLY); (3) a decrease in the hepatic abundance of these acetyl-coA and glycolysis enzymes is common to several longlived mouse models. These data suggest the hypothesis that enhanced CMA, downstream of PTEN, promotes a shift in energy production to favor oxidative phosphorylation over glycolysis by selective degradation of ACLY, IDH1, PKLR and TKFC. This hypothesis will be evaluated in two Specific Aims: (1) Characterize the mechanism through which CMA regulates the balance between glycolysis and oxidative phosphorylation, downstream of PTEN, and (2) Evaluate lysosomal targeting of glycolysis and cytoplasmic acetyl-coA enzymes in PTEN OE and PTEN KO mice. We anticipate that successful completion of this project will demonstrate an important mechanistic link between CMA and the longevity promoting PTEN transgene, providing a strong justification for future grant applications developing CMA-enhancing drugs for modulating aging.

4. Project Title: **Intersection of Insomnia and Centralized Pain in Older Adults: Effects on Medication Use**

Leader: **Michael Smith, Pharm.D.**

PESC Year 18 (7/1/22-6/30/23) Insomnia and centralized pain are common and difficult to manage in older adults. Medications used to treat these conditions are included in the American Geriatrics Society Beers Criteria® for Potentially Inappropriate Medication (PIM) Use in Older Adults. Use of PIMs for these conditions is associated with poor outcomes, including increased risk of mortality. Our central hypothesis is that centralized pain in older adults with insomnia will confer a greater PIM burden than insomnia alone. Since both chronic pain and insomnia individually are associated with increased PIM use, it is likely that co-occurrence of these conditions would be associated with greater likelihood of PIM use. The primary objective of this pilot study is to understand medication use in the context of how increasing age mediates the interaction between insomnia and centralized pain. This will be achieved through the following Specific Aims: Aim 1: Determine the effect of age on rates of centralized pain in older adults with insomnia. H1: Increasing age will be associated with greater likelihood of centralized pain in older adults with insomnia. This quantitative aim will utilize a newly validated method (Schrepf et al. 2020) to quantify the proportion of older adults ? 55 years of age, stratified by age group, with insomnia who have co-occurring centralized pain using University of Michigan Health System Electronic Health Record (EHR) data. Aim 2: Quantify

the effect of centralized pain on PIM use in older adults with insomnia. H2: Older adults with both centralized pain and insomnia will have greater PIM burden, quantified using the Drug Burden Index (DBI), than those with insomnia alone. This quantitative aim will advance the previous method using centralized pain diagnosis codes combined with a validated measure to determine the burden of anticholinergic and sedative use in older adults with insomnia and centralized pain. This study will provide a targeted population and baseline medication risk description for future intervention studies.

5. Project Title: **Cross-national comparisons of disability among older adults with diabetes in 23 countries**

Leader: **Shen Dewar, M.D.**

PESC Year 18 (7/1/22-6/30/23) Obesity is a growing health problem and current models of obesity care are limited in older adults. Despite the unique health care needs of older adults with obesity, currently there is no evidence-based model for this age group to manage obesity and associated disability (such as in mobility), symptoms (such as pain), multiple health issues due to long term effects of obesity (such as heart failure), and care complexity related to social determinants of health. As proof of concept, PI Dewar developed the Optimal Health, Weight, and Lifestyle (OHWL) clinic to optimize treatment of comorbid health conditions, physical function and diet in older adults with obesity. Only 1/3 of the 44 initial participants were adherent to medical specialist and therapist referrals. The remaining patients faced challenges such as lack of support for adherence to lifestyle change, low self-efficacy, and poor linkage to community resources. To address these barriers, a more comprehensive OHWL Program is proposed that features three primary components: 1) an OHWL Care Provider (oriented to obesity-centered older adult care); 2) an OHWL care manager (to assess and guide the custom intervention); and 3) a social worker to provide linkage to community resources as well as caregiver support/education. The goal of this PESC pilot is to test the feasibility and preliminary outcomes of this new model of care for older adults with obesity. In older adults (n=40, aged ?60) with obesity (BMI?35), and at least 2 obesity related comorbidities, aims in this PESC pilot are to: 1) Evaluate extent of changes in key quantitative outcomes (such as mobility and pain); and 2) Conduct a mixed methods process evaluation, guided by the RE-AIM model, of program feasibility, barriers and facilitators. The goal of the OHWL Program is to promote a patient-centered model of care to improve the functioning and quality of life of older adults with obesity, especially those from vulnerable populations who face barriers to lifestyle change. These pilot data will inform the creation of materials for a larger NIA-funded trial to be led by PI Dewar and mentors Alexander and Janevic as MPIs, to demonstrate scalability, efficacy, and costeffectiveness of this new model.

6. Project Title: **Establishment of aged microbiota in germ free mice**

Leader: **Vincent Young, M.D., Ph.D.**

LAC Year 17 (7/1/21-6/30/23) *RAPID PILOT* The normal microbe populations of the gut contribute to fostering immune system maturation, digestion assistance, and protection against pathogen invasion. Many age-associated conditions such as cardiovascular disease, cancer, and diabetes have been associated with abnormal host-microbe interactions. Elderly individuals are also moresusceptible to Clostridiodes difficile with an increased risk of developing disease-related complications. We are specifically interested in understanding how age-relatedchanges in the microbiota affect the outcomes of infection with Clostridioides difficile.

7. Project Title: **Inflammation and the risk for cognitive decline and dementia after COVID-19**

Leader: **Natalie Tronson, Ph.D.**

PESC Year 17 (7/1/21-6/30/22) Illness and stress are common risk factors for age-related cognitive decline, Alzheimer's Disease, and other dementias, likely via activation of neuroimmune inflammatory pathways in the brain. This has been difficult to study, however, because altered neuroinflammation is also a consequence of aging and of neurodegeneration. We have recently developed a mouse model within which to study the persistent consequences of immune challenge on memory, and in this project propose to apply this model to understand how transient illness during midlife increases risk for later, age-related cognitive decline, memory impairments, and dementia. Here, we will develop modified protocols to specifically examine COVID-19-like inflammatory pathways on memory across adulthood. COVID-19 is of particular relevance for cognitive decline and dementias because, unlike other illnesses including influenza, many patients experience a post-acute COVID-19 syndrome that includes memory impairments and "brain fog". Given the immense number of people affected by COVID-19, the pandemic is likely to dramatically increase the number of people impacted by age-related cognitive decline and dementias in the years to come. Here, we will determine whether and how single-stranded RNA (ssRNA)-viral mimic triggered inflammation accelerates aging-related cognitive decline in males and females long after resolution of illness.

8. Project Title: **The gut microbiome as a mediator of age-related changes in fever response in sepsis**

Leader: **Rishi Chanderraj**

Aging results in a blunted fever response in sepsis, which predicts adverse clinical outcomes. Fever response is a readily-measured index of systemic inflammation and metabolism. I have recently shown that gut microbiota (specifically Lachnospiraceae, a prominent producer of systemically-active metabolites), influences temperature response in humans and animal models. I have also shown that anti-anaerobic antibiotics 1) cause greater microbiome disruption than other antibiotics and 2) increase patient risk of mortality. The central hypothesis of this proposal is that age-related changes in the immune response and metabolic response in sepsis are mediated by gut microbiota. The specific objectives of the study are to: 1) determine how aging modulates the relationship between gut microbiota and fever response and 2) determine how gut anaerobe depletion modulates temperature response in geriatric patients with sepsis.

9. Project Title: **Visuomotor Integration as a Predictor of Mobility and Fall Risk in Autistic Older Adults**

Leader: **Haylie Miller**

Our study objective is to quantify effects of visuomotor integration on postural control, falls, and mobility in autistic vs. neurotypical older adults, accounting for cognitive, sensory, and physical capacities. To do this, we will use our computer vision algorithm to analyze multimodal visuomotor data during experimental tasks with varying demands. We have separate sets of preliminary data showing that autistic children, adolescents, and young adults have unstable postural control and eye movement, a high rate of falls, and functional mobility

problems, but there are knowledge gaps in the relationship between these domains and their presentation in older adulthood. Our central hypothesis, informed by these data, is that cognitive skills mediate the relationship between the autistic phenotype of sensory/physical capacities and falls/mobility problems.

10. Project Title: **Exploring the Relationship between the Social Determinants of Health and Systemic Markers of Mitochondrial Bioenergetics Among Older Adults**

Leader: **Kate Duchowny**

The social determinants of health (SDOH), defined as the conditions by which people are born, grow, live work and age, are strongly associated with individual and population health outcomes across the life course. Despite the critical role the SDOH play in shaping health and well-being, the specific mechanisms by which social factors influence biologic properties of aging remains poorly understood. Recent work on mitochondrial function offers promise as a cellular mechanism by which the social determinants become biologically embedded and may therefore be implicated in long-standing inequities in aging-related decline and disease. However, to date, our understanding of mitochondrial function as a key biologic mechanism to aging has been hampered by methodological challenges. This proposal addresses these obstacles by leveraging blood-based markers of mitochondrial bioenergetics via the respirometry in frozen samples (RIFS) method while also linking these measures to the SDOH. Our approach offers a unique opportunity to harness cost-effective and minimally invasive techniques from frozen blood while laying the groundwork for larger-scale, population health studies. Our overall objective is to examine whether novel systemic markers of mitochondrial bioenergetics derived from frozen blood samples are associated with chronologic age and key social determinants of health.

11. Project Title: **Detection and Prediction of Mild Cognitive Impairment in Seniors with Memory Complaints**

Leader: **Tongtong Li**

Developing economically viable assessment tools and biomarkers that are highly sensitive to cognitive decline and neural dysfunction, before frank Alzheimer's disease (AD) pathology, is critical for the study of neurodegenerative mechanisms and interventions to promote cognitive resiliency. In this interdisciplinary research, taking the brain as a communication network, our goal is to develop a cost effective, highly sensitive and reliable tool for early detection of people at risk for mild cognitive impairment (MCI), based on EEG data and neuropsychological assessments and by exploiting advanced techniques in communication networking, information theory and artificial intelligence.

12. Project Title: **Assessing CT-based Biomarkers of Cardiovascular Disease in Older Adults**

Leader: **Steven Horbal**

Cardiovascular disease is attributed to 1 in 4 deaths United States. Among theses deaths, 50% have no prior clinical symptoms or diagnosis. Most major cardiovascular events, even in older individuals, are preventable through the early identification and mitigation of modifiable risk factors. The fundamental tenet of primary prevention is that treatment decisions are carefully matched by accurate risk assessments. Biomarkers obtained from medical imaging can provide detailed body composition information that may improve cardiovascular risk prediction models. Among other biomarkers and methodologies, aortic calcification is an emerging clinical correlate that shows strong promise in preventative surveillance of clinical populations. Aortic calcification can be extracted from abdominal computed tomography scans, contextualized among population-level cohorts, and added to cardiovascular risk prediction models. Further investigation of clinically relevant populations is necessary to strengthen the internal and external validity of aortic calcification and other biomarkers of aging. This study will develop a cohort of 8000+ participants with abdominal CT-scans and are over the age of 65.

DEVELOPMENT PROJECTS (2 Development Projects Listed)

1. **Project Title:**   **Software tools for extracting data from HRS database**
   Leader: **Andrzej Galecki; Julie Bynum**
   Core(s):   Design, Data, and Biostatistics Core (DDBC)

   Core Development Project is designed to develop and maintain a library of SAS macros and functions that can be used by researchers to derive commonly used variables in Health Retirement Study. The goal is developing streamlined SAS codes using SAS Function Compiler (FCMP) procedure that could be used by researchers to extract data directly from the HRS raw datasets. Tools developed for this project have a potential to be implemented in international HRS-like dataset, including data from US, England, SHARE (European Countries), China, Mexico, South Korea, Japan, and South Africa.

2. **Project Title: Develop a real time sensor to detect hyponatremia**
   Leader: **James Ashton-Miller**
   Core(s):   Biomechanics Core (BC)

   Develop a real time sensor to detect hyponatremia

RESEARCH (25 Projects Listed)

1. Project Title: **AZD1222 Vaccine Trial: A Phase III Randomized, Double-blind, Placebo-controlled Multicenter Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vaccine for the Prevention of COVID-19**

Leader(s): **LUGOGO, NJIRA**
UNIVERSITY AT MICHIGAN AT ANN ARBOR
ASTRAZENECA PLC / (2020 - 2023)

Core(s):

The University of Michigan is a site for this clinical trial and 200 subjects are anticipated for the Main Study, 70 are anticipated for the Sub-Study and 20 are anticipated for the Illness Visits. The aim of the study is to assess the safety, efficacy, and immunogenicity of AZD1222 for the prevention of COVID-19. The COVID-19 pandemic has caused major disruption to healthcare systems with significant socioeconomic impacts. Currently, there are no specific treatments available against COVID-19 and accelerated vaccine development is urgently needed. A safe and effective vaccine for COVID-19 prevention would have significant public health impact.

2. Project Title: **LEVERAGING SOCIAL NETWORKS: A NOVEL PHYSICAL ACTIVITY INTERVENTION FOR SENIOR HOUSING**

Leader(s): **WEBSTER, NOAH JAMES**
UNIVERSITY OF MICHIGAN AT ANN ARBOR
NIH K01AG062754 / (2020 - 2024)

Core(s):

This K01 application proposes career development and research activities customized to facilitate the candidates (Dr. Noah Webster) transition from conducting basic social science research to behavioral intervention research. The candidates long-term career goals include becoming an independent research scientist conducting research aimed at: a) improving the health and independence of older adults; and b) reducing later life health disparities. This will involve developing, testing, implementing, and disseminating a social network-based intervention to improve participation in behavioral health (e.g., physical activity) interventions within low resource settings. Career Development/Training Aims: In order to accomplish career goals the candidate is in need of targeted and interdisciplinary training in: 1) intervention development; 2) intervention evaluation; and 3) objective assessment of physical activity. This training will be facilitated through coursework and interactions with an interdisciplinary mentoring team led by Dr. Neil Alexander. Training Environment: The candidate is situated within the largest academically-based social science institute in the world. The resources available to him at the Institute for Social Research as well as the University of Michigans Schools of Medicine and Public Health together offer an unparalleled supportive and stimulating environment for conducting research at the intersection of social science and intervention research. Research Aims: While only 16% of people age 65+ engage in recommended physical activity levels, increases may be achieved through activation of social resources. A social network-based approach that systematically identifies and involves influential agents of change in a community is proposed to facilitate physical activity-related information dissemination and behavior change. This project will leverage Go4Life, NIAs evidence-based physical activity campaign and capitalize on the strength of social ties. The intervention addresses socio- economically linked health disparities by developing the intervention for use in affordable (HUD subsidized) senior housing. The project will address three specific aims: Aim 1) Identify agents of change in an affordable senior housing community who will then be invited to form a committee to disseminate Go4Life materials through planning, publicizing, and participating in community-wide activities over 12 months. Aim 2) Evaluate intervention feasibility using a mixed methods approach. Aim 3) Establish preliminary network effect on changes in physical activity and identify influential network mechanisms. The proposed feasibility study is the first step in using locally available and low-cost resources to affect behavior change among socio-economically vulnerable senior housing residents. In the short-term, findings will provide preliminary data to conduct a multi- site efficacy trial which will implement and evaluate successful components of the intervention. In the long- term, understanding how to leverage social networks to promote and sustain increases in physical activity will provide key information to advance the science of behavior change as well as reduce health disparities.

3. Project Title: **Measurement of cognition and functional decline in Latinx older adults for detection of Alzheimer?s Disease and Related Dementias: A mixed-methods approach**

Leader(s): **BRICENO, EMILY MARIE**

UNIVERSITY OF MICHIGAN AT ANN ARBOR

NIH K23AG080035 / (2023 - 2028)

Core(s):

Accurate and valid measurement of cognitive and functional decline for the detection of Alzheimer s Disease and Related Dementias (AD/ADRD) in Latino/a/x older adults is a critical public health priority. The Latinx population is rapidly growing and aging in the U.S. with enormous expected growth of AD/ADRD in older Latinx adults in the coming years. It is unknown whether cognitive assessment instruments measure cognitive health with equal precision and validity across Latinx and non-Latinx white (NLW) older adults, which is a critical barrier to the accurate detection of AD/ADRD, its determinants, and its impact. This study will use a mixed-methods approach to evaluate the validity and equivalence of measures of cognitive and functional decline in Latinx and NLW older adults, using the Harmonized Cognitive Assessment Protocol (HCAP) cognitive test battery (HCAP-R) and informant ratings of cognitive and functional decline (HCAP-I). Specific Aim 1 will examine the extent to which the HCAP-R and HCAP-I exhibit statistical evidence of measurement bias across years of education, assessment language (English/Spanish), and ethnicity (Latinx/NLW), using a series of psychometric analyses. Data from the Health and Retirement Study (HRS)-HCAP study will be combined with data from the Brain Attack Surveillance in Corpus Christi (BASIC)-Cognitive study for this analysis. Specific Aim 2 will utilize longitudinal data from the BASIC-Cognitive study to examine whether the HCAP-R is equally predictive of longitudinal trajectories of informant-rated cognitive and functional decline (HCAP-I) between Latinx and NLW older adults and whether adjustment for statistical measurement bias eliminates any differences in this predictive equivalence. Specific Aim 3 will perform new data collection using a qualitative methodology (cognitive interviewing) to examine the linguistic and cultural validity of HCAP-R and HCAP-I items in a sample of Mexican American older adults with varying levels of education and Spanish language use. These data will provide a novel integration of mixed methods (psychometric, longitudinal prediction of cognitive and functional decline, and qualitative) to inform the equivalence and validity of the HCAP across culturally, linguistically, and educationally diverse older adults. This K23 program will provide PI Dr. Brice o with training to develop expertise in psychometric and longitudinal data analysis, qualitative research, population-based cognitive aging and health disparities research, and research leadership. Training will occur through individual mentoring, formal workshops and seminars, and international conferences. The K23 mentors are international leaders in Latinx brain health equity, psychometrics, population-based cognitive aging, and cross-cultural neuropsychological assessment of AD/ADRD. The K23 will provide Dr. Brice o with expertise and preliminary data to submit an R01 and to become an independent researcher in cognitive health disparities in AD/ADRD. The University of Michigan provides an ideal environment to conduct the proposed research and career development, with abundant resources, facilities, training opportunities, and collaboration.

4. Project Title: **Ectonucleotidase modulation of age-dependent vascular calcification and stiffness**

Leader(s): **SUTTON, NADIA RAZAQ**

UNIVERSITY OF MICHIGAN AT ANN ARBOR

NIH K76AG064426 / (2020 - 2025)

Core(s):

Abstract With increasing age, blood vessels become stiffer and more calcified. In the latter years of the human lifespan, the process of vascular aging accelerates. The reason that blood vessels lose their youthful elasticity and ability to retard the deposition of calcium precipitously later in life is poorly understood. Ectonucleotidases are found on the surface of endothelial cells which line the inner surface of blood vessels, vascular smooth muscle cells, and leukocytes. The ectonucleotidase CD39 is responsible for cleaving ATP and ADP to form AMP, and subsequently, CD73 is responsible for generating adenosine from AMP. Since ATP and ADP are pro- inflammatory and act in a paracrine fashion, I hypothesize that ectonucleotidase activity plays a role in the vascular stiffness and calcification that occurs as a consequence of age. This is supported by my preliminary data in wild type (C57BL/6) mice, which demonstrates CD73 protein levels declined with age (up to 24 months) in the heart and kidney. This is also supported by preliminary data in mice and human tissues demonstrating that loss of CD73 expression promoted expression of the transcription factor Runx2, which is critical for osteogenesis. We hypothesize that loss of ectonucleotidase expression with age could have deleterious consequences on the

vessel wall, resulting in an environment which promotes vascular calcification and stiffness. Since the role of ectonucleotidases in vascular aging is unknown, we will elucidate mechanisms which mediate age-dependent vascular calcification through the following aims. Aim 1: We will determine how age-dependent decline in vascular ectonucleotidase expression renders vessels susceptible to vascular calcification and fibrosis in a murine model. Aim 2: We will determine how ectonucleotidase activity mitigates arterial fibrosis and stiffness. Aim 3: We will determine if ectonucleotidase expression plays a role in age-driven human coronary artery calcification. Achievement of these aims will elucidate the role of ectonucleotidases in age-dependent vascular calcification and stiffness in mice and humans. The mechanistic insights obtained from these experiments will define my future investigative direction and serve as a foundation for a subsequent RO1 application as an independent investigator studying vascular biology and aging.

5. Project Title: Multicenter clinical trial of telehealth vs. in-person delivery of palliative care to Stage IV lung cancer patients

Leader(s):   **SILVEIRA, MARIA**

UNIVERSITY AT MICHIGAN AT ANN ARBOR

PCORI PLC-1609-35995 / (2018 - 2024)

Core(s):

Early and longitudinal involvement of palliative care (PC) in the outpatient management of patients with advanced cancer improves patient-reported and end of life (EOL) care outcomes. While recommended by national organizations as the standard of care, this early integrated care model utilizes substantial PC resources, which has limited its dissemination across care settings. Telehealth (i.e., the use of information and communication technology in health care delivery) is an effective strategy to increase patients access to health care services when the numbers of specialty-trained clinicians are limited. We seek to perform a multi-site comparative effectiveness trial of early integrated telehealth versus in-person PC in patients with advanced lung cancer. By demonstrating the equivalence of the telehealth delivery modality, we seek to define a role for this more accessible, scalable and patient-centered approach to PC.

6. Project Title: Immunosenescence, socioeconomic disadvantage and dementia in the US aging population

Leader(s):   **NOPPERT, GRACE A; AIELLO, ALLISON E;**

UNIVERSITY OF MICHIGAN AT ANN ARBOR

NIH R01AG075719 / (2022 - 2026)

Core(s):

While risk factors for cognitive decline and Alzheimer's Disease and related dementias (ADRD) have been widely studied, there is still much unknown about the biological pathways that lead to ADRD. This project seeks to improve our understanding of the pathophysiology of cognitive decline and ADRD by examining the role of peripheral immunosenescence in these processes. A major gap in existing research is a lack of longitudinal studies that can establish an etiologic link between peripheral immunosenescence and development of incident ADRD. In addition, there are few population-based studies examining these processes in U.S. representative samples. Population-based studies can evaluate whether clinical findings among ADRD patients are generalizable to the broader population as well as examine the role of social determinants in these processes. Despite consistently observed social inequalities in ADRD, including on the basis of race/ethnicity, sex/gender, and socioeconomic status, the pathways by which social disadvantage lead to ADRD are not well understood, limiting population-wide ADRD prevention strategies. Our long-term goal is to elucidate the role of population immunity in predicting ADRD. The overall objective of the current proposal is to evaluate the relationship between peripheral immunosenescence and domain-specific cognitive function, decline, and ADRD diagnoses in a nationally representative sample of older US adults, and, to examine the extent to which immunosenescence explains social inequalities in cognitive function, decline, and ADRD. Our central hypothesis is that immunosenescence, characterized by an increased number of senescent immune cells (e.g., CD8+CD45RA-, CD4+CD45RA-) and elevated inflammatory cytokines (C-Reactive Protein (CRP), interleukin (IL)-6, TNF-alpha) will be associated with worse cognitive outcomes, and that immunosenescence will partially explain some of the social inequalities in cognitive outcomes. The rationale for the proposed research is that immunosenescence may be an important early risk factor for ADRD, potentially representing a biological mechanism explaining population heterogeneity and inequalities in ADRD risk. To investigate these relationships, we will pursue three specific aims:1) Determine the association between peripheral immunosenescence and cognitive function and decline in the Health and Retirement Study (HRS); 2) Determine the association between peripheral

immunosenescence and incident ADRD measured both by HRS cognitive assessment and linked Medicare claim data; and 3) Determine the extent to which immunosenescence explains social inequalities in cognitive function, decline, and ADRD. This proposal is innovative as it will be the first large-scale population-based study of immunity and cognition. It will yield critical insights to our understanding of the pathophysiology of cognitive decline and ADRD, and inequalities in these processes. This project is significant because the results could point to new diagnostic tools able to discern profiles of immunosenescence predictive of ADRD in the peripheral blood.

7. Project Title: Regional genomic epidemiology to identify drivers of resistance, transmission and infection with carbapenem-resistant Klebsiella pneumoniae

Leader(s):   **SNITKIN, EVAN**
UNIVERSITY OF MICHIGAN AT ANN ARBOR
NIH R01AI148259 / (2020 - 2024)

Core(s):

The emergence and worldwide dissemination of antibiotic resistant organisms represents a significant threat to global public health. An organism that epitomizes both the urgency and challenges associated with this threat is carbapenem-resistant Klebsiella pneumoniae (CRKP). CRKP was first observed in a clinical case in 1996 in a hospital in North Carolina. Since that time, successful lineages of CRKP have spread across the globe, becoming endemic in healthcare networks in many regions. This increasing prevalence of CRKP poses a great risk to hospitalized patients, as crude mortality rates for CRKP infections can be upwards of 50%. Moreover, the threat associated with CRKP continues to escalate, with numerous reports of CRKP that are resistant to even last-line antibiotics, leaving affected patients with limited treatment options. The seriousness of the CRKP epidemic has led to both the U.S. Centers for Disease Control and the World Health Organization ranking it as their most urgent antibiotic resistant threat. However, despite the attention given to CRKP, it remains highly prevalent in many areas. Our central hypothesis is that our inability to effectively control CRKP, as well as other urgent antibiotic resistant threats, is due to a lack of understanding of the clinical and epidemiologic factors that drive the emergence and spread of antibiotic resistant organisms across regional healthcare networks. Here, we seek to overcome this knowledge gap by first applying whole-genome sequencing to construct regional transmission networks for CRKP, and then overlaying rich epidemiologic and clinical meta-data to identify drivers of transmission, resistance evolution and infection across regional healthcare facilities. These goals will be accomplished through the following three aims: 1) apply phylogenetic methods to reconstruct regional transmission networks, and perform data analysis and modeling to identify drivers of transmission within and between hospitals, 2) identify genetic determinants of resistance to last line antibiotics and analyze in the context of the regional transmission network and clinical metadata to identify factors associated with both the evolution and acquisition of resistance and 3) identify genetic determinants associated with CRKP infection and analyze in the context of the regional transmission networks and patient meta-data to identify virulent sub-lineages and convergent variation that are associated with poor patient outcomes. The totality of these aims will provide critical insight into the factors driving transmission, resistance evolution and infection with CRKP as it spreads across regional healthcare networks. Moreover, we believe our approach of integrating genomic, clinical and epidemiologic data to study the proliferation of antibiotic resistant threats at a regional level can be applied in other contexts to help guide regional infection prevention.

8. Project Title: Leveraging large-scale national data to understand, reduce, and prevent benzodiazepine-related harms among older adults

Leader(s):   **MAUST, DONOVAN T**
UNIVERSITY OF MICHIGAN AT ANN ARBOR
NIH R01DA045705 / (2018 - 2023)

Core(s):

Benzodiazepine (BZD) use in the U.S. is common and increases with age. In a recent analysis, 8.7% of adults aged 65-80 years were prescribed BZDs during one year, even though a robust set of studies have established their association with a variety of adverse outcomes in older adults, including increased risk of falls and fractures, motor vehicle accidents, impaired cognition, and pharmaceutical overdose. Patients and their providers are then reluctant to change use once started, which may account for why older adults experience the highest rates of long-term BZD use. Relatively little is known about the patient, provider, and community characteristics associated with starting and continuing BZD prescribing to older adults, yet this is critical to develop effective selective and indicated prevention strategies. In Aim 1, we will describe the patient,

provider, and community characteristics associated with BZD initiation and continuation using a national 20% sample of Medicare beneficiaries (n=3.6 million) linked to provider data from the American Medical Association (AMA) Physician Masterfile and community characteristics from the Area Health Resources File (AHRF). We will extend our analysis with OptumInsight data (n=6.7 million) to gain additional insights among commercially insured adults aged 50-64 given increased substance use among the Baby Boom cohort. Those patients currently prescribed BZDs and most at risk for BZD misuse (e.g., overlapping BZD prescriptions from multiple providers) and BZD-related overdose should receive indicated prevention strategies to address this potentially harmful use. In Aim 2, among those prescribed BZD, we will determine specific risk factors associated with BZD misuse and BZD-related overdose; these data will be used to develop a misuse clinical prediction tool. Using BZD users 50+ years old identified in Medicare and Optum, we will determine characteristics of patients and their prescribed BZD (e.g., high potency) most associated with misuse and overdose. We will then use machine learning to create a simple clinical prediction tool that providers can use to identify older adults at risk for misuse in their practices. Finally, in Aim 3 we will conduct semi-structured interviews with providers and patients to package and script the use of the clinical prediction tool for providers seeking to engage high-risk BZD use patients. This aim is critical to improve the impact of our findings since psychological dependence on BZD can make reducing use a difficult topic for physicians and patients to address. We will conduct interviews with providers and older adult primary care patients (n=15 each) to obtain feedback to package and script the use of the clinical prediction tool, which we will make publicly available by website. The impact of our work will be to: 1) provide a detailed, national portrait of the factors that contribute to BZD use and misuse; 2) determine the older adults most at risk for serious adverse events; and 3) develop and package a clinical prediction tool to help providers address BZD use in their high-risk patients.

9. Project Title: **Understanding the role of the Complement Proteome in progressive Diabetic Kidney Disease**

Leader(s):   **NIEWCZAS, MONIKA ANNA**
JOSLIN DIABETES CENTER
NIH R01DK123459 / (2020 - 2025)

Core(s):

PROJECT SUMMARY / ABSTRACT There is a critical need to identify novel mechanisms of diabetic kidney disease (DKD) that will provide targets for new interventions. Chronic inflammation is one plausible mechanism. Using untargeted high-throughput aptamer proteomics, our recently published study has shed new light on specific, key inflammatory drivers of DKD. This was a large prospective three-cohort study that identified a novel and extremely robust circulating signature (KRIS) associated with risk of ESRD in diabetes. Our pilot study points to the data-driven connection between circulating KRIS and urinary profiles of the Complement pathway. Our hypothesis is that the Complement involvement in the kidney is a downstream effect of the systemic inflammatory processes mediating an increased DKD risk. The overarching goal of this proposal is to provide a high-resolution view of the involvement of the Complement proteome in progressive diabetic kidney disease. Aim 1 will comprehensively evaluate the etiological role of the urinary Complement proteome in progressive DKD leading to ESRD. This evaluation will leverage a prospective two-cohort population of Joslin Kidney Study (JKS) participants with an overt DKD at baseline followed for 10 years (primary outcome incident ESRD). Measurements will utilize an aptamer proteomic technology (SOMAscan). Aim 2 will extend generalizability of the urinary Complement proteome to earlier DKD stages. The proposed study will be conducted in participants of the Preventing Early Renal Loss (PERL) clinical trial with predominantly normal renal function at baseline followed for 3 years (primary outcome - renal slope). Aim 3 proposes to gain direct insight into the intra-renal Complement proteome by targeted and untargeted protein studies in diabetic kidney tissue (Susztaklab Biobank). This project focuses on a significant public health problem, leverages the progressiveness of the disease, employs an innovative proteomic technology and stems from strong preliminary data. Advances in this project will pinpoint missing key components of DKD etiology, thereby accelerating drug development strategies for patients with diabetes.

10. Project Title: **Kidney Tubular Functions in Type 1 Diabetes**
Leader(s):   **DE BOER, IAN H; KESTENBAUM, BRYAN R;**
UNIVERSITY OF WASHINGTON
NIH R01DK125084 / (2020 - 2024)

Core(s):

ABSTRACT Chronic kidney disease is a common and serious complication of type 1 diabetes (T1D). Historically, diabetes has been viewed as a primary glomerular kidney disorder based on classic pathological features. However, diabetes also promotes injury to kidney tubular epithelial cells and their microenvironment through increased work of glucose reabsorption and direct stimulation of pro-inflammatory and pro-fibrotic pathways. Sodium glucose co-transporter-2 inhibitors, which block glucose entry into proximal tubular cells, are the most promising new treatment for slowing the progression of kidney disease in type 2 diabetes. Compelling mechanisms of kidney tubular injury in diabetes have been incompletely translated into human disease, impeding new strategies for monitoring and treatment. The goal of this proposal is to advance understanding of the evolution, determinants, and clinical consequences of kidney tubular functions in persons with type I diabetes (T1D). We will add novel measurements of tubular functions and damage to two landmark clinical trials of T1D spanning the course of kidney disease. Through these measurements, we will for the first time characterize the natural history of tubular functions over time in T1D, identify potential risk factors for the loss of tubular functions, and test whether measures of tubular functions and damage are associated with metabolic complications, changes in key pathologic features, and a decline in glomerular kidney functions. The construction of a detailed natural history of kidney tubular functions in T1D will lay needed groundwork for the future development of new interventions to improve prevention, monitoring, and treatment.

11. Project Title: Skeletal Health in Type 1 Diabetes and the Role of Diabetic Kidney Disease

Leader(s): SCHAFER, ANNE LOUISE; SCHWARTZ, ANN V;
NORTHERN CALIFORNIA INSTITUTE/RES/EDU
NIH R01DK125646 / (2020 - 2024)

Core(s):

PROJECT SUMMARY/ABSTRACT Type 1 diabetes (T1D) is associated with increased risk of fracture throughout the lifespan. As individuals with T1D now live to older ages, when morbidity and mortality from fracture are greatest, it is crucial to understand this skeletal fragility and identify strategies to mitigate fracture risk. Bone mineral density is reduced, but fracture is elevated out of proportion to this reduction, indicating that other factors bone quality also contribute to the skeletal fragility. These may include low bone turnover and compromised bone geometry and microstructure. The presence of a diabetes microvascular complication is associated with particular skeletal fragility, but studies to date have been unable to disentangle specific contributions of each complication, nor to determine whether associations are independent of glycemic control. Of the microvascular complications, diabetic kidney disease may be especially detrimental, as other skeletal effects of T1D may be compounded by bone and mineral derangements of chronic kidney disease, including abnormal bone turnover and vitamin D metabolism. Our central hypothesis is that diabetic kidney disease particularly affects the already vulnerable T1D skeleton and plays a key role in the pathophysiology of diabetic skeletal fragility. The PERL trial presents a unique opportunity to understand the overlapping impact of these effects, as it has extensively characterized the kidney function of adult participants with T1D and diabetic kidney disease of varied severity. This 3-year trial of the effects of allopurinol vs. placebo on kidney function has ended, and participants are enrolled in an observational post-trial cohort study. In the 148 participants at 7 PERL centers, we propose an ancillary study that will add skeletal imaging for bone density (with dual-energy X-ray absorptiometry) and bone microstructure and estimated strength (with high-resolution peripheral quantitative computed tomography). We will also add analyses on stored serum specimens from 3 time points during PERL. A subset of participants (N=25) will undergo tetracycline-labeled bone biopsy. We will estimate relationships of gold-standard iohexol GFR and albuminuria measured longitudinally with skeletal parameters (Aim 1a). Then, we will determine if those relationships vary across a wider spectrum of kidney function, by combining data from PERL with consistently-acquired skeletal imaging data from 220 adults in the EDIC study, many of whom have normal GFR and no albuminuria (Aim 1b). We will next determine if glycemic control is independently associated with skeletal parameters in PERL (Aim 2). Finally, we will examine whether high or low parathyroid hormone and bone turnover marker levels are associated with skeletal parameters, and whether altered vitamin D metabolites partially explain the kidney-bone relationship (Aim 3). In the biopsy subset, we will explore whether PTH and bone turnover markers correlate with histomorphometric turnover. This research has the potential to shape the care of patients with T1D by informing screening approaches and interventions. Ultimately, it could help reduce fracture risk in our aging T1D population.

12. Project Title: Development of Prognostic Algorithms to Identify Subjects at High Risk of ESKD in Type 2 Diabetes

Leader(s): KROLEWSKI, ANDRZEJ S

JOSLIN DIABETES CENTER
NIH R01DK126799 / (2021 - 2025)

Core(s):

PROJECT SUMMARY/ABSTRACT With the rising prevalence of diabetes in the US and other countries, there is an ongoing research effort to find biomarkers allowing the identification of patients with diabetes at high risk of end stage kidney disease (ESKD). With support from NIH and JDRF, we have identified 21 serum proteins that were significantly associated with increased risk of kidney function loss and ESKD in the Joslin Kidney Study, and have developed an ad hoc OLINK multiplex assay (so called Joslin Kidney Panel [JKP]) to measure these biomarkers. Preliminary data strongly suggest that a subset of the JKP can significantly improve the ability to predict ESKD risk in subjects with type 2 diabetes (T2D) when added to GFR and allbuminuria. In this proposal, we aim to validate these preliminary findings in other settings, in order to develop improved algorithms for ESKD risk prediction. We intend to accomplish these goals using existing data and specimens from individuals with and without T2D from 1. the Chronic Renal Insufficiency Cohort (CRIC) Study; and 2. the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and its follow-up study ACCORDION. Our Specific Aims are: 1: To identify the most informative of the 21 biomarkers in the Joslin Kidney Panel and evaluate their performance, when added to GFR and albuminuria, in predicting ESKD risk among subjects with T2D and chronic kidney disease. We will measure the 21 proteins of the JKP in baseline serum specimens from ~1,500 CRIC participants with T2D, and will use these data together with GFR and albuminuria to develop and internally validate multi-marker prognostic algorithms predicting the risk of ESKD (primary outcome) or the composite of ESKD and/or 50% loss of kidney function (secondary outcome) during 10 years of follow-up. 2: To evaluate the generalizability of findings from CRIC to T2D individuals with a broader spectrum of kidney function. We will assay the JKP in baseline serum specimens from a case- cohort sample of ~2,000 ACCORD/ACCORDION participants and will use these data to investigate the generalizability of the predictive algorithms built in CRIC to diabetic patients with different characteristics. The prognostic models developed in Aim 1 and externally validated in Aim 2 will be used to build a web-based Kidney Risk Calculator for the estimation of the 10-year risk of ESKD in a clinical setting. 3: To evaluate the transferability of the Kidney Risk Calculator from diabetic to non-diabetic kidney disease. We will measure the 21 JKP biomarkers in baseline serum samples from ~1,700 non-diabetic subjects from the CRIC study and will assess the performance of the Kidney Risk Calculator developed in Aim 2 in predicting the risk of ESKD and ESKD/50% kidney function loss in patients with non-diabetic kidney disease. The proposed research has a high likelihood of resulting in the development of improved prognostic tools for the stratification of patients with diabetes according to their risk of progression to ESKD. This would be a great advancement for optimizing patient care and for improving the efficiency of clinical trials of new ESKD-preventing interventions.

13. **Project Title:** **Early myocardial remodeling and progressive kidney function decline in type 1 diabetes**

Leader(s): **DORIA, ALESSANDRO**

JOSLIN DIABETES CENTER

NIH R01HL161858 / (2021 - 2026)

Core(s):

SUMMARY A large proportion of the excess CVD morbidity and mortality experienced by individuals with T1D occur in conjunction with diabetic kidney disease (DKD), which is associated with a striking increase in the risk of coronary artery disease (CAD) and heart failure. The latter is frequently due to the development of diabetic cardiomyopathy a diabetes-specific alteration of the myocardium. The etiologic links between DKD and cardiomyopathy are not clear, but preliminary data from our group suggest a pivotal role of the kidney function decline component of DKD rather than albuminuria. Specifically, using an MRI-derived marker of cardiomyocyte size, we have observed that patients with T1D who are losing kidney function but still have preserved GFR have subclinical signs of myocardial remodeling, as indicated by a larger cardiomyocyte size and a reduction of myocardial fiber shortening during systole as compared to T1D patients with stable kidney function. The overall goal of this collaborative proposal, which is in response to RFA-HL-21-014, is to take advantage of the latest developments in cardiac imaging and biomarker platforms to characterize the cardiac involvement in patients with T1D and DKD, focusing on the initial events in the development of diabetic cardiomyopathy. GFR Decliners (GFR loss in the previous 3-6 years =3 ml/min/year, n=100) and GFR Non- Decliners (n=100) with T1D and CKD stage 1-3A, along with Non-diabetic controls (n=100) of similar age and CKD stage, will undergo a gadolinium-enhanced cardiac magnetic resonance (CMR) and a gated cardiac CT scan to quantify coronary artery calcium (CAC). Through these studies, we will address the following Specific Aims: 1. To evaluate the presence and severity of myocardial remodeling among T1D patients and assess its relationship with early progressive kidney function decline.

Cardiomyocyte size (tic) and interstitial fibrosis (measured as extracellular volume [ECV]) will be quantified by CMR and compared among GFR Decliners, GFR Non-Decliners, and Non-Diabetic subjects, and also related to albuminuria and presence and severity of CAD. 2. To assess the relative contribution of cardiomyocyte hypertrophy and interstitial fibrosis to impaired cardiac function among T1D patients. Indices of cardiac function and myocardial strain will be derived from the CMR data and evaluated for their association with cardiomyocyte size (tic) and interstitial fibrosis (ECV), in relation to the severity of concomitant CAD. 3. To gain insights into the disease processes involved in the etiology of myocardial remodeling and assess whether these overlap with those involved in the progressive kidney function decline. In targeted studies, we will focus on serum proteins implicated in heart failure or previously associated with increased risk of GFR loss. In untargeted studies, we will leverage the latest developments in multiplexed assays to evaluate serum protein profiles in a systematic fashion. With the information generated by this study on hand, we will be optimally positioned to develop new strategies and possibly new drugs to prevent CVD in T1D.

14. Project Title: DATA-DRIVEN INTERVENTIONS FOR REDUCING C. DIFFICILE INCIDENCE

Leader(s):   **RAO, KRISHNA; WIENS, JENNA**
UNIVERSITY OF MICHIGAN AT ANN ARBOR
AHRQ R01HS027431 / (2020 - 2024)

Core(s):

Considered one of the most urgent microbial threats by the Centers for Disease Control and Prevention (CDC), estimates of the excess costs of C. difficile infection (CDI) to the healthcare system range from $897 million to over $4 billion. Our long-term goal is to develop tools to identify patients at risk for CDI that could reduce its incidence, decrease transmission, improve patient outcomes, and reduce healthcare expenditures. We have developed and validated an algorithm using the electronic health record (EHR) to identify patients at high risk for CDI several days in advance of their diagnosis. However, there is a gap in knowledge as to whether real- world data-driven risk models can improve outcomes by guiding interventions in a clinical setting. To fill this gap in knowledge and improve CDI prevention efforts in hospitals, we propose the following specific aims: 1) to prospectively deploy an institution-specific daily risk prediction model for CDI and assess how elevated risk relates to colonization with C. difficile; 2a) to conduct a quality improvement study assessing a hospital-wide intervention bundle that incorporates patient risk for CDI; and 2b) to identify heterogeneous intervention effects across different subgroups (e.g., colonized versus not colonized; specific ribotypes) and secondary outcomes (e.g., reduced severity/complications). We will apply our model to daily extracts of EHR data, collect discarded rectal swabs and stool after standard clinical testing is completed to determine colonization status / ribotypes, and assess our model with respect to colonization status, potentially incorporating it to further improve the model. Using rates of hospital-acquired CDI, we will also assess the impact of a hospital-wide, risk-based prevention bundle rolled out for each ward in stepped-wedge, cluster- randomized fashion. The bundle will include both infection prevention and antimicrobial stewardship components. This project s successful completion would provide a model for improving the prevention of CDI and other healthcare associated infections in hospitals and health centers.

15. Project Title: The Effect of Lower Blood Pressure over the Life Course on Late-life Cognition in Blacks, Hispanics, and Whites (BP-COG)

Leader(s):   **LEVINE, DEBORAH**
UNIVERSITY OF MICHIGAN AT ANN ARBOR
NIH R01NS102715 / (2017 - 2023)

Core(s):

Project Summary/Abstract There is a fundamental gap in understanding how racial/ethnic differences in blood pressure (BP) control influence ra- cial/ethnic disparities in cognitive impairment and dementia (CID). Poor understanding of the biological factors driving socio-demographic disparities in CID is a critical barrier to the design of interventions aimed to eliminate these dispari- ties. The long-term goal of this research is to develop, test, and disseminate interventions that prevent CID and can be ap- plied to diverse populations. The objectives of this study are to quantify the effects of racial/ethnic differences in BP con- trol on racial/ethnic differences in CID, to quantify the potential impact of optimal BP treatment intensity to reduce ra- cial/ethnic disparities in CID, and to design a feasible BP intervention trial to reduce the risk of CID or cognitive decline. CID is an excellent model of a serious, chronic illness with racial/ethnic disparities in prevalence and costs. High BP is an ideal biological risk factor because it is modifiable with a wide range of effective

therapies for management. Our central hypothesis is that racial/ethnic differences in the control of high BP across the life course contribute to racial/ethnic dis- parities in late-life CID. The rationale for the proposed research is that understanding how racial/ethnic differences in BP control from young adulthood to late-life contribute to racial/ethnic disparities in CID has the potential to translate into targeted interventions aimed to improve the quality and outcomes of high BP, resulting in new and innovative approaches to the prevention of CID and other serious, chronic illnesses disproportionately affecting Blacks and Hispanics. Guided by strong preliminary data, this hypothesis will be tested by pursuing 3 specific aims: 1) Determine the influence of lower BP levels from young adulthood to late-life on CID risk in Blacks, Hispanics, and Whites; and 2) Estimate the potential impact of optimal BP treatment intensity to reduce racial/ethnic disparities in CID; and 3) Determine the sample size and duration of a trial that is adequately powered to find an effect size of BP lowering on CID that is clinically im- portant. Under Aim 1, a health services research approach with pooled cohort studies shown to be feasible in the appli- cants' hands will be used to measure the effects of BP levels and use of antihypertensive medication from young adult- hood to late-life on CID risk. Under Aims 2 and 3, a simulation modeling approach, which also has been proven as feasi- ble in the applicants' hands, will be used to quantify the individual and societal effects of eliminating racial/ethnic differ- ences in BP control from young adulthood to late-life on racial/ethnic disparities in late-life CID, and to determine the sample size and duration of a BP intervention trial to reduce the risk of CID or cognitive decline in diverse groups. This research proposal is innovative because it includes young adults and Hispanics. Not only do racial/ethnic disparities in BP control begin in young adulthood, but the effect of high BP on cognition also appears to begin in young adulthood. Hispanics are an understudied population that has greater risk of worse BP control and CID than Whites. The study will improve current BP-related risk prediction models by incorporating new population-based risk estimates from diverse co- horts and by adding CID as a BP-related outcome to an existing cardiovascular disease computer simulation model. This CID-enhanced computer simulation model will estimate the individual and societal benefits of optimal BP treatment in- tensity on CID to inform clinical care and policy and determine the sample size and duration of a BP intervention trial to reduce the risk of CID. The proposed study is significant because it will generate new knowledge and methods needed to understand the impact of racial/ethnic differences in optimal BP treatment intensity over the life course on racial/ethnic disparities in CID and to improve the design of BP lowering trials and their application to diverse populations. Ultimately, such knowledge has the potential to inform the development of targeted interventions that will help to improve the pre- vention of CID and to reduce CID-related disability in older Americans particularly minorities.

16. Project Title: **Evaluation of treatment patterns and prescription medication use among older adults with late-onset rheumatoid arthritis**

Leader(s):   **LEE, JIHA**
UNIVERSITY OF MICHIGAN AT ANN ARBOR
NIH R03AG067975 / (2020 - 2023)

Core(s):

PROJECT SUMMARY / ABSTRACT Rheumatoid arthritis (RA) is a chronic, debilitating and costly disease that disproportionally affects older adults. Disease modifying antirheumatic drugs (DMARDs) improve outcomes of RA and, in recent years, the treatment paradigm has evolved to promote early initiation, escalation, and combination of DMARDs. And yet, older adults are less likely to receive aggressive treatment due to issues of polypharmacy and multimorbidity. Older adults with late-onset RA (LORA) experience higher disease activity, more radiographic progression, and greater functional decline. Thus, less aggressive treatment raises greater concerns for poorer outcomes and greater levels of disability among older adults with LORA. In addition to achieving disease remission, pain control is an important goal in the treatment of RA and prescription medications including NSAIDS, glucocorticoids and opioids are in common use among patients with RA. However, these prescription medications are generally considered inappropriate for use in older adults because of associated adverse effects such as risk of falls, fractures and osteoporosis. Moreover, older adults have more limited tolerance to common adverse effects of medications and are more prone to the additive or even multiplicative risk of polypharmacy, further complicating the care of medically complex older adults with RA. Information on use of DMARDs for new diagnosis of LORA, and potential unintentional reliance on other prescription medication use is scarce because older adults are often excluded from randomized controlled trials. This leaves a gap in our understanding of how, in the face of polypharmacy and multimorbidity, variation in patterns of treatment impact outcomes for medically complex older adults with RA. In the absence of trial data, large observational studies that leverage administrative data serve an important role in filling this type of scientific knowledge gap and also allow for understanding drivers of treatment choices in usual care. In this retrospective cohort study using Medicare data we propose to achieve 2 aims. In Aim 1, we will characterize patterns of and factors associated with DMRADs and other prescription medication use among older adults with a new diagnosis of LORA. And in Aim 2 we will compare outcomes related to treatment and timing of DMARD-initiation for new cases of LORA. This proposal provides a real-world and population-level study of the care received by older RA patients treated with DMARDs. Preliminary data and analyses obtained from this study will form the

basis of future career development awards to address unique challenges related to prescribing high risk medications for older adults. Support from the GEMSSTAR award, mentorship, and training will be invaluable as I progress towards a career as an independent researcher focused on the design, implementation and evaluation of care models to improve quality of care in older patients with rheumatic diseases.

17. Project Title: **Validation and application of wearable sensors for capturing kinematic responses to real-world losses of balance among balance-impaired older adults**

Leader(s): **MADIGAN, MICHAEL L; ALEXANDER, NEIL ;**
VIRGINIA POLYTECHNIC INST AND ST UNIV
NIH R21AG075430 / (2022 - 2024)

Core(s):

The broad objective of this application is to establish a methodology to measure kinematic (i.e. bodily movement) responses to losses of balance (LOBs) in the real-world during daily life. Falls are the leading cause of injuries and injury-related deaths among older adults, with tripping and slipping being responsible for an estimated 60% of these falls. Numerous laboratory studies have shown that these falls generally result from an age-related decline in balance recovery responses to these LOBs. Unfortunately, technical challenges have limited our ability to assess LOB responses outside the lab, and therefore has allowed a disconnect to persist between lab studies of trips and slips and actual trips and slips in the real-world. We recently developed a novel technique to capture the kinematics of real-world LOBs and their context using wearable sensors and voice recorders. Aim 1 of this application will investigate the feasibility of this technique for extended use by asking balance-impaired community-dwelling older adults to wear the system daily during their waking hours for three weeks. Aim 2 will involve a laboratory validation of this technique by inducing trips and slips among Aim 1 participants while measuring LOB response kinematics simultaneously with the wearable sensor system and a gold-standard optoelectronic motion capture system. Aim 3 will use wearable sensor data from Aims 1 and 2 to begin to explore differences between real-world and laboratory LOB responses. The ability to capture detailed kinematics of LOB responses and their context in the real-world would have a profound and fundamental impact on fall prevention efforts. First, it would clarify any differences between laboratory and real-world LOBs to enhance the generalizability of lab studies to the real-world. Second, it would overcome well-known limitations of using memory recall when evaluating the frequency and characteristics of real-world falls. Third, it would greatly enhance the critical evaluation of fall prevention interventions and their mechanisms to maximize training benefits. Fourth, it would assist researchers developing algorithms to automatically detect real-world LOBs among individuals using wearable sensors.

18. Project Title: **Translational Geroscience Network**

Leader(s): **KIRKLAND, JAMES L.; KRITCHEVSKY, STEPHEN B.; KUCHEL, GEORGE A; TCHKONIA, TAMARA ;**
MAYO CLINIC ROCHESTER
NIH R33AG061456 / (2019 - 2023)

Core(s):

Aging is the leading risk factor for the disorders that account for the bulk of the nation's morbidity, mortality, and health costs. Recent findings suggest it is feasible to alleviate such disorders as a group by targeting fundamental aging processes. Several such interventions are near the point of entering human proof-of-concept clinical trials. Since interventions that increase lifespan and healthspan in mammals now exist, we hypothesize that clinical interventions targeting fundamental mechanisms of aging may delay, prevent, or treat age-related diseases and disabilities as a group, instead of one at a time. To accelerate testing this hypothesis, we propose a Translational Geroscience Network (TGN). Planning began 4 years ago through an NIA R24 grant involving 122 investigators in the biology of aging and clinical geriatrics. Our goal is to mature this network into a national resource starting with a subgroup of centers committed to working together using common measures and protocols allowing network-wide learning from complementary, small-scale, proof-of- concept use case clinical studies. Aim 1 is to establish a TGN to develop, implement, test, and harmonize methods and standard operating protocols (SOPs) for translational early phase trials of agents that target fundamental aging processes. The TGN will support development, coordination, and infrastructure around independently-funded use case trials (2-3 per year) using re-purposed drugs for which preclinical or clinical data already exist, such as a multicenter trial of senolytics for idiopathic pulmonary fibrosis, a trial of a different drug to reduce senescent cell burden and alleviate frailty in older women, and a

trial of metformin to enhance immune responses to influenza vaccination. Based on these use case trials, we will streamline and harmonize approvals, recruitment, sample collection, SOPs, and analytic procedures across the TGN. Aim 2 is to select, optimize, and validate ancillary measures of fundamental aging processes to be assayed across all trials to establish reference analytical capabilities. An existing cell senescence assay facility will be expanded to analyze blood, other body fluids, cells, and biopsies from trials across and beyond the TGN to serve as a national resource. New assays will be developed and optimized. The facility will expand to include laboratories beyond the TGN and incorporate assays of key basic aging mechanisms, including mTOR activity, proteostasis, autophagy, mitochondrial function, and epigenetics. Aim 3 is to provide statistical and data management support to select efficient study designs, provide sample size estimates and support a TGN-wide data entry platform to facilitate cross-study comparisons. Aim 4 is to develop a biobanking and repository network for samples from the clinical trials to permit future analyses as new ancillary research questions are developed and assays become available. A system for disseminating samples to the basic biology of aging community, biobanking protocols, and operating manuals will be developed. Translating agents targeting basic aging processes into interventions for the major chronic diseases and age-related disabilities could be transformative.

19. Project Title: **The Effect of Vascular Risk Factors on Risk of Alzheimer's Disease and Related Dementias after Stroke (STROKE COG)**

Leader(s): **LEVINE, DEBORAH**
UNIVERSITY OF MICHIGAN AT ANN ARBOR
NIH RF1AG068410 / (2020 - 2024)

Core(s):

PROJECT SUMMARY/ABSTRACT Alzheimer s disease and Alzheimer s disease-related dementia (AD/ADRD) incidence is high in older adults with stroke. There is a fundamental gap in understanding how vascular risk factors (VRFs) influence risk of post-stroke AD/ADRD. Poor understanding of the biological factors driving post-stroke AD/ADRD risk is a critical barrier to the design of interventions aimed to protect the brain health of stroke survivors. The long-term goal is to develop, test, and disseminate VRF interventions that reduce post-stroke AD/ADRD for diverse populations. The study objective is to quantify how VRFs influence post-stroke AD/ADRD risk to inform preventive interventions tailored to stroke survivors and inform clinical care and policies. Post-stroke AD/ADRD is an excellent model of a serious, chronic illness of aging with high prevalence and costs. High blood pressure (BP), diabetes, and high cholesterol are ideal biological VRFs because they are common and modifiable with a wide range of effective therapies for management. Our central hypothesis is that post-stroke VRF levels contribute to post-stroke AD/ADRD. The rationale for the proposed research is that knowing the impact of VRF levels and stroke (sub)type on post-stroke AD/ADRD will improve our understanding of vascular biology and translate into new and innovative approaches for prevention of post-stroke AD/ADRD. Guided by strong preliminary data, this hypothesis will be tested through 3 specific aims: 1) Quantify the influence of post-stroke VRF levels on post-stroke cognitive trajectories and AD/ADRD, and explore how sex and race affect these relationships; 2) Clarify the relationships between stroke subtype and post-stroke cognitive trajectories and AD/ADRD, and explore how VRFs, sex, and race affect these relationships; and 3) Refine and expand an existing AD/ADRD-CVD computer simulation model by adding post-stroke AD/ADRD and results from Aims 1 and 2 to quantify the subset of stroke events, sample size, and duration of trials that are adequately powered to find clinically important and plausible effect sizes of VRF lowering on post-stroke AD/ADRD. The results of Aims 1 and 2 will be the identification of both VRF targets for interventions to reduce post-stroke AD/ADRD risk and the sub-groups of stroke survivors most likely to benefit from VRF lowering. The results of Aim 3 will be a new simulation model applicable to stroke survivors that can be used to inform clinical research trials, clinical care, and policies. This research is innovative because it will ultimately yield a novel simulation model that could provide new guidance that may change clinical practice and health policy for stroke survivors. The proposed study is significant because it will generate new knowledge and methods to understand the impact of optimal VRF treatment intensity on post-stroke AD/ADRD risk and improve the design of VRF lowering trials in stroke survivors. Ultimately, such knowledge has the potential to inform the development of targeted interventions to improve the prevention of post-stroke AD/ADRD and to reduce AD/ADRD-related disability in older Americans.

20. Project Title: **Interventions Testing Program at UM**

Leader(s): **MILLER, RICHARD A**
UNIVERSITY OF MICHIGAN AT ANN ARBOR
NIH U01AG022303 / (2003 - 2024)

Core(s):

Identification of small molecules that extend mouse lifespan provides new insights into mechanisms of longevity determination in mammals, and may lay the groundwork for eventual anti-aging therapies in humans. The NIA Interventions Testing Program (ITP) evaluates agents proposed to extend mouse lifespan by retardation of aging or postponement of late life diseases. Interventions proposed by multiple collaborating scientists from the research community are tested, in parallel, at three sites (Jackson Laboratories, University of Michigan and University of Texas), using identical, standardized protocols, and using sufficient numbers of genetically heterogeneous mice to provide 80% power for detecting changes in lifespan of 10%, for either sex, after pooling data from any two of the test sites. Seventy-two such lifespan experiments, involving various doses of 44 distinct agents, have been initiated in the first fifteen years of the ITP. Thirty-seven experiments have involved comparative tests of multiple doses of effective agents, variable starting ages, or alternative dosing schedules. Significant effects on longevity, in one or both sexes, have been documented and then confirmed for NDGA, rapamycin, acarbose, and 17-a-estradiol (17aE2), with significant (but currently unconfirmed) effects also noted for Protandim, glycine and, in an interim analysis, canagliflozin. Lifespan trials are now underway for 18 new agents. ITP survival results have also documented longevity benefits from three agents started in middle-age: rapamycin, acarbose, and 17aE2. The previous five year period has introduced three new features to the ITP: increased emphasis on health outcomes (functional tests relevant to human health not necessarily linked to lifespan), a Collaborative Interactions Program to provide tissues from ITP drug-treated mice to an open, growing, international network of scientific collaborators, and a publicly accessible data repository and display engine hosted by the Mouse Phenome Database at the Jackson Laboratory. Plans for the next five-year period include additional lifespan (\Stage I\) trials, detailed analyses (\Stage II\) of agents found to increase lifespan, continued growth in data on health outcomes, and collaborative work with scientists to study drug effects on postulated aging mechanisms and links to disease. Studies at Michigan will follow up our analyses of cellular pathways relevant to stress resistance and inflammation, by continuing ongoing studies of cap-independent protein translation, chaperone mediated autophagy, and browning of white adipose cells. The work proposed should allow the ITP to continue to make major contributions to mammalian aging biology.

21. Project Title: Interventions Testing Program at UM
Leader(s):   MILLER, RICHARD A
UNIVERSITY OF MICHIGAN AT ANN ARBOR
NIH U01AG022303 / (2003 - 2024)

Core(s):

Identification of small molecules that extend mouse lifespan provides new insights into mechanisms of longevity determination in mammals, and may lay the groundwork for eventual anti-aging therapies in humans. The NIA Interventions Testing Program (ITP) evaluates agents proposed to extend mouse lifespan by retardation of aging or postponement of late life diseases. Interventions proposed by multiple collaborating scientists from the research community are tested, in parallel, at three sites (Jackson Laboratories, University of Michigan and University of Texas), using identical, standardized protocols, and using sufficient numbers of genetically heterogeneous mice to provide 80% power for detecting changes in lifespan of 10%, for either sex, after pooling data from any two of the test sites. Seventy-two such lifespan experiments, involving various doses of 44 distinct agents, have been initiated in the first fifteen years of the ITP. Thirty-seven experiments have involved comparative tests of multiple doses of effective agents, variable starting ages, or alternative dosing schedules. Significant effects on longevity, in one or both sexes, have been documented and then confirmed for NDGA, rapamycin, acarbose, and 17-a-estradiol (17aE2), with significant (but currently unconfirmed) effects also noted for Protandim, glycine and, in an interim analysis, canagliflozin. Lifespan trials are now underway for 18 new agents. ITP survival results have also documented longevity benefits from three agents started in middle-age: rapamycin, acarbose, and 17aE2. The previous five year period has introduced three new features to the ITP: increased emphasis on health outcomes (functional tests relevant to human health not necessarily linked to lifespan), a Collaborative Interactions Program to provide tissues from ITP drug-treated mice to an open, growing, international network of scientific collaborators, and a publicly accessible data repository and display engine hosted by the Mouse Phenome Database at the Jackson Laboratory. Plans for the next five-year period include additional lifespan (Stage I) trials, detailed analyses (Stage II) of agents found to increase lifespan, continued growth in data on health outcomes, and collaborative work with scientists to study drug effects on postulated aging mechanisms and links to disease. Studies at Michigan will follow up our analyses of cellular pathways relevant to stress resistance and inflammation, by continuing ongoing studies of cap-independent protein translation, chaperone mediated autophagy, and browning of white adipose cells. The work proposed should allow the ITP to continue to make major contributions to mammalian aging biology.

22. Project Title: Centenarian Consortium Project

Leader(s):	PERLS, THOMAS T
	CALIFORNIA PACIFIC MED CTR RES INSTITUTE
	NIH U19AG023122 / (2004 - 2024)

Core(s):

With our previous Longevity Consortium (LC) support, we brought together four extreme longevity (EL) studies that have agreed to share their individual level genetic and phenotypic data for more powerful genetic association analyses of human EL. Working closely with the other LC projects and cores, we will utilize these and developed unique resources to achieve 3 primary goals: (1) discover additional rare/uncommon EL and compression of morbidity genetic variants; (2) analyze gene expression profiles associated with EL-genetic variants to be used to search for healthy aging therapeutics; (3) strategically enroll new participants in the New England Centenarian Study (NECS) to provide biomaterial and phenotypic and genetic data for discovery- phase and validation/replication and follow-up experiments for this and other LC projects and cores. Specifically, in Aim 1 (Discovery) we propose to conduct a genome-wide association mega-analysis of EL and selected sub-phenotypes using data from 2,070 centenarians and 6,259 controls aggregated from the 4 longevity studies. The Japanese Centenarian Study, Health and Retirement Study, the Danish Longevity Study, and new data from Aim 3 will provide independent replication. In Aim 2 (Translation) we will link genetic data to whole blood gene expression data generated from 400 Long Life Family Study (LLFS) subjects, ages ranging from 50 to 110 years. These data will be used to generate expression quantitative trait loci (eQTLs) and gene/protein sets associated with significant eQTLs that are also associated with EL. Bioinformatics analyses in conjunction with the Chemoinformatics core will be aimed at discovering biomolecules and existing drugs that mimic the effects of the EL-associated mechanisms naturally occurring in people with EL genotypes. Mediation analysis will be used to investigate the joint effects of EL-promoting variants and their associated molecular signatures on age of onset of dementia, diabetes, cardiovascular disease, stroke, and cognitive impairment. These analyses will characterize the healthy aging patterns that might be enabled by the candidate compounds. In Aim 3 (discovery, validation and follow-up) we will identify 10-15 already enrolled families with informative patterns of familial EL from the collaborating EL studies. We will enroll additional critical family members from these families (e.g. siblings, cousins, etc) and use next generation whole genome sequencing to discover novel, rare EL-variants and to perform fine mapping of variants discovered in Aim 1. Newly enrolled subjects from these families as well as non-familial 103+ year olds will also provide data and biomaterial for planned studies by the other LC projects and cores. Through these aims and in collaboration with other LC projects and cores, the Centenarians Project will build on resources and findings from the previous cycle of the LC to discover new genetic variants associated with EL, integrate genetic and molecular data to identify targets for healthy-aging therapeutics, and generate unique biomaterial and data resources for work described by the other LC projects.

23. Project Title: ASPirin in Reducing Events in the Elderly - eXTension

Leader(s):	MURRAY, ANNE M; CHAN, ANDREW T; LIEW, DANNY ; MCNEIL, JOHN JAMES;
	HENNEPIN HEALTHCARE RESEARCH INSTITUTE
	NIH U19AG062682 / (2019 - 2024)

Core(s):

OVERALL RESEARCH PLAN - ABSTRACT / SUMMARY In the U.S., low dose aspirin (LDA) is one of the most widely used medications given its established role in the secondary prevention of cardiovascular disease (CVD). In recent years, several expert bodies, including the U.S. Preventive Services Task Force (USPSTF), have recommended the routine use of LDA for the primary prevention of both CVD and colorectal cancer (CRC) based on substantial data from prior randomized controlled trials (RCTs) primarily conducted among younger adults. However, for adults aged 70+, the USPSTF deemed current evidence supporting a net benefit insufficient. Furthermore, the need to prolong healthy independent life, free of dementia and significant disability, is critical given the rising social and economic costs of the increasingly aging population. To address these knowledge gaps, the NIA/NCI- sponsored ASPirin in Reducing Events in the Elderly (ASPREE) study was developed as a ground-breaking RCT that recruited 19,114 initially healthy older individuals aged 70+ years (65+ for U.S. minorities) from 2010- 2014 in the U.S. and Australia to examine whether initiation of 5 years of low-dose daily aspirin (LDA; 100 mg/day) prolonged the healthy lifespan of older adults. In June 2017, the randomized treatment phase of ASPREE was suspended after a median of 4.6 years of treatment due to lack of an effect of LDA on the primary outcome of disability-free survival (DFS). For secondary outcomes, LDA unexpectedly was associated with an increased risk of all-cause mortality (HR 1.14; 95% CI, 1.01,1.28) driven by an excess of deaths due to cancer, despite no increase in incident cancer. Furthermore, LDA showed a trend toward lower incident physical disability overall. These provocative initial findings obligate continued study and follow-up of the ASPREE cohort

through this U19 proposal. Our overall goal is to generate fundamental knowledge about the role of aspirin in older adults, a population in which aspirin's risk/benefit for primary prevention of chronic disease has been understudied. Our overarching hypothesis is that extended follow-up of the ASPREE cohort will demonstrate a long-term `legacy' benefit of LDA on cancer, dementia and disability. We further hypothesize that extensive genomic, biochemical, and imaging correlates collected during follow-up will offer unique biological insight into LDA's effects on these endpoints that may lead to mechanistically-inspired biomarkers for more `precision' prevention approaches to chronic disease prevention. Thus, we propose to establish ASPREE-XT to extend follow-up in ASPREE participants over the next 5 years to pursue three Projects focused on cancer, dementia (including Alzheimer's), and physical disability that will be supported by 6 Cores, facilitating synergy and collaboration. Together, this U19, led by a multidisciplinary, international team of leading investigators, will provide an unprecedented opportunity to define the long-term efficacy of LDA to guide clinical recommendations and offer fundamental insights into the biological underpinnings of the leading causes of dementia, disability and death among older adults.

24. Project Title: PRagmatic EValuation of evENTs And Benefits of Lipid-lowering in oldEr Adults (PREVENTABLE)

Leader(s):   **ALEXANDER, KAREN P; AMBROSIUS, WALTER T; HERNANDEZ, ADRIAN ; WILLIAMSON, JEFF DOUGLAS; DUKE UNIVERSITY**
NIH U19AG065188 / (2019 - 2027)

Core(s):

There is an urgent need for evidence to guide clinical care of older adults due to demographic shifts, including longer life expectancy and a recent doubling of the older adult population. Statins reduce recurrent CVD events and prevent initial events in patients younger than 75 years. However, clinical research has often excluded persons older than 75 years due to a higher prevalence of comorbidity and frailty so little to no evidence is available to guide care in this population. For older adults living longer, the promise of preventing cognitive impairment is as compelling as preventing a CVD event, but some evidence suggests statins may contribute to memory difficulty or muscle symptoms. There is equipoise regarding the usefulness of statins for primary CVD, dementia, and disability prevention in adults older than 75 years, especially in the setting of multiple chronic conditions, advanced age, or frailty. Evidence to improve cognitive and functional outcomes in older populations with diverse race/ethnicity and health status will require new clinical trial approaches with sustainable methodology and infrastructure. We propose PREVENTABLE (PRagmatic EValuation of evENTs And Benefits of Lipid-lowering in oldEr adults), the first statin trial with a non-CVD primary outcome survival free of dementia or persisting disability. Using a placebo-controlled pragmatic clinical trial (PCT) design across PCORnet and VA network, the trial will be under the leadership of Dr. Karen Alexander at DCRI, Dr. Jeff Williamson at WFSM, Dr. Adrian Hernandez at DCRI, and Dr. Walter Ambrosius at WFSM. This team has established experience and track-record of accomplishment in the design and conduct of PCTs, trial expertise in ascertaining cognitive and disability outcomes in older adults, and is supported by a robust administrative infrastructure for coordinating these shared responsibilities for success. The overarching goal of PREVENTABLE is to generate knowledge about the role of statins in older adults, a population in which risk/benefit for primary prevention has been under studied. The hypothesis is that a large trial conducted in an older adult population will demonstrate the benefit of statins for reducing dementia, disability, and CV events. We further hypothesize that extensive genomic, biochemical and imaging ancillary studies will offer unique insights into these key outcomes. PREVENTABLE has the following specific aims: AIM 1: Determine the role of a moderate-intensity statin in preventing dementia and prolonging disability-free survival in patients 75 years and older without clinically evident coronary heart disease, including those with frailty, impaired physical function, mild cognitive impairment, polypharmacy, and multi-morbidity. AIM 2: Determine the role of moderate- intensity statin in preventing hospitalization for myocardial infarction/acute coronary syndrome, stroke, heart failure, revascularization or cardiovascular-related death, and preventing either mild cognitive impairment or dementia. AIM 3: Test the safety and tolerability of statins in older adults and collect 17,000 bio-specimens to advance precision health.

25. Project Title: Janssen COVID-19 Vaccine Trial (\Ensemble\): A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older

Leader(s):   **LUGOGO, NJIRA**

UNIVERSITY AT MICHIGAN AT ANN ARBOR
JANSSEN VACCINES AND PREVENTION BV VAC31518COV3001 / (
2020 - 2023)

Core(s):

University of Michigan is a site for this clinical trial and 147 subjects are anticipated to engage in the revised Month 6 Visit. A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older. This study is being conducted under the sponsorship of Janssen (Janssen Vaccines & Prevention B.V) in collaboration with Operation Warp Speed (OWS), which also encompasses the Biomedical Advanced Research and Development Authority (BARDA), the National Institutes of Health (NIH), and the COVID-19 Prevention Trials Network (COVPN). Ad26.COV2.S (previously known as Ad26COVS1) is a monovalent vaccine composed of a recombinant, replication-incompetent adenovirus type 26 (Ad26) vector, constructed to encode the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein. Information about the disease, correlates of immunity, and safety issues concerning this new pandemic-causing virus are rapidly evolving. Therefore, it is critical to recognize that the approach outlined in this document might or will change as insights and discussions evolve.

PUBLICATIONS

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Citations: 54 | AltScore: 3.35

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Citations: 36 | AltScore: 0.5

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Citations: 79 | AltScore: 52.93

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Citations: 23 | AltScore: 76.6

98. **Mechanisms of pelvic floor muscle training for managing urinary incontinence in women: a scoping review.**
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Strong R, Miller RA, Cheng CJ, Nelson JF, Gelfond J, Allani SK, Diaz V, Dorigatti AO, Dorigatti J, Fernandez E, Galecki A, Ginsburg B, Hamilton KL, Javors MA, Kornfeld K, Kaeberlein M, Kumar S, Lombard DB, Lopez-Cruzan M, Miller BF, Rabinovitch P, Reifsnyder P, Rosenthal NA, Bogue MA, Salmon AB, Suh Y, Verdin E, Weissbach H, Newman J, Maccchiarini F, Harrison DE
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Citations: 30 | AltScore: 72.808

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Suri H, Rothschild G
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Citations: 70 | AltScore: 0.5

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Suwanabol PA, Li Y, Abrahamse P, De Roo AC, Vu JV, Silveira MJ, Mody L, Dimick JB
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Citations: 50 | AltScore: 8.2

105. **Cardiometabolic multimorbidity, genetic risk, and dementia: a prospective cohort study.**
Tai XY, Veldsman M, Lyall DM, Littlejohns TJ, Langa KM, Husain M, Ranson J, Llewellyn DJ
Lancet Healthy Longev, 2022 Jun, 3(6): e428-e436

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Citations: 45 | AltScore: 1202.5

106. **Pelvic floor muscle injury during a difficult labor. Can tissue fatigue damage play a role?**
Vila Pouca MCP, Parente MPL, Natal Jorge RM, DeLancey JOL, Ashton-Miller JA
Int Urogynecol J, 2022 Feb, 33(2): 211-220
https://doi.org/10.1007/s00192-021-05012-5 | PMID: 34783861 | PMCID: PMC8959084
Citations: 42 | AltScore: 2.85

107. **Multi-label classification of pelvic organ prolapse using stress magnetic resonance imaging with deep learning.**
Wang X, He D, Feng F, Ashton-Miller JA, DeLancey JOL, Luo J
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Citations: 33 | AltScore: 0.25

108. **Metals and risk of incident metabolic syndrome in a prospective cohort of midlife women in the United States.**
Wang X, Karvonen-Gutierrez CA, Herman WH, Mukherjee B, Park SK
Environ Res, 2022 Jul, 210: 112976
https://doi.org/10.1016/j.envres.2022.112976 | PMID: 35202625 | PMCID: PMC9869389
Citations: 106 | AltScore: 0.5

109. **Functional aging trajectories of older cancer survivors: a latent growth analysis of the US Health and Retirement Study.**
Westrick AC, Langa KM, Eastman M, Ospina-Romero M, Mullins MA, Kobayashi LC
J Cancer Surviv, 2022 Feb 26
https://doi.org/10.1007/s11764-022-01185-0 | PMID: 35218520 | PMCID: PMC9411262
Citations: 46 | AltScore: 2.5

110. **Rapamycin, Acarbose and 17a-estradiol share common mechanisms regulating the MAPK pathways involved in intracellular signaling and inflammation.**
Wink L, Miller RA, Garcia GG
Immun Ageing, 2022 Feb 1, 19(1): 8
https://doi.org/10.1186/s12979-022-00264-1 | PMID: 35105357 | PMCID: PMC8805398
Citations: 76 | AltScore: 7.6

111. **Association of Perceived Job Insecurity With Subsequent Memory Function and Decline Among Adults 55 Years or Older in England and the US, 2006 to 2016.**
Yu X, Langa KM, Cho TC, Kobayashi LC
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https://doi.org/10.1001/jamanetworkopen.2022.7060 | PMID: 35416992 | PMCID: PMC9008497
Citations: 48 | AltScore: 30.5

112. **Does Aspirin Prevent Incident Heart Failure in Healthy Older Adults? Examining the Evidence From the ASPREE Trial.**
Zhou Z, Nelson M, Ernst ME, Reid C, McNeil J, Tonkin A, ASPREE Investigator Group
Circ Heart Fail, 2022 Jun, 15(6): e009511
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Citations: 5 | AltScore: 12.5

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RECOGNITION AND AWARDS (2022-2023)

<u>Richard Miller</u> (2022)

- Geriatrics Center and Department of Pathology Distinguished Scientist Award

MINORITY RESEARCH

General Brief Description of Minority Activities:

University of Michigan

Claude D. Pepper Older Americans Independence Center

Minority Research: List activities with minority trainees and research focusing on hypotheses dealing with minority health. Clinical research that has an expected number of minority subjects (a NIH requirement) is NOT what is desired for this section. Only work that has a comparison of minority members to majority members such as work on health disparities should be included.

Minority Trainee(s):

Emily Briceño-Abreau, PhD, Assistant Professor, Physical Medicine and Rehabilitation, is supported by the REC. Her research focus is on the measurement of cognition across language and education among Mexican American and non-Hispanic white older adults.

Jaclynn Hawkins, MSW, PhD, supported by PESC and REC in 2019-2020, was promoted to Associate Professor with Tenure, School of Social Work in 2022. She also was appointed as the new Associate Director of the Vivian A. and James L. Curtis Center for Health Equity Research and Training in 2021. Her research supported by the OAIC focuses on Type 2 diabetes self-management in older African American men.

Trainees Focusing on Minority Health Issues.

Emily Briceño-Abreau, Ph.D.

Research Articles:

Becker CJ, Heeringa SG, Chang W, **Briceño EM**, Mehdipanah R, Levine DA, **Langa KM**, Gonzales XF, Garcia N, Longoria R, Springer MV, Zahuranec DB, Morgenstern LB. Differential Impact of Stroke on Cognitive Impairment in Mexican Americans and Non-Hispanic White Americans. Stroke. 2022 Nov;53(11):3394-3400. doi: 10.1161/STROKEAHA.122.039533. Epub 2022 Aug 12. PMID: 35959679; PMCID: PMC9613525.

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Briceño EM, Dong L, Levine DA, Kwicklis M, Lisabeth LD, Morgenstern LB. Cognitive recovery trajectories 3 months following stroke in Mexican American and non-Hispanic white adults. J Stroke Cerebrovasc Dis. 2023 Feb;32(2):106902. doi: 10.1016/j.jstrokecerebrovasdis.2022.106902. Epub 2022 Nov 29. PMID: 36459957; PMCID: PMC10249629.

Briceño EM, Mehdipanah R, Gonzales XF, Heeringa SG, Levine DA, **Langa KM**, Zahs D, Garcia N, Longoria R, Vargas A, Morgenstern LB. Differential Relationships Between the Montreal Cognitive Assessment and Informant-Rated Cognitive Decline Among Mexican Americans and Non-Hispanic Whites. J Geriatr Psychiatry Neurol. 2021 Jul 22:8919887211029383. doi: 10.1177/08919887211029383. Epub ahead of print. PMID: 34291678; PMCID: PMC8782915.

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Davis MA, Lee KA, Harris M, Ha J, **Langa KM**, **Bynum JPW**, **Hoffman GJ**. Time to dementia diagnosis by race: A retrospective cohort study. J Am Geriatr Soc. 2022 Nov;70(11):3250-3259. doi: 10.1111/jgs.18078. Epub 2022 Oct 6. PMID: 36200557; PMCID: PMC9669160.

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MOUNT SINAI MEDICAL CENTER
Claude D. Pepper Older Americans Independence Center

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CENTER DESCRIPTION

The overarching goal of the Mount Sinai OAIC is to improve independence for older adults with serious illness and to consolidate the substantial progress made in the first eight years of the OAIC at the Icahn School of Medicine at Mount Sinai (ISMMS). The OAIC support s research in seriously ill older adults (geriatric palliative care research) with the overall goal of creating the needed evidence base that, in the words of Claude D. Pepper, will *"...lighten the burden of those who suffer."* Our specific aims are:

1. To expand a transdisciplinary research program focused on: a) improving quality of life and independence and b) healthcare delivery models that improve care for seriously ill older adults and their families.

2. To identify, recruit, and train leaders in aging and palliative care research through: a) mentoring relationships with successful investigators; b) strengthening and expanding Mount Sinai's existing research training programs in aging and palliative care; and c) support for pilot projects, statistical and analytic consultation, use of population-based data, and instrument development and measurement.

3. To expand research infrastructure that will support new and ongoing research in the care of seriously ill older adults by a) providing expertise in research design, measurement, and analysis, b) developing and applying innovative research designs, analytic techniques, and measures to OAIC and externally supported projects, c) applying to aging research relevant methods not currently in widespread use (e.g. item response theory, propensity score methods, latent class growth analyses), d) supporting innovative research employing newly available population-based data; and e) supporting two new cross-cutting themes focused on dementia and implantation science.

4. To expand ongoing collaborations with other OAICs and National Palliative Care Research Center (NPCRC) and create new collaborations with NIA's ADRCs, RCMARs, and others

5. To develop a research center that bridges geriatrics and palliative care and that will serve as a model for research that has not been well addressed previously by these two transdisciplinary specialties.

The OAIC consists of the following cores: 1) Leadership and Administrative Core (LAC), 2) Research Education Component (REC), 3) Pilot Exploratory Studies Core (PESC), 4) Measurement, Methods, and Analyses Core (RC-MMA), 5) Population Research and Methods Core (RC-PRM), and 6) Population Data Use and Management Core (RC-PDM). Through the REC, we are providing junior faculty with educational activities and training experiences in improving the care of older adults with serious illness. These young investigators will have opportunities to participate in research through the PESC and external projects linked to the OAIC. They and research

supported in the OAIC are supported by three resource cores. Our RC-MMA core provides statistical, methodological and programming expertise to investigators, as well as mentoring in those areas. The RC-MMA provides our investigators with access to measurement support including measures developed through item response theory. The new RC-PDM core was developed to assist investigators with database management, sampling procedures, and analytic techniques needed for the increasing numbers of population-based datasets (e.g., NIA"s Health and Retirement Study [HRS] and National Health and Aging Trends Study [NHATS]). All these cores are coordinated and integrated by the LAC In sum, our aim is to ensure that all health care professionals have the knowledge and evidence base necessary, and that our institutions have the necessary clinical models to provide high quality geriatric palliative care to the rapidly increasing numbers of older adults living with serious illness and their families.

CORES

Leadership and Administrative Core (LAC)

<u>Leader 1:</u>   Albert Siu, MD, MSPH   albert.siu@mssm.edu

<u>Leader 2:</u>   R. Sean Morrison, MD   sean.morrison@mssm.edu

The Leadership and Administrative Core is housed in the offices of the Chairman of the Mount Sinai Department of Geriatrics. Core staff consists of: Center Primary Investigator and Core Leader: Albert L. Siu, MD The Leaders of the Research Education Component: Nathan Goldstein, MD, R. Sean Morrison, MD, and Juan Wisnivesky, MD, PhD; Pilot and Exploratory Studies Core leaders: Kenneth Boockvar, MD; Population Research and Effectiveness Core leaders: Melissa Aldridge, PhD; Measurement and Data Management Core: Jeanne Teresi, PhD Vice Chair for Education of the Department of Geriatrics and Palliative Medicine: Rosanne Leipzig, MD, PhD Director of the Center to Advance Palliative Care: Diane Meier, MD Three standing committees advise the Center regarding policy and conduct of its programs: An OAIC Executive Committee (OAIC EC or EC) of OAIC core leaders and institutional leadership A Research Advisory Committee (RAC) of senior investigators not currently involved in the OAIC as investigators or mentors

Research Education Component (REC)

<u>Leader 1:</u>   Nathan Goldstein, MD   nathan.goldstein@mssm.edu

<u>Leader 2:</u>   Juan Wisnivesky, MD, PhD   juan.wisnivesky@mountsinai.org

The OAIC's Research Education Component (REC) at the Icahn School of Medicine reinforces junior faculty's interest in improving the care of seriously ill, older adults with educational activities and training experiences while promoting the development of future research leaders. The REC's specific objectives are to: Recruit talented faculty from different disciplines who are committed to academic careers improving the care of older adults with serious illness Provide advanced training in research methodologies needed to conduct high quality, ethical, and multidisciplinary palliative care research for seriously ill older adults Provide multidisciplinary mentorship and individually tailored career development plans Support trainees in conducting and disseminating research studies to assess questions related to the health and independence of older adults or related palliative care issues Facilitate attainment of academic and life skills to sustain long-term success as independent investigators and future leaders in geriatric and palliative care medicine Prepare and assist trainees in obtaining external funding to continue an academic research career.

Pilot and Exploratory Studies Core (PESC)

<u>Leader 1:</u>   William Hung, MD   william.hung@mssm.edu

<u>Leader 2:</u>   Barbara Vickrey, MD, MPH   barbara.vickrey@mssm.edu

The Pilot and Exploratory Studies Core (PESC), builds upon a 15-year foundation of research in palliative care, disability, and function at Mount Sinai; an established record of successful mentorship by the OAIC senior investigators; and a strong and consistent track record in conducting collaborative and interdisciplinary research that will accomplish the following specific aims: Facilitate pilot and exploratory studies that will examine the relationship of pain and other distressing symptoms to independence, function, and disability; develop interventions directed at the treatment of pain and other distressing symptoms in older adults; and explore interventions to

improve quality of life and promote function and independence for older adults living with serious and chronic illness Encourage the development of junior faculty by providing a mechanism to obtain mentored, hands-on research training and develop preliminary data in aging and palliative care that will lead to the development of larger federally or foundation-funded research projects and career development awards focused on improving care and promoting independence for older adults with advanced illness Support senior and mid-level faculty who are conducting studies in palliative care and aging who are embarking on new research projects requiring pilot data; palliative care research in younger populations who would like to expand or shift their research into aging; and aging research unrelated to palliative care who would like to refocus their work to fit within our OAIC theme Foster collaborative research among investigators from different disciplines, specialties, and institutions

Measurement, Methods and Analysis Core (RC-MMA)

Leader 1:   Jeanne Teresi, PhD   teresimeas@aol.com
Leader 2:   Mildred Ramirez, PhD   milramirez@aol.com

The goal of the proposed RC-MMA is to improve independence for older adults with serious illness through research and leadership training in geriatric palliative care methods. RC-MMA will support this effort by providing measurement consultation, evaluation and analyses for selected core projects.

Population Data Use and Management Core (RC-PDM)

Leader 1:   Carolyn Zhu, PhD   carolyn.zhu@mssm.edu
Leader 2:   Claire Ankuda, MD, MPH, MSc   claire.ankuda@mssm.edu

The Population Data Use and Management (RC-PDM) Core has pursued its objectives of leveraging existing national survey, administrative and health system data to support OAIC research on geriatric palliative care. As a newly established Core, this core has been highly productive in providing data management and operational support to OAIC investigators working with existing data sources through close partnership with RC-PRM and RC-MMA.

Population Research and Methods Core (RC-PRM)

Leader 1:   Melissa Aldridge, PhD   melissa.aldridge@mssm.edu
Leader 2:   Lihua Li, PhD   lihua.li@mssm.edu

The Population Research and Effectiveness (PRE) Core contributes to the goals of the OAIC by providing statistical, methodological, and programming expertise, as well as mentoring in those areas, to investigators in the School's OAIC. This core has been highly productive in providing consultations and support for numerous OAIC investigators confronted with methodological and analytic issues that occur in the study of older adults with serious illness. Our Core's consultants have a broad range of knowledge regarding research methods to serve as potential consults to OAIC investigators. Resources and expertise are provided in a variety of ways and throughout all phases of the research process—from design to interpretation and presentation of findings to: To provide sophisticated, cutting edge methodological, statistical, and programming support to OAIC investigators. To apply advanced research and statistical methodology (e.g., propensity scores, instrumental variable estimation, competing risk analysis) used in other fields but not commonly applied to aging-related research. To collaborate closely with the RCDC and RCDSC to ensure that junior faculty obtain research methods training to advance their current knowledge and expertise. To develop the infrastructure for population based research by hiring and training data analysts

who will conduct data management and programming functions and provide statistical expertise in cutting edge research methods.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications
Rebecca Rodin MD, MS / Assistant Professor <u>Dementia and the Opioid Epidemic: The Impact of the 2016 CDC Opioid Guidelines on Disparities in Pain Management</u> Aim 1: Identify the association of opioid prescribing and the publication of the 2016 CDC guidelines among community-dwelling older adults with and without dementia who have a pain-associated, opioid-responsive condition (either cancer or traumatic hip/pelvic fracture) H1: Opioid prescribing after 2016 will decrease to a greater extent for PWD than for PWoD Aim 2: Examine and compare racial/ethnic disparities in opioid prescribing after the publication of the 2016 CDC guidelines among community-dwelling older adults with and without dementia who experience a pain-associated, opioid-responsive condition (cancer or traumatic hip/pelvic fracture)	2022-2025 / 8 (total) 5 (1st/Sr)

Past Scholars

Lili Chan, Mount Sinai Division of Nephrology (2019-2020)

Raj G. Kumar, Mount Sinai Department of Rehabilitation and Human Performance (2020-2021)

Rita C Crooms, Mount Sinai Department of Neurology (2020-2022)

Leah Blank, Mount Sinai Department of Neurology (2020-2022)

Aaron Baum, Mount Sinai Division of General Internal Medicine (2020-2021)

Julia L. Frydman, Mount Sinai Department of Geriatrics & Palliative Medicine (2020-2022)

Matthew R Augustine, Mount Sinai Division of General Internal Medicine (2020-2021)

Zainab Toteh Osakwe, College of Nursing and Public Health, Adelphi University (2021-2022)

PILOT/EXPLORATORY PROJECTS (8 Pilot Projects Listed)

1. Project Title: **Geriatric Surgery Co-Management Program: A New Model to Optimize Pre-Operative Care For Frail Older Adults**

Leader: **Stephanie Chow, MD, MPH; Fred Ko, MD, MSCR**

ABSTRACT: Frail older adults undergoing surgery encounter higher rates of adverse post-operative outcomes as compared to non-frail older adults. Currently, much of geriatric surgery co-management takes place in the inpatient setting, as a collaboration primarily between surgeons and geriatricians, and without deliberate social work guidance on the social determinants of health. This Pepper Center pilot study proposes to explore Geriatric Surgery CO-Management (SCOM) in the ambulatory setting as a pre-emptive approach to optimizing comprehensive geriatric medical and social work care in the frail older patient. It aims to characterize patients referred to and enrolled in SCOM and evaluate their relevant clinical outcomes, examine the feasibility of delivering SCOM program elements in real-world clinical settings, and identify facilitators and barriers to SCOM implementation. This knowledge will provide the foundation to inform future grant proposals and definitive effectiveness trials that aim to study the post-surgical benefits of a pre-operative, collaborative interprofessional co-management intervention in frail older patients in the Mount Sinai Health System.

2. Project Title: **Developing Training for MyChart Use for Older Persons with Mild Cognitive Impairment: A pilot study**

Leader: **Maria Loizos, PhD**

There is an increasing number of patients who utilize technology to promote a healthy lifestyle. Various forms of telehealth services, including text messaging, email, patient portals, videoconferencing visits, and evisits are becoming increasingly available. In fact, patients are increasingly utilizing electronic personal health records (PHR), which include the most up to date information about a patient's health care. At the Icahn School of Medicine at Mount Sinai, patients can use MyChart, which is linked to EPIC (electronic medical record). Utilizing PHR allows patients the ability to more easily manage their health, increase their independence, increase access to care, and reduce health disparities among rural and underserved populations. However, older adults, and especially older adults with Mild Cognitive Impairment (MCI) overwhelmingly underutilize PHR. Not having access to and being able to use technology may put older adults with MCI at a disadvantage in terms of their ability to live independently. Additionally, many older adults with MCI depend on spouses or other family members to assist with telehealth visits, and these are often also older frail individuals. Rapidly changing technology does not allow for patient ease of use, and many older adults with MCI become agitated and more symptomatic trying to adapt to it. Presently, there exists a need to assist older persons with MCI with utilizing PHR to manage their health and maintain their independence. To address the issue of older adults with MCI underutilizing PHR, we will develop a training module which will utilize feedback from patients and caregivers both familiar and unfamiliar with MyChart. Utilizing direct patient feedback allows the training module to be tailored specifically to patient need and will allow the inclusion of language and verbiage that older patients are familiar with. The proposed project is supported by the fact that while these patient portal systems are not intuitive for older adults with MCI, they can be trained to utilize these systems by incorporating their preferred learning method. Thus, it is hypothesized that older individuals with MCI can identify what makes it difficult for them to use MyChart and can

inform a training module to improve their utilization. The potential increase in use of patient portals will promote independence in managing health care which is particularly important for older adults. The specific aims of this project are: 1) Understand nature of user difficulties and knowledge needs with regard to MyChart use and determine preferred training method for older adults with MCI and their caregivers with and without MyChart experience. This includes multiple focus groups with older adults with MCI consumers of MyChart and novice older adults with MCI users and their caregivers. Focus groups will be carried out by a clinical psychologist. Feedback generated from these focus groups will provide the basis for the development of the training module. 2) Develop a MyChart training module based on identified knowledge needs. The training module will be created utilizing direct feedback regarding the way older adult consumers with MCI and their caregivers prefer to receive information and training regarding technology (e.g., video, written materials, or live instruction). Identified difficulties gleamed from prior focus groups will be reviewed and verbiage that older adult consumers with MCI and their caregivers have identified will be utilized. 3) Assess the feasibility of providing training to improve use of MyChart amongst older adults with MCI. This includes utilizing multiple focus groups with older adults unfamiliar with MyChart and ascertaining participant satisfaction via questionnaire as well as participant's ability to carry out health tasks via MyChart. It is hypothesized that older individuals can identify what makes it difficult for them to use MyChart and can inform a training module to improve their utilization. Results will demonstrate the feasibility of providing a training module to improve MyChart usage amongst older adults as well as determine the preferred learning method of older adults with MCI. The goal of this proposed pilot project is to identify the causes of low use of MyChart among older adults and assess the feasibility of using a training module based on patient feedback and experience regarding the use of MyChart.

3. Project Title:	**Understanding discordance between goals of care and admission to the emergency department at the end of life (2.0)**
Leader:	**Bevin Cohen PhD, MPH, MS, RN, Associate Professor; Kimberly Souffront, PhD, RN, FNP-BC, Assistant Professor**

The purpose of this mixed methods study is to characterize the patient, family, provider, and system level processes and factors that lead to ED admissions near the end of life when this is inconsistent with patients' documented advance directives and goals of care (DADGOC). The specific aims are: 1. To describe the prevalence and characteristics of patients with advanced serious illness who are admitted to the ED at the end of life, and within this cohort: a. Describe the differences in characteristics between patients who have DADGOC that are inconsistent with admission to the ED versus those who do not; b. Describe the proportion and characteristics of DADGOC that contain inconsistent, contradictory, outdated, or vague statements regarding goals of care. 2. To qualitatively explore the factors that contribute to discordance between DADGOC and admission to the ED at the end of life by interviewing patients, family members, and healthcare workers. 3. To characterize the factors that contribute to discordance between DADGOC and admission to the ED using a process mapping approach.

4. Project Title:	**Home Health Aide Continuity Among Home-based Long-Term Care Clients and Its Relationship with Health Outcomes**

Leader: **Jennifer M. Reckrey, MD Associate Professor Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai**

Due to both individual and family preference as well as growing evidence that community-based long-term services and supports (LTSS) can be cost effective, the locus of long-term care is shifting from institutions into the community. Concerns about safety in congregate settings like nursing homes during the COVID-19 pandemic may accelerate this trend. While paid caregivers (e.g., home health aides, personal care attendants, and other direct care workers in the home) play an important role making sure older adults receive needed assistance, few studies have examined how paid caregivers themselves or the characteristics of the services they provide shapes health outcomes for care recipients. Consistency in the paid caregiver(s) providing care to an individual with long-term care needs may make it possible for paid caregivers to establish trust, support, and familiarity with their client's personal care and health needs. This in turn may enable paid caregivers to meaningfully contribute to the health outcomes of their clients. A large body of health services research suggests that consistency in the individual providing healthcare services (e.g., doctors, nurses, physical therapists) is important for patient outcomes; this is known as "provider continuity". However, limited research has empirically explored continuity of paid caregivers such as home health aides (i.e., "home health aide continuity") in the home-based long-term care setting. Previous work on this topic has largely been qualitative, conducted outside of the U.S., or focused on paid caregivers providing short-term post-acute home-based care. The impact of home health aide continuity on home-based long-term care clients has not been studied. Given the integral but often underappreciated role that paid caregivers play in the health care team, information about home health aide continuity is essential to both guide paid caregiver workforce development and to maximize the potentially positive impact of paid caregivers on those for whom they care. Existing data from the Visiting Nurse Service of New York (VNSNY) provides a unique opportunity to simultaneously explore long-term care client health outcomes (using Medicaid Managed Long-Term Care records) and patterns of continuity among the home health aides who care for them (using Licensed Home Care Service Agency records). We propose to conduct a retrospective cohort study using secondary analysis of these data in order to: Aim 1. Describe home health aide continuity (i.e., number of home health aides providing care to a given client over time) among a population of older adults receiving Medicaid-funded, home-based long term care. Aim 2: Identify client factors associated with greater home health aide continuity. H2: Those with greater service needs will experience greater discontinuity of home health aides. Aim 3: Determine the association between home health aide continuity and client health outcomes across multiple domains (i.e., quality of life, safety, psychosocial well-being, and healthcare utilization). H3: Greater home health aide continuity will be associated with better health outcomes

5. Project Title: **"TIER PALLIATIVE CARE: A palliative care delivery model to match palliative care services for community-based patients with heart failure or cancer"**

Leader: **Laura P. Gelfman, MD, MPH: Associate Professor Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai**

Older adults with serious illness suffer from poor symptom control, decreased quality of life (QoL) and poor communication with their healthcare providers, especially with regards to goals of care discussions (GOCD). Palliative care, when offered alongside disease management, offers the benefits of improved symptom control, QoL and communication (increased prognostic awareness, GOCDs, goal concordant care). Due to a limited specialty-trained palliative care workforce, patients often cannot access these benefits, particularly outside of the hospital. These needs are particularly acute in advanced cancer and HF, which are the two leading causes of death in the US and the prototypical examples of the most common illness trajectories. Indeed the dynamic nature of these two illnesses present distinct symptom patterns and change in functional status that can create challenges with regard to the optimal delivery of palliative care. To improve the quality of care for these two populations, new models are needed to deliver community-based palliative care tailored to patient's illness trajectory and changing needs. TIER-PALLIATIVE CARE (TIER-PC) is an innovative and adaptive model of delivering palliative care that provides the right level of care to the right patients at the right time. TIER-PC increases the number and intensity of disciplines added to the patient's care team as their symptoms worsen and function declines. In Tier 1, patients who are able to care for themselves and no/mild symptoms receive a community health worker (CHW) trained to elicit illness understanding in a culturally competent way. In Tier 2, for patients with poorer function and mild symptoms, a social worker (SW), trained in serious illness communication, joins the CHW to further elicit patients' goals and prognostic understanding while communicating symptom needs to their primary clinician. In Tier 3, as function decreases and symptoms increase, an advance practice nurse (APN) joins the CHW+SW to manage complex symptoms. Finally, in Tier 4, for those older adults with the poorest function and most complex symptoms, a physician joins the team to assure that the most complex needs (e.g., end-of-life treatment preferences and multifaceted symptom control) are met. The CHW follows patients longitudinally across all tiers and re-allocates them to the appropriate tier based on their evolving needs. We will adapt an existing model and refine TIER-PC (SA1), and evaluate the efficacy of TIER-PC in a single-site, two-arm randomized controlled trial (RCT) of TIER-PC vs. usual care in a population of community-based older adults with advanced cancer or HF (SA2). We will enroll and randomize 40 older adults to receive TIER-PC or a CHW-delivered augmented control and follow patients for 6 months. Patients with either advanced cancer or HF will receive regular assessments by the TIER-PC team to: address their specific symptom and psychosocial needs; improve illness/prognostic understanding; prescribe medications; and address goals of care. As a result of this work, we will have pilot data (symptom control; QoL) for an R01 efficacy trial. Our model has the potential to improve care for older adults with cancer or HF and match demand to the limited specialty-trained palliative care workforce.

6. Project Title: **Understanding Discharge Destination Decisions from Patient and Caregiver Perspectives in the Context of Self-Efficacy and Social Determinants of Health**

Leader: **Shira Winter, PhD, RN, FNP-BC**

This study aims to advise future efforts to discharge patients from hospital to home safely with appropriate services rather than discharge to a facility), accounting for both patient and caregiver preferences as well as for social determinants of health. The findings from this pilot study will: 1) help elucidate the phenomena surrounding the complexity of discharge destination decisions beyond medical and functional status, and 2) provide insight on ways to design evidence-based methods that will help hospital teams determine when discharges to

home with rehabilitation services are likely to yield optimal medical and psychosocial outcomes for patients and caregivers. The overall objective of this project is to understand the interplay between self-efficacy and social determinants of health in the context of determinations of discharge destination.

7. Project Title: **Defining a cohort of chronically ill patients with repeated hospitalizations for future research on segregation of care**

Leader: **Louisa Holoday, MD, MHS**

Racial disparities in healthcare outcomes persist despite decades of research and interventions. One reason for these ongoing racial disparities may be segregation in care. Hospital care in the United States is de facto racially segregated, with Black and Hispanic patients generally cared for in different hospitals than White patients. Hospitals that serve primarily Black patients have lower quality measures, receive less revenue, and have lower profits. Individuals with serious illness may be more vulnerable to poor outcomes from low quality hospital care. Despite this, relatively few studies have demonstrated that the hospital used for care is an explanatory variable for observed racial disparities among seriously ill older adults. However, whether site of care mediates racial health disparities among older adults with serious illness is unknown. Further, examining segregation of care as a driver of poor outcomes is understudied. Research on the segregation of care has been limited in part due to unreliable race and ethnicity data in administrative datasets, which may be overcome with novel methods. Recently published work has identified significant racial and ethnic segregation of Medicare patients among Asian, Black, and Hispanic patients in the New York City metropolitan region. This paper also found hospitals primarily serving minoritized individuals had lower quality measures and poorer performance overall. Thus, segregation of care may indeed drive racial health disparities, and deserve further study as potentially modifiable drivers of racial health disparities. In order to study the effects of receipt of care in segregated hospitals on health outcomes, we propose identifying a cohort of chronically ill patients using data from the Medicare Current Beneficiary Survey. We will also characterize hospitals used by chronically ill, high utilization patients.

8. Project Title: **Improving Psychological Adjustment and Care Quality for Men on Active Surveillance (ImPACt)**

Leader: **Nihal E. Mohamed, MD**

Active surveillance (AS) is an evidence-based observation strategy to manage men with low-risk prostate cancer (PCa) to prevent a decrease in men's quality of life typically associated with definitive treatment (e.g., surgery, radiation therapies). In spite of the benefits of AS, 90% of eligible patients opt for treatment and 25% of patients discontinue the AS protocol within the first 2 years without clinical evidence of PCa progression. We have developed an educational intervention to improve patients' adherence to AS. In this study, we aim to enhance the intervention by including an 8-session on cognitive-behavioral skills to reduce distress.

DEVELOPMENT PROJECTS (0 Development Projects Listed)

No development projects.

RESEARCH (0 Projects Listed)

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Nehlsen AD, Sindhu KK, Moshier E, Richter J, Richard S, Chari A, Sanchez L, Parekh S, Cho HJ, Jagannath S, Dharmarajan K
Clin Lymphoma Myeloma Leuk, 2022 Mar, 22(3): 192-197
https://doi.org/10.1016/j.clml.2021.09.015 | PMID: 34736880 | PMCID: PMC9040190
Citations: 26 | AltScore: 6.45

31. **Polypharmacy in older adults with cancer undergoing radiotherapy: A review.**
Novak J, Goldberg A, Dharmarajan K, Amini A, Maggiore RJ, Presley CJ, Nightingale G
J Geriatr Oncol, 2022 Feb 25, 13(6): 778-783
pii: S1879-4068(22)00035-2. https://doi.org/10.1016/j.jgo.2022.02.007 | PMID: 35227626 | PMCID: PMC9283217
Citations: 60 | AltScore: 6.35

32. **Home, but Not Homebound: A Prospective Analysis of Persons Living With Dementia.**
Reckrey JM, Leff B, Kumar RG, Yee C, Garrido MM, Ornstein KA
J Am Med Dir Assoc, 2022 Jan 19, 23(10): 1648-1652.e1
pii: S1525-8610(21)01103-8. https://doi.org/10.1016/j.jamda.2021.12.029 | PMID: 35063398 | PMCID: PMC9294063
Citations: 30 | AltScore: 1.6

33. **Caring Together: Trajectories of Paid and Family Caregiving Support to Those Living in the Community with Dementia.**
Reckrey JM, Li L, Zhan S, Wolff J, Yee C, Ornstein KA
J Gerontol B Psychol Sci Soc Sci, 2022 Jan 16, 77(Supplement_1): S11-S20
pii: gbac006. https://doi.org/10.1093/geronb/gbac006 | PMID: 35034123 | PMCID: PMC9122661
Citations: 49 | AltScore: 4.1

34. **Plasma Amyloid and in vivo Brain Amyloid in Late Middle-Aged Hispanics.**
Rippon B, Palta P, Tahmi M, Sherwood G, Soto L, Cespedes S, Mesen Y, He H, Laing K, Moreno H, Teresi J, Razlighi Q, Brickman AM, Zetterberg H, Luchsinger JA
J Alzheimers Dis, 2022, 87(3): 1229-1238
https://doi.org/10.3233/JAD-210391 | PMID: 35466933
Citations: | AltScore: 9.25

35. **Cost of home hospitalization versus inpatient hospitalization inclusive of a 30-day post-acute period.**
Saenger PM, Ornstein KA, Garrido MM, Lubetsky S, Bollens-Lund E, DeCherrie LV, Leff B, Siu AL, Federman AD
J Am Geriatr Soc, 2022 May, 70(5): 1374-1383
https://doi.org/10.1111/jgs.17706 | PMID: 35212391 | PMCID: PMC9307069
Citations: 42 | AltScore: 9.8

36. **Health equity in Hospital at Home: Outcomes for economically disadvantaged and non-disadvantaged patients.**
Siu AL, Zhao D, Bollens-Lund E, Lubetsky S, Schiller G, Saenger P, Ornstein KA, Federman AD, DeCherrie LV, Leff B

J Am Geriatr Soc, 2022 Apr 1, 70(7): 2153-2156
https://doi.org/10.1111/jgs.17759 | PMID: 35363372 | PMCID: PMC9283257
Citations: 6 | AltScore: 59.322

37. **Evaluation of Family Characteristics and Multiple Hospitalizations at the End of Life: Evidence from the Utah Population Database.**
Tay DL, Ornstein KA, Meeks H, Utz RL, Smith KR, Stephens C, Hashibe M, Ellington L
J Palliat Med, 2022 Mar, 25(3): 376-387
https://doi.org/10.1089/jpm.2021.0071 | PMID: 34448596 | PMCID: PMC8968848
Citations: 56 | AltScore: 4.35

38. **The Lake Wobegon Effect-Where Every Medicare Advantage Plan Is \Above Average\.**
Teno JM, Ankuda C
JAMA Health Forum, 2022 Oct 7, 3(10): e224320
https://doi.org/10.1001/jamahealthforum.2022.4320 | PMID: 36264547 | PMCID: PMC10107699
Citations: 3 | AltScore: 33.5

39. **Examination of the Measurement Equivalence of the Functional Assessment in Acute Care MCAT (FAMCAT) Mobility Item Bank Using Differential Item Functioning Analyses.**
Teresi JA, Ocepek-Welikson K, Ramirez M, Kleinman M, Wang C, Weiss DJ, Cheville A
Arch Phys Med Rehabil, 2022 May, 103(5S): S84-S107.e38
https://doi.org/10.1016/j.apmr.2021.03.044 | PMID: 34146534 | PMCID: PMC10243473
Citations: 65 | AltScore: 2.75

40. **Guidelines for Designing and Evaluating Feasibility Pilot Studies.**
Teresi JA, Yu X, Stewart AL, Hays RD
Med Care, 2022 Jan 1, 60(1): 95-103
https://doi.org/10.1097/MLR.0000000000001664 | PMID: 34812790 | PMCID: PMC8849521
Citations: 50 | AltScore: 2.35

EXTERNAL ADVISORY BOARD MEMBERS

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RECOGNITION AND AWARDS (2022-2023)

Recognition and Awards not specified.

MINORITY RESEARCH

General Brief Description of Minority Activities:

No minority trainee information specified.

No minority grant information specified.

NORTHWESTERN UNIVERSITY
Claude D. Pepper Older Americans Independence Center

Michael S Wolf, PhD, MPH   312-503-5592   mswolf@northwestern.edu
Principal Investigator

Jeffrey A. Linder, MD, MPH   312-503-6202   jlinder@northwestern.edu
Principal Investigator

Julia Benavente   312-503-5585   julia.benavente@northwestern.edu
Center Manager

CENTER DESCRIPTION

The Northwestern Pepper Center's mission is to improve primary care management of older, more medically complex adults living with multiple chronic conditions (MCC). We will identify and train future leaders in geriatrics and gerontology research through mentorship, sharing of resources, and pilot projects. The training emphasizes care for older adults with MCC, as they are at higher risk of poor outcomes and costly care.

The specific aims of the Northwestern Pepper Center are to:

Aim 1 Formalize a comprehensive, multidisciplinary, aging research program dedicated to improving healthcare, functional independence, and quality of life for older adults with MCC.

We will unite internationally recognized geriatricians and aging research faculty to establish a formal presence as a collaborative center promoting new investigations around improving the primary care management, and overall health of medically complex older adults with MCC. Through an Information Dissemination Core, the Northwestern OAIC will leverage broad local, regional and national primary care networks to rapidly translate research findings, share evidence-based practices, and support their implementation.

Aim 2 Expand Northwestern training and mentoring activities to develop future leaders in geriatrics and aging research who will transform healthcare to meet the needs of older adults with MCC.

Junior faculty and fellows across multiple disciplines who have aging and MCC-related research interests will participate as mentored scientists within our OAIC, working closely with affiliated faculty to establish a successful career trajectory to becoming independent investigators. Our linked Research Education and Pilot/Exploratory Studies Cores, supported by three Resource Cores will provide trainees with substantive & methodological mentorship and extensive research opportunities through relevant External, Developmental and Pilot Projects.

Aim 3 Stimulate applied research on the innovative design of primary care models that align with the priorities of older adults with MCC through aging-specific research resources and expertise in healthcare system & technology design ('Design Core'), patient-reported outcomes measurement ('Measurement Core') and quantitative & qualitative data analytics ('Analytics Core').

The Northwestern OAIC will provide 3 essential Resource Cores (Design, Measurement, Analytics) to support MCC-related Developmental Projects, such as: 1) developing multifaceted, technology-enabled interventions to promote clinician adherence to best practices in the management of older adults with MCC, and supporting older patients and their caregivers' engagement in primary care and self-management of MCC; 2) the routine collection of

patient-reported outcomes and priorities in primary care to improve clinical decision making; 3) developing assessment tools to quantify patients' disease burden, treatment burden and overall medical care complexity for purposes of risk stratification; and 4) new methodological approaches to data harmonization across healthcare systems to better capture older adults' health and frailty status. We will also seek out new MCC-related investigations through our Pilot/Exploratory Studies Core and an extensive portfolio of ongoing External Projects.

CORES

Leadership & Administrative Core (LAC)

Leader 1:   Michael S. Wolf, PhD, MPH   mswolf@northwestern.edu

Leader 2:   Jeffrey A. Linder, MD, MPH   jlinder@northwestern.edu

Leader 3:   Lee Lindquist, MD, MPH, MBA lal@northwestern.edu

The Leadership/Administrative Core (LAC) oversees the daily operations of the Northwestern OAIC and the implementation of its mission, coordinating activities amongst all of the center Cores and organizational partners from the community, government, healthcare system, industry and other academic institutions.

Research Education Core (REC)

Leader 1:   Sara M. Bradley, MD   sara.bradley@northwestern.edu

Leader 2:   Allen Heinemann, PhD   a-heinemann@northwestern.edu

Leader 3:   June McKoy, MD JD MBA j-mckoy@northwestern.edu

The Research Education Core (REC) is the mentorship arm of the OAIC, developing programs to assess the formative needs of Pepper Scholars and provide them with personalized educational, career development, and networking opportunities to facilitate their research.

Pilot/Exploratory Studies Core (PESC)

Leader 1:   Mary McDermott, MD mdm608@northwestern.edu

Leader 2:   Emily Rogalski, PhD   e-rogalski@northwestern.edu

The Pilot/Exploratory Studies Core (PESC) is a primary home to our OAIC's scientific and scholarly training, responsible for the review and selection of at least 15 pepper scholars and 12 pilot project funding recipients and overseeing their progress throughout the award period.

Healthcare System & Technology Design Core (Design Core)

Leader 1:   David C Mohr, PhD   d-mohr@northwestern.edu

Leader 2:   Rachel Kornfield, PhD rachel.kornfield@northwestern.edu

Leader 3:   Andrew Berry, PhD   andrew.berry@northwestern.edu

The Healthcare System & Technology Design Core provides expertise to junior investigators, Core and National Pepper Center Network faculty in the design, development, evaluation, and implementation of technology-enabled services for older adults with MCC.

Information Dissemination Core (IDC)

Leader 1:   Ron Ackermann, MD, MPH   r.ackermann@northwestern.edu
Leader 2:   David Liebovitz, MD   davidl@northwestern.edu

The Information Dissemination Core (IDC) distributes research findings through an array of communication channels to patients, families, care practices and policymakers. The IDC also solicits ideas from stakeholders to inform the development of new research projects and products.

Patient-Reported Outcomes Measurement Core (Measurement Core)
Leader 1:   David Cella, PhD   d-cella@northwestern.edu
Leader 2:   Daniel K Mroczek, PhD   daniel.mroczek@northwestern.edu
Leader 3:   Eileen Graham, PhD   eileen.graham@northwestern.edu

The Patient-Reported Outcomes Measurement Core provides measurement expertise for the entire Northwestern OAIC and national Pepper Center Network and serves as a resource to the Research Education Core for junior faculty seeking skills in measurement and the deployment of tools in primary care.

Quantitative and Qualitative Data Analytics Core (Analytics Core)
Leader 1:   Leah Welty, PhD   lwelty@northwestern.edu
Leader 2:   Kenzie Cameron, PhD, MPH k-cameron@northwestern.edu
Leader 3:   Laura Curtis, MS   l-curtis@northwestern.edu
Leader 4:   Mary Kwasny, ScD   m-kwasny@northwestern.edu

The Data Analytics Core provides expertise on quantitative and qualitative research design and analytic methods supporting affiliated faculty, cores, and pilot projects, while developing new methods for determining older adults' health status to better inform clinical decision making.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications
Diana Chirinos, PhD Assistant Professor / Northwestern University, Feinberg School of Medicine, Department of Preventive Medicine (Epidemiology) <u>Differential Associations Between Spousal Bereavement, Physical Functioning, and Health Outcomes Among White and Latino Older Adults</u>	2023-2025 / 19 (total) 5 (1st/Sr)
Allison Pack, PhD Research Assistant Professor / Northwestern University, Feinberg School of Medicine, Department of Medicine (General Internal Medicine & Geriatrics) <u>Adaptation and Pilot Testing of the Phenotyping Adherence Through Technology-Enabled Reports and Navigation (PATTERN) Study</u>	2022-2024 / 3 (total) 1 (1st/Sr)
Daniel Rees Lewis, PhD Research Assistant Professor / Northwestern University, Segal Design Institute & Mechanical Engineering <u>Leveraging Human-Computer Interaction and Learning Sciences to Support Older Adults' Use of Telehealth Software for Chronic Disease Self-care</u>	2022-2024 / 15 (total) 5 (1st/Sr)
Minjee Kim, MD Assistant Professor / Northwestern University, Feinberg School of Medicine, Department of Neurology <u>Technology-Enabled Screening Strategy for Obstructive Sleep Apnea (TEST-OSA) in Primary Care Older Patients with Multiple Chronic Conditions</u>	2022-2024 / 6 (total) 4 (1st/Sr)
Kelly Jarvis, PhD Research Assistant Professor / Northwestern University, Feinberg School of Medicine, Department of Radiology <u>Heart-brain MRI evaluation of hemodynamic coupling in hypertension and healthy aging</u> ● Heart-brain MRI for the evaluation of hemodynamic coupling in aging and Alzheimer's disease (1K01AG080070)	2022-2024 / 1 (total) 0 (1st/Sr)
Prakash Jayabalan, MD Assistant Professor / Northwestern University, Feinberg School of Medicine, Department of Physical Medicine & Rehabilitation <u>The Development of Novel Therapeutic Walking Exercise Strategies in Sedentary Individuals with Knee Osteoarthritis</u>	2022-2024 / 5 (total) 1 (1st/Sr)

Emi C. Bretschneider, MD
Assistant Professor / Northwestern University, Feinberg School of Medicine, Department of Obstetrics and Gynecology (Female Pelvic Medicine and Reconstructive Surgery (Urogynecology))
<u>Ready for Advances in Bladder health for Older Women (The RAInBOW Study)</u>

2022-2024 /
11 (total)
3 (1st/Sr)

Marquita Lewis-Thames, PhD
Research Assistant Professor / Northwestern University, Feinberg School of Medicine, Department of Medical Social Sciences
<u>Designing a Telehealth-Based Tool for Rural Older Adults with Cancer and Cancer-Related Distress: Testing for Usability and Acceptability</u>
- Assessing the usability and utilization of telehealth among COVID-era rural older cancer survivors (IRG-21-144-27)

2021-2023 /
14 (total)
5 (1st/Sr)

Whitney Welch, PhD
Research Assistant Professor / Northwestern University, Feinberg School of Medicine, Department of Preventive Medicine (Behavioral Medicine)
<u>Remote Sensor-Based Frailty Detection in Older Adults</u>
- Micro-randomized trial of a physical activity intervention to manage pain symptoms among older cancer survivors (1K01CA255414)

2021-2023 /
8 (total)
2 (1st/Sr)

Emma L Barber, MD
Assistant Professor / Northwestern University, Feinberg School of Medicine, Department of Obstetrics and Gynecology (Gynecologic Oncology)
<u>A pilot study of prehabilitation during the neoadjuvant window of opportunity in older women with ovarian cancer (Fit4Surgery)</u>
- Patient-Tailored Physical Activity Intervention Among Older Women with Gynecologic Cancers Undergoing Chemotherapy (FIT4TREATMENT) (1R01AG081291)

2021-2023 /
17 (total)
3 (1st/Sr)

Mary Clare Masters, MD
Fellow / Northwestern University, Feinberg School of Medicine, Department of Medicine (Infectious Diseases)
<u>Associations between plasma biomarkers of the Senescence-Associated Secretory Phenotype and frailty in older persons with HIV</u>
- Associations between plasma biomarkers of the Senescence-Associated Secretory Phenotype and frailty in older persons with HIV (UWSC14341 BPO#71232//5R33AG067069)
- Associations between sleep disorders and frailty in older PWH (K12)

2021-2023 /
6 (total)
5 (1st/Sr)

Rebecca Lovett, PhD
Fellow / Northwestern University, Feinberg School of Medicine, Department of Medicine (General Internal Medicine & Geriatrics)
<u>Development and Pilot Testing of the 'EHR-enabled Activity promotion using CBT via Telehealth for Depression (ENACT-D)' Intervention for Older Adults in Primary Care</u>

2021-2023 /
7 (total)
2 (1st/Sr)

Past Scholars

Rachel O'Conor, PhD, MPH, Northwestern University, Feinberg School of Medicine, Department of Medicine (General Internal Medicine & Geriatrics) (2020-2022)

Miriam Rafferty, DPT PhD, Northwestern University, Feinberg School of Medicine, Department of Physical Medicine & Rehabilitation (2020-2022)

Katherine O'Brien, MD, Northwestern University, Feinberg School of Medicine, Department of Medicine (General Internal Medicine & Geriatrics) (2020-2022)

Theresa Rowe, DO MS, Northwestern University, Feinberg School of Medicine, Department of Medicine (General Internal Medicine & Geriatrics) (2020-2022)

Sadiya Khan, MD MSc, Northwestern University, Feinberg School of Medicine, Department of Medicine (Cardiology) and Department of Preventive Medicine (Epidemiology) (2020-2022)

PILOT/EXPLORATORY PROJECTS (9 Pilot Projects Listed)

1. Project Title: **Prevalence of microvascular dysfunction and association with functional limitation in older adults with chronic obstructive pulmonary disease**

Leader: **Sadiya Khan, MD, MSc**

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are major public health epidemics and commonly coexist in older adults (65+ years). Broadly, cardiovascular causes account for 50% of all deaths in patients with COPD. Specifically, 1 in 3 patients with COPD also have prevalent HF, and this associated with greater functional intolerance, worse health-related quality of life, and increased healthcare expenditures compared with patients with COPD and without HF. Given the high burden of mortality and morbidity with comorbid COPD and HF, identifying key risk factors to prevent functional decline related to HF risk in older adults is critically important. Therefore, we propose an observational, cross-sectional study in older adults (?65 years) with COPD who have no known history of coronary artery disease or heart failure to examine cross-sectional associations between severity of COPD and microvascular dysfunction, functional status with 6-minute walk test, dyspnea symptoms, and cardiac biomarkers.

The specific aims of this pilot are: (1) Determine the cross-sectional association between severity of COPD (GOLD Stages) and microvascular dysfunction; (2) Determine the cross-sectional association between severity of COPD (GOLD Stages) and 6-minute walk test, patient reported outcome for dyspnea, and cardiovascular biomarkers.

2. Project Title: **Designing a Telehealth-Based Tool for Rural Older Adults with Cancer and Cancer-Related Distress: Testing for Usability and Acceptability**

Leader: **Marquita Lewis-Thames, PhD**

Older adults have difficulties identifying symptoms of anxiety and reduced likelihood of knowing when to access mental health services. One in four adults >65 years old lives in a rural or small town, where mental health specialists and similar resources are often dispersed or located in distal urban centers. To this end, rural older adults with cancer-related anxiety or distress (CRD) are particularly vulnerable to poorer mental health and cancer-related outcomes. This project proposes a strategy to improve CRD outcomes for rural older adults via a telehealth–based program that supports the management of CRD by integrating clinical and community-based resources.

The specific aims of this pilot are:

Aim 1: Assess barriers and facilitators of telehealth access from rural older cancer patients, caregivers, and healthcare professionals to guide the development of a telehealth delivered CRD management tool.

Aim 2: Develop a theoretically-grounded telehealth CRD management tool using a human-centered design.

Aim 3: Conduct user testing to inform the final version and an intervention protocol to test the implementation an effectiveness of the telehealth CRD management tool.

3. Project Title: **Adaptation and Pilot Testing of the Phenotyping Adherence Through Technology-Enabled Reports and Navigation (PATTERN) Study**

Leader: **Allison Pack, PhD**

We will adapt and pilot test a technology-enabled, primary care strategy for routinely monitoring medication use and adherence among older adults with multiple chronic conditions and polypharmacy. An ongoing Northwestern trial ('TAKE IT'; R01DK110172) has been able to leverage an electronic health record (EHR) platform and its linked patient portal (Epic, MyChart [MyNM]) to: 1) routinely engage new adult kidney transplant recipients via monthly portal-based adherence assessments; 2) flag and phenotype reported adherence concerns; 3) alert care teams via secure messaging of the specific adherence concern(s); and 4) mobilize available resources tailored to identified barriers (e.g. SMS text reminders for cognitive barriers, a comprehensive medication review via phone or video telehealth to address regimen complexity, social work referral for social or economic concerns, etc.) following a standard protocol. With this award, we will adapt the TAKE IT strategy for use in primary care, targeting older adults with MCC and polypharmacy (using Medicare Part D medication therapy management criteria of ?8 medications). This intervention, renamed as the PATTERN study (Phenotyping Adherence Through Technology-Enabled Reports and Navigation) will then be pilot tested at one Northwestern Medicine (NM) primary care practice to determine its acceptability, feasibility, and preliminary fidelity.

The specific aims are:

Aim 1: Adapt the PATTERN intervention for use in primary care using input from key stakeholders.

Aim 2: Assess the PATTERN intervention's feasibility and acceptability for use in primary care.

4. Project Title: **Leveraging Human-Computer Interaction and Learning Sciences to Support Older Adults' Use of Telehealth Software for Chronic Disease Self-care**

Leader: **Daniel Rees Lewis, PhD**

There is currently a gap between the existing and needed clinical support to help older adults learn to manage their conditions. The current system of care does not help patients with chronic conditions (e.g., diabetes) learn effective self-care, and there are few programs developed for older adults. Consequently, there is increased pressure on primary care clinicians, who must help teach older adults to manage their conditions in just a few short minutes they have to meet. This project will seek to leverage Human Computer Interaction (HCI) and Learning Science (LS) methods and designs to create telehealth supports for older adults responsible for learning to manage their own health. I will focus on older adults with type II diabetes, and at least one of hypertension and high cholesterol. While older adults can find software challenging, HCI research shows by attending to their needs we can help them effectively use software (Brewer et al., 2016). Helping older adults to better use telehealth can increase learning and improve health outcomes for older adults while reducing the burden on primary care.

Aim 1: Use cognitive task analysis (CTA) methods to understand the barriers older adults have when using telehealth for self-care management.

Aim 2: Apply findings from Aim 1 to design a learning module to support using existing

diabetes telehealth software and then engage in iterative redesign for and with older adults.

5. Project Title: **Technology-Enabled Screening Strategy for Obstructive Sleep Apnea (TEST-OSA) in Primary Care Older Patients with Multiple Chronic Conditions**

Leader: **Minjee Kim, MD**

We will adapt and pilot test a technology-enabled, primary care strategy to promote the timely detection and treatment of sleep apnea among older adults at high risk due to multiple chronic conditions.

Obstructive sleep apnea (OSA), characterized by repeated episodes of upper-airway obstruction during sleep, is estimated to affect up to 35% of older adults 65 and older, yet it is vastly underdiagnosed. Undiagnosed and untreated OSA is associated with an increased risk for incident hypertension, coronary heart disease, heart failure, stroke, and mortality, as well as increased motor vehicle crashes, mood disorders and reduced quality of life. OSA is a leading cause of sleep disturbance in older adults and has been linked to more rapid accumulation of chronic diseases and multimorbidity.

Many approaches have been taken to improve primary care detection of OSA, yet evidence has been highly variable with regard to the acceptability, feasibility, and effectiveness of what has been recently summarized as a range of 'fragmented' interventions not limited to high-risk older adults. Yet with widespread use of electronic health records (EHR), there are opportunities to overcome existing screening barriers, streamline clinical workflows, and activate care teams to enable the timely diagnosis of OSA and initiation of appropriate treatment. With this Pepper Scholar application, I will model an existing intervention (Toolbox Detect; R01AG069762) leveraging consumer technology (iPad), tethered to the EHR for routinely screening for cognitive impairment as part of Medicare Annual Wellness Visits (AWV), for use in the early detection of OSA among high-risk adults meeting AHA criteria or with MCC. This Technology-Enabled Screening Targeting Obstructive Sleep Apnea (TEST-OSA) strategy will promote the primary care detection and treatment of OSA among high-risk adults.

It is hypothesized that TEST-OSA, compared to usual care, will increase timely diagnosis of OSA and treatment initiation, without added burden to clinicians. My specific aims are to:

Aim 1 Develop and refine the TEST-OSA primary care strategy for high-risk older adults, including those with MCC using input from key stakeholders.

Aim 2 Pilot Test the TEST-OSA strategy to determine its acceptability, feasibility, and fidelity in primary care and explore any patient, provider, or health system barriers to implementation.

6. Project Title: **Heart-brain MRI evaluation of hemodynamic coupling in hypertension and healthy aging**

Leader: **Kelly Jarvis, PhD**

Cardiovascular risk factors, such as hypertension and physical inactivity, are among "potentially modifiable" dementia risk factors that can be influenced in mid to later life. However, mechanisms underlying heart-brain hemodynamic coupling are not well understood. In order to successfully inform new approaches for preventing, delaying or improving quality of life for those suffering from multiple chronic conditions of the heart and brain, interactions between these two major organs need to be further explored.

MRI is an established diagnostic tool for assessing cardiovascular function and neuroimaging markers of cerebrovascular disease and neurodegeneration. In the past decade, 4D flow MRI has emerged as a powerful technique for measuring 3D hemodynamics in the heart and brain vessels. Previously, I developed imaging tools for visualization and quantification of cardiovascular hemodynamics, demonstrating the comprehensive and individualized analysis of complex flow pathways. Using these techniques, I found significant age-related changes in aortic stiffness assessed by pulse wave velocity (PWV). Results in 100 healthy controls (19-79 years) showed a strong correlation with age ($r=0.79$, p

Abnormalities in heart and brain regions, however, have been historically assessed independently in scanners dedicated for either cardiovascular or neuroimaging studies. Recent developments in MRI provide the ability to image faster and thus an opportunity for integrating cardiovascular 4D flow MRI with neuroimaging in a single patient exam. I have designed a preliminary "heart-brain MRI" protocol and acquired pilot data in 12 healthy individuals (age: 24-76) to demonstrate feasibility (Jarvis et. al. ISMRM abstract 2022). This novel approach will be used for comprehensive assessment of heart-brain coupling in an initial study of cognitively healthy adults.

AIM: Apply novel heart-brain MRI methods in study of hypertension and normal cognitive aging.

a. Establish normative heart-brain MRI values and quantify interactions across adult lifespan.

b. Evaluate potential impacts of hypertension on hemodynamic coupling.

7. Project Title: **The Development of Novel Therapeutic Walking Exercise Strategies in Sedentary Individuals with Knee Osteoarthritis**

Leader: **Prakash Jayabalan, MD**

Knee osteoarthritis (OA) and cardiovascular disease (CVD) are the two most prevalent medical conditions in individuals above the age of 70. Physical inactivity resulting from OA is known to increase CVD risk in elderly patients and thus shorten their lifespan. Muscle weakness and chronic inflammation are also known to be a significant component of both diseases, and non-steroidal anti-inflammatory drugs (NSAIDs), commonly used to treat OA-related pain are also associated with an increased risk of CVD. Moderate intensity physical activity is strongly advocated for the treatment of both diseases. Randomized clinical trials of walking exercise have shown significant short-term improvements in knee pain, functional status, and quality of life in patients with OA and, in turn, beneficial effects on cardiovascular parameters. However, more recent randomized controlled trials of walking exercise programs in elderly persons with knee OA reported dropout rates as high as 20-40%, indicating reluctance to adopt walking as a lasting form of exercise. Evidence suggests that patients stop exercising due to exercise-induced exacerbation of symptoms, beliefs that exercise could be damaging to their knees, and reduced capacity to perform exercises at intensities and durations recommended,

further worsening concurrent CVD parameters. In elderly sedentary individuals with knee OA and CVD, there remains a pivotal need for a physical activity intervention that allows for sustained walking exercise engagement, reducing joint pain and cardiometabolic risk while improving function and cardiovascular parameters.

The study we propose is a randomized controlled trial in individuals with mild to moderate knee OA (n=30 in each group), evaluating the symptomatic, biochemical, and biomechanical benefits of 3 walking exercise treatments: 1) LBPP treadmill walking 2) aquatic walking 3) standard of care land-based walking exercise for the same duration.

Specific Aim 1: Delineate within-participant longitudinal changes in joint pain, quadriceps strength, function (Knee Osteoarthritis Outcome score, KOOS), quality of life (SF-36), NSAID use and serum biomarkers of joint disease, following 12 weeks of off-loaded walking exercise (either LBPP or aquatic walking versus land walking exercise).

Specific Aim 2: Delineate differences in longitudinal changes of cardiovascular parameters (blood pressure, VO2 max, HbA1c and lipid profile) and cardiometabolic markers (serum adiponectin, and inflammatory mediators), following 12 weeks of these respective walking strategies.

8. Project Title: **Ready for Advances in Bladder health for Older Women (The RAInBOW Study)**

Leader: **Emi C. Bretschneider, MD**

I will develop a patient-centered, individualized overactive bladder (OAB) program uniquely designed for older women that: 1) systematically assesses baseline comorbid conditions and medication use using an integrated online portal-based tool; 2) closely monitors OAB symptoms, treatment response and adverse effects via an online portal-based tool; and 3) proactively adjusts treatments to minimize bothersome OAB symptoms utilizing telehealth visits and expediting the transition to advanced therapies as indicated. I aim to study the impact of this program on patient symptom severity and bother, overall health status and overall quality of life. Over 1-year, women 65 years of age or older with OAB who present to Northwestern's Integrated Pelvic Health Program (N=60) will be invited to participate in a study comparing outcomes in women (n=30) treated via normal care pathway and (n=30) treated in an OAB program with the integrated online portal-based tools.

Specific aim 1: To develop an online portal-based tool using a human-centered design to systematically assess patient-reported medication use, comorbid conditions and overall health status as well as OAB-condition specific questions such as symptoms, symptom severity, treatment adherence, treatment response, treatment-related adverse effects and patient satisfaction.

Specific aim 2: To perform a pilot study of the online portal-based technology compared to usual care in order to test the usability, acceptability and feasibility of the tool.

9. Project Title: **Differential Associations Between Spousal Bereavement, Physical Functioning and Health Outcomes Among White and Latino Older Adults**

Leader: **Diana Chirinos, PhD**

Our study will examine how bereavement impacts physical functioning and overall health in a diverse sample of older adults. We will capitalize on two ongoing NIH-funded studies of older adults (5R01HL152442-03) and bereavement (5K01HL149987-03) with harmonized measures and recruit additional bereaved participants (predominantly Latino) allowing us to test novel hypotheses that go beyond the goals of the parent studies. New participants will complete an in-person visit where data on physical functioning, mental and physical health will be collected. In addition, Latino bereaved spouses will participate in an in-depth interview aimed at identifying potential resilience factors during the visit. Individual differences in coping with a loss arise from individual perceptions, social contexts, and cultural beliefs. Thus, Latino culture-specific values (e.g., familism, religiosity) as well as factors such as social support and household composition may play an important role in the grieving process and have a protective effect on the impact of bereavement on physical functioning and health outcomes. Identification of those factors will not only inform our understanding of risk but will also aid in the development of culturally sensitive interventions.

Specific aims:

Aim 1: To examine the association between bereavement status (bereaved vs. non-bereaved), physical functioning (perceived functional limitations), physical (# of chronic conditions, inflammation), and mental health (quality of life, depressive and anxiety symptoms) outcomes among older adults.

Aim 2: To assess differences by ethnicity (Latino vs. NHW) in the association between bereavement status, physical functioning, and physical and mental health outcomes among older adults.

Aim 3. To identify contextual and cultural factors that facilitate coping with bereavement among Latino older adults.

DEVELOPMENT PROJECTS (5 Development Projects Listed)

1. Project Title: **Minimizing Misclassification of Comorbidities**

    Leader: **Mary Kwasny, ScD and Laura Curtis, MS**

    Core(s):   Quantitative and Qualitative Data Analytics Core (Analytics Core)

- Misclassified comorbidities limit accurate estimation of relationships between risk factors and health outcomes.
- Comorbidities are often self-reported rather than derived from health records
- This Development Project combines and expands methods using EHR data (e.g. PheKB) to better classify comorbidities.

2. Project Title: **New index representing medical complexity**

    Leader: **Laura Curtis, MS and Mary Kwasny, ScD**

    Core(s):   Quantitative and Qualitative Data Analytics Core (Analytics Core)

- Most existing health care indices are either disease specific or designed to assess overall health of the patient
- This Development Project will create a new index combining the burden of illness in the health care system (e.g. more conditions or providers) and the burden of treatment for the patient (self-monitoring, lab visits, patient's perception).
- Ultimate goal: better inform the health care system about patient needs to obtain the maximum benefit of health care interactions.

3. Project Title: **An Individualized, Patient-Centered PRO Monitoring System**

    Leader: **Eileen Graham, PhD**

    Core(s):   Patient-Reported Outcomes Measurement Core (Measurement Core)

Conduct a DP to build an individualized, patient-centered system for primary and specialist care settings to monitor relevant patient-reported outcomes (PROs) among older adults living with MCC and determine whether PROs can predict clinical outcomes.

4. Project Title: **Technology-Enabled Primary Care for Mental and Physical Health MCCs**

    Leader: **Andrew Berry, PhD**

    Core(s):   Healthcare System & Technology Design Core (Design Core)

This Development Project will:

- identify patient barriers to effective communication with internal medicine providers among older adults with symptoms of anxiety and depression and their caregivers

- develop a low fidelity prototype of a patient organizational system to enhance communication with providers that will be detailed in a design document.

5. Project Title: **Summative Design Guideline Development**
   Leader: **Andrew Berry, PhD**
   Core(s):   Healthcare System & Technology Design Core (Design Core)

This Development Project will:

- Develop and disseminate a methodology guide that summarizes best practices for applying user-centered design (UCD) to optimize technology-enabled services for older adults with MCC.

RESEARCH (12 Projects Listed)

1. Project Title: **Management of Complex Medication Regimens among Older Adults with Alzheimer's Disease and Related Dementias and their Caregivers**

Leader(s):   **O'CONOR, RACHEL**
NORTHWESTERN UNIVERSITY AT CHICAGO
NIH K01AG070107 / (2021 - 2025)

Core(s):

Alzheimer s disease and related dementias (ADRD) are progressive diseases characterized by their debilitating impact on cognitive function. Adults ages 65 years and older represent the majority of cases, and are managing not only ADRD, but multiple chronic conditions (MCC) that are common with advancing age. Adherence to prescribed medication regimens is critical to optimize both cognitive and physical health, but is especially difficult in the context of multidrug regimens. Little is known about how older adults with ADRD self-manage their medications, how these responsibilities transition to caregivers as the disease progresses, how capable caregivers are to fulfill these responsibilities, and how ambulatory care practices support patients and caregivers to ensure safe medication use and adherence. This K01 application seeks to provide training for Dr. Rachel O Conor to launch an independent research agenda focused on understanding the cognitive and psychosocial determinants of chronic disease self-management behaviors and health outcomes for older adults and their caregivers as they manage complex chronic conditions, including ADRD. To achieve this goal, her short-term training goals are to: acquire scientific knowledge in ADRD pathophysiology and care, gain exposure to the clinical management of older adults with ADRD in geriatric and specialty memory clinics, gain experience conducting research with cognitively impaired individuals and their caregivers, and obtain formal training in longitudinal data analysis and advanced statistical techniques. The objective of the proposed research is to examine medication self-management behaviors among a diverse sample of older adults with ADRD + MCC and their caregivers. Dr. O Conor will partner with the Northwestern Alzheimer s Disease Center and an ongoing, NIA-funded cognitive aging cohort study to conduct complementary mixed methods investigations. The research aims are to 1) Examine the evolving strategies employed by older adults with ADRD and their caregivers to self- manage multidrug regimens as the disease progresses over time; 2) Characterize barriers primary care clinicians face engaging older adults and caregivers in the management of ADRD and MCC; 3) Investigate associations between cognitive decline and medication self-management behaviors among older adults managing complex multidrug regimens; 4) Explore factors influencing associations between cognitive decline and medication self- management behaviors. The proposed investigations will inform the development and evaluation of a primary care based intervention to support older adults with ADRD + MCC and their caregivers in their medication management, and serve as the foundation for a unique cohort study to prospectively investigate how older adults with early stage ADRD + MCC and their caregivers transition medication self-management roles over the disease course, and its impact on health outcomes.

2. Project Title: **LITCOG IV: HEALTH LITERACY AND COGNITIVE FUNCTION AMONG OLDER ADULTS**

Leader(s):   **WOLF, MICHAEL S**
NORTHWESTERN UNIVERSITY AT CHICAGO
NIH R01AG030611 / (2007 - 2025)

Core(s):

We request to continue our NIA cohort study (LitCog ; R01AG030611). LitCog studies the confluence of increased medical morbidity resulting in complex patient self-management (SM) roles, and cognitive decline, which may affect older patients health literacy (HL) skills and chronic illness self-care. Functionally independent, cognitively normal adults ages 55-74 (N=900) were recruited from community primary care practices in Chicago. Participants have completed comprehensive cognitive, psychological, social, behavioral, and functional health assessments every 3 years (4 interviews; 2008-2018). The sample is diverse by race, socioeconomic status and medical morbidity; uncommon among cognitive aging studies. A 1st renewal award (LitCog II) examined changes in cognition, HL and SM skills over 6 years and their associations with physical and mental health. We found cognitive function to be strongly associated with HL; both decline together over time. Cognitive function and HL also determine older adults SM skills; all predict functional health status and its decline. A 2nd renewal (LitCog III) has allowed us to capture new health behaviors, chronic disease outcomes, and healthcare use from medical, pharmacy records a decade post-baseline. Cognitive function, HL and SM skills impact all of these outcomes. LitCog III is almost complete; 774 of 900 (86%) subjects are alive and available for further study. We now propose to

conduct follow-up assessments 12 and 15 years post-baseline (LitCog IV). With 6 interviews over 15 years, specific trajectories of decline in cognition, HL, SM skills and health status can be closely studied. The prevalence of and adjustment to increasing morbidity, disability, cognitive impairment (including Alzheimer s Disease & Related Dementias (ADRD)) allow for new outcomes for investigation. Mortality data will also now be available with extended follow-up. Our primary aim is to 1) evaluate trajectories in cognitive function, HL and SM skills over 15 years among older adults, and their associations with health outcomes. LitCog is an exceptionally unique cognitive aging cohort study as it is framed in the context of health services research. Our goal has been to inform health system strategies for effectively managing older patients by understanding how cognition changes and influences HL and SM skills necessary for achieving optimal health. Modifiable factors that may mediate/moderate associations are also explored as potential intervention targets. The involvement and roles of caregivers has specifically emerged as an important social determinant of patients health. An administrative ADRD supplement (LitCog IIIA) has expanded our inquiry by including interviews with caregivers (informal or paid) involved in supporting the care of 60% of participants. In LitCog IV, we will create a parallel caregiver cohort, with the secondary aims to 2) investigate associations between the presence of an involved caregiver with treatment adherence, chronic disease outcomes, and functional health status among older adults; 3) identify factors influencing associations between caregiver involvement and patient outcomes

3. Project Title: DECISION MAKING AND IMPLEMENTATION OF AGING-IN-PLACE/LONG TERM CARE PLANS AMONG OLDER ADULTS

Leader(s): LINDQUIST, LEE A
NORTHWESTERN UNIVERSITY AT CHICAGO
NIH R01AG058777 / (2019 - 2024)

Core(s):

The goal of this research is to better understand how older adult aging-in-place decision making and implementation is impacted by cognitive changes seen with Alzheimer s disease, functional loss, social influences, and environmental factors. Remaining in one s own home is a priority for many older adults. Decision making and planning is critical to ensure successful aging-in-place, especially when older adults are diagnosed with Alzheimer s disease. The most important decision that many adults navigate is how to balance progressively worsening cognition, seen in Alzheimer s disease, and increasing disability with their support needs. Although a great number of older adults will need support, prior research has shown that many may dismiss planning for their home support needs outright (e.g. I plan to die in my sleep before I ever need help). Most older adults do not want to leave their home and yet very few people plan for their home-based needs that they will require to age-in-place safely, as their cognition and function worsens. Through our previously PCORI-funded research, we developed a tool, PlanYourLifespan (PYL), which facilitates making decisions and planning to age-in-place, specifically with Alzheimer s disease. Through education about future health and home-based needs as well as access to these resources, older adults can make choices and share them with loved ones for their future needs. PYL was tested in a multi-site randomized controlled trial of 385 community-dwelling older adults with 3 month follow-up and found to be significantly efficacious in improving decision making behaviors towards aging-in-place options among older adults. With the short follow-up, we were limited in determining how these decision making plans of older adults translated into goal concordance towards aging-in-place. A gap exists in how decision making for aging-in-place is impacted by older adults changes in cognition, functional loss, social factors, and environments. How these plans translate into timely adoption as well as the impact that loved ones have on goal concordance have also been unexplored. Through this research, we aim to: Aim 1. Determine how decision making and planning for aging-in-place is impacted by older adults cognition changes (e.g. as experienced with Alzheimer s disease), functional changes, multi-chronic conditions, social influences (e.g. adult offspring, spouses), and environments (e.g. rural/urban, home type). Aim 2. Examine the mediating/ moderating interactions between older adult cognition, function, social influences, and environments in decision making for aging-in-place choices. Aim 3. Assess whether decision making and planning for aging-in-place translates into timely adoption and goal concordance for older adults and their surrogate/caregiver decision makers. To achieve these aims, we will leverage both an NIA-funded cohort (LitCog, n=700) with extensive cognitive testing and a PCORI-funded intervention: PlanYourLifespan.org. We will conduct a 42 month longitudinal study of older adults from the LitCog cohort who will receive the PYL intervention on Day 1. Surveys will be conducted every 6 months in conjunction with the active LitCog research, where cognitive, social, functional, health literacy data is being collected. Additionally, data will be collected on decision changes, resource use, timing of plan implementation, and goal concordance.

4. Project Title: **Novel gastrocnemius muscle characteristics in peripheral artery disease patients associated with impaired functional performance**

Leader(s):   **PETERSON, CHARLOTTE A.; KOSMAC, KATE**
UNIVERSITY OF KENTUCKY
NIH R01AG066724 / (2021 - 2025)

Core(s):

Lower extremity peripheral artery disease (PAD) significantly affects aging populations and results in functional impairment. Although the clinical importance of finding efficacious interventions for PAD is well-recognized, few medical therapies are currently available. PAD is diagnosed using the ankle brachial index (ABI), a measure of blood flow to the lower extremities. Lower ABI is associated with worse function; however, low ABI alone cannot fully explain functional impairments in PAD. Small studies have reported oxidative stress, mitochondrial dysfunction and/or fiber damage in gastrocnemius muscle biopsies from PAD patients, suggesting skeletal muscle perturbations may contribute to functional decline. We reported highly variable fiber type composition and fiber type grouping in a small cohort of PAD patients, and observed lack of intermyofibrillar mitochondria (IMFM-) in oxidative, myosin heavy chain (MyHC) type I fibers. We have provocative new preliminary data suggesting variability in response to ongoing denervation, and in fiber type and mitochondrial adaptations, with PAD. The purpose of this study is to define specific characteristics of muscle in PAD associated with impaired walking performance through detailed immunohistochemical analyses of 400 baseline gastrocnemius muscle biopsies stored in the Northwestern biorepository, collected from 9 different clinical trials. This biorepository of muscle from PAD patients is one-of-a-kind and is associated with detailed clinical and functional characteristics of the donors. We hypothesize that variability in fiber size, fiber type and mitochondrial adaptations in response to ischemia-reperfusion damage and denervation in individuals with PAD will have value in predicting walking impairment. In Aim 1, we will quantify the proportion of IMFM- areas in type I fibers with normal type I MyHC abundance, or accumulation of type IIX MyHC and/or LC3, a marker of autophagy, and determine associations with fiber type composition and fiber size, as well as relationships of muscle features to walking performance in PAD. We hypothesize that LC3 will co-localize with IIX MyHC in IMFM- areas, suggesting both incomplete autophagic clearance of IIX MyHC and mitochondrial biogenesis during fiber transition from type IIX to type I as a result of denervation and reinnervation. In Aim 2 we will quantify denervated, NCAM+ fibers and fibers with elevated oxidative damage markers by fiber type. We hypothesize that denervation in PAD will preferentially affect fibers expressing IIX MyHC and that only IMFM- areas that accumulate IIX MyHC will be NCAM+. In Aim 3 we will perform predictive modeling of PAD disease severity and functional impairment using morphological characteristics of muscle quantified in Aims 1 and 2 as biomarkers in conjunction with supervised classification approaches. In Aim 4 we will test the hypothesis that baseline muscle characteristics will predict longitudinal functional outcomes at 6-month follow up. This model will provide a powerful tool to aide in identifying biologic processes for targeted interventions and to assess the mechanism of action and effectiveness of current pharmacological and exercise interventions in ongoing PAD clinical trials.

5. Project Title: **PERSONALITY PREDICTION OF DEMENTIA RISK AND PROGRESSION**

Leader(s):   **MROCZEK, DANIEL K.**
NORTHWESTERN UNIVERSITY AT CHICAGO
NIH R01AG067622 / (2019 - 2024)

Core(s):

This project will evaluate the role of personality and other non-cognitive risk factors (e.g., affect, resilience) that impact and moderate the pattern and progression of Alzheimer s disease (AD) and AD-related dementia, as well as change in physical and cognitive impairment. The impact of an individual s personality, their affect, and resilience are critical factors to take into account in the context of individual changes in onset and progression of Alzheimer s disease, AD-related dementia, general cognitive impairment, and physical health status. We embrace the concept of precision medicine, in the sense of understanding individual differences factors that underlie risk and resilience to health changes, including Alzheimer s disease and AD-related dementia.Individual differences in risk factors are at the heart of this project. An important aspect of this multi-study project is the potential to focus on explanations for variation in findings across independent studies of Alzheimer s disease, AD-related dementia, and physical and cognitive impairment. . We have found that in previous coordinated analyses there is often wide variation in effect sizes across studies that utilize identical measures of personality and have been analyzed using identical models, hence we propose systematic meta-regression analyses to evaluate better these individual and study-level differences. This approach promises a more in- depth understanding of lifestyle factors related to Alzheimer

s disease and AD-related dementia, as well as general cognitive impairment and physical health. Impact: This project addresses NIA research goals supporting the examination of the interplay between psychological and social factors and their role in Alzheimer s disease and AD-related dementia, as well as more general cognitive impairment and physical health declines. It also promotes robustness, replicability and reproducibility, particularly in the context of Alzheimer s disease and AD-related dementia research, through the very nature of our multi-study coordinated analysis format.

6. Project Title: COGNITIVE SUPERAGING: A MODEL TO EXPLORE RESILIENCE AND RESISTANCE TO AGING AND ALZHEIMERS DISEASE

Leader(s):   **ROGALSKI, EMILY J; GEULA, CHANGIZ ; MESULAM, MAREK-MARSEL M ;**
NORTHWESTERN UNIVERSITY AT CHICAGO
NIH R01AG067781 / (2020 - 2025)

Core(s):

Memory complaints are widespread among the elderly and aging is a major risk factor for Alzheimer's disease (AD), leading to the impression that a gradual loss of memory ability, eventually culminating in dementia, may be a nearly universal consequence of getting old. Our studies explore an alternative aging trajectory by studying 80+ year olds, who have episodic memory performance that appears to have escaped age-related decline and that remains in the range that is at least normal for 50-60 year-olds and we have labelled `SuperAgers'. We enrolled a dedicated and unique cohort of SuperAgers and Controls committed to longitudinal assessment and brain donation at death. Our initial studies identified domain-specific biologic, psychosocial, and genetic features of the SuperAgers, including maintenance of cortical integrity (especially in the anterior cingulate), an abundance of anterior cingulate Von Economo neurons and sparse cortical Alzheimer pathology compared to their cognitively average peers. These features may contribute in part to maintenance of superior memory performance past the 8th decade of life. This Project plans to extend the characterization of the SuperAging phenotype through hypothesis-driven novel evaluations of functional brain network connectivity, regional distribution of gene expression, and integrity of dendritic, synaptic and axonal markers. The proposed project will allow us to expand our unique group of SuperAgers and cognitively average peers and address important questions related to the neurobiology of resilience and cognitive reserve. By identifying neurobiologic features that contribute to superior memory performance in old age, outcomes from this project will help isolate factors that promote successful cognitive aging and perhaps also prevent age-related brain diseases such as AD. The project's reliance on a cohort that has already been partially recruited, its longitudinal design, multidisciplinary structure, and collaboration-friendly organization increases the likelihood that consequential progress will be achieved.

7. Project Title: NEGOTIATION TRAINING TO OPTIMIZE CAREGIVER COMMUNICATION IN ALZHEIMER'S DISEASE

Leader(s):   **LINDQUIST, LEE A**
NORTHWESTERN UNIVERSITY AT CHICAGO
NIH R01AG068421 / (2020 - 2025)

Core(s):

The goals of this proposal are to adapt and test a negotiation and dispute resolutions (NDR) training program for caregivers of patients with Alzheimer s disease (AD), who experience conflicts when they act as patient advocates in the health system [Stage 1A and 1B]. Teaching NDR to family caregivers has the potential to improve caregiver communication, wellbeing, mood, and the care of the adult with AD. Alzheimer s disease (AD) affects more than 5 million older adults nationally, with the prevalence expected to increase as our population ages. An integral driver in the care of older adults with AD is the family caregiver. Our prior research has shown that family caregivers act as patient navigators for their loves ones with AD, often interacting with the health system for a multitude of conflicts (e.g. determining if a test/medication/hospitalization is necessary, responding to insurance denials, billing errors). A reoccurring theme is that family caregivers experience frustration, anxiety, and stress as they deal with these health system conflicts. Whether it is spending hours on the phone trying to get answers from a health care provider s team or navigating complex insurance hoops, these conflicts contribute to the burden experienced by a family caregiver. Unfortunately, family caregivers are vastly underprepared to effectively negotiate through these conflicts. Northwestern University s Kellogg School of Business is an innovator in the field of negotiations and dispute resolution training. Previously, we have tailored the negotiations training for health professionals with positive results. We hypothesize that teaching negotiation and dispute resolution tactics to family caregivers of patients

with AD will help improve communication, caregiver stress, anxiety, and empowerment. To test this hypothesis, we aim to: Aim 1: Employ a caregiver (user)-centered design approach to modify and tailor a negotiations and dispute resolution (NDR) training intervention to support communication skills of family caregivers of adults with AD. Aim 2: Utilizing Multiphase Optimization Strategy (MOST), conduct a randomized pilot trial of the NDR intervention that targets better communication between caregivers and health teams, using a 2X3 full factorial design, to (2a) determine the feasibility of delivering the intervention, and (2b) derive estimates of the effect of 3 intervention components on changes in patient-centered outcomes at post-intervention and follow-up to inform a future RCT trial. Exploratory Aim 3: Explore if intervention components (lectures/exercises) interact to change communication between caregivers and health care teams at post-intervention and follow-up. The factorial design will enable testing if the effect of a component is moderated by another component, to ensure the optimized intervention retains components that directly or indirectly impact outcomes. We have partnered with community-based family caregivers who will provide feedback for tailoring the NDR and assist with recruiting family caregivers for the study. Our goal is to improve communication of family caregivers of adults with AD with healthcare providers and others through the negotiation and dispute resolution training.

8. Project Title: **COCOA flavanols to improve walking performance in PAD: the COCOA-PAD II Trial**

Leader(s):   **MCDERMOTT, MARY MCGRAE**
NORTHWESTERN UNIVERSITY AT CHICAGO
NIH R01AG068458 / (2021 - 2026)

Core(s):

Lower extremity peripheral artery disease (PAD) affects 10-15% of people age 65 in the U.S. and will be increasingly common as the U.S. population lives longer with chronic disease. People with PAD have greater walking impairment and faster functional decline than those without PAD. Yet few therapies have been identified that improve walking impairment or prevent functional decline in people with PAD. In people with PAD, ischemia-reperfusion of calf muscle during walking activity causes pathophysiologic changes in calf skeletal muscle, including increased oxidative stress, myofiber injury, and reduced mitochondrial activity. These calf muscle abnormalities are associated with functional impairment and functional decline in PAD. Cocoa flavanols, from the seeds of theobroma cacao, the cocoa tree, have therapeutic properties that may improve calf muscle perfusion and reverse the calf muscle abnormalities in PAD. Pre-clinical evidence shows that cocoa flavanols increase nitric oxide (NO), capillary density, and limb perfusion and also reduce oxidative stress and improve mitochondrial activity in skeletal muscle. Consistent with this pre-clinical evidence, in our NIA-funded pilot clinical trial of 44 participants with PAD, cocoa flavanols significantly improved 6-minute walk distance by 42.6 meters at six-month follow-up, compared to placebo (P=0.005). Therefore, we now propose a Phase III double-blinded, multi-centered randomized trial in 190 participants with PAD, to definitively determine whether 6-months of cocoa flavanols significantly improves 6- minute walk distance at six-month follow-up, compared to placebo. In this revised application (original score: 36, percentile: 17), we will also assess the effects of cocoa flavanols on measures of nitric oxide (measured by brachial artery flow-mediated dilation, calf muscle endothelial nitric oxide synthase (eNOS) and calf muscle phosphorylated eNOS), calf muscle perfusion, whole body oxygen consumption, physical activity, maximal treadmill walking distance, and additional calf muscle biopsy measures at six-month follow-up. In response to reviewer comments, new analyses are proposed to delineate mechanisms and assess persistence of the cocoa flavanols effect on improved walking performance in PAD. If results from our pilot study of cocoa flavanols are confirmed in a definitive Phase III randomized trial, this inexpensive, safe, accessible, and well- tolerated therapy has the potential to meaningfully improve mobility in the large and growing number of older people disabled by PAD.

9. Project Title: **TOOLBOX DETECT: LOW COST DETECTION OF COGNITIVE DECLINE IN PRIMARY CARE SETTINGS**

Leader(s):   **GERSHON, RICHARD; WOLF, MICHAEL S ;**
NORTHWESTERN UNIVERSITY AT CHICAGO
NIH R01AG069762 / (2020 - 2025)

Core(s):

Our objective is to widely implement and evaluate a user-centered, scalable, electronic health record (EHR) - linked strategy for the routine detection of cognitive decline among diverse primary care settings. Cognitive impairment is most prevalent among adults 65 and older, yet less than half of cases are detected and/or diagnosed in primary care settings. It is now increasingly accepted that early detection is critically important to optimize care planning, sustained independence, management of chronic conditions and appropriate caregiver involvement. In 2011, Medicare initiated a covered, Annual Wellness Visit (AWV) that includes a cognitive assessment to detect impairment, Alzheimer s disease and related dementias (ADRD). While this has presented new opportunity for case finding, implementation of AWVs has been variable, including how cognitive function is assessed. Clinicians may rely on more basic, paper-based, interviewer-administered tests that may be less precise and more cumbersome to clinical workflow affecting the fidelity of an early detection strategy. Further, many practices lack a clear protocol for referral when impairment is determined, and a process for family involvement and establishing care goals. Practical, sustainable, scalable strategies are urgently needed to help primary care providers who are on the frontlines of healthcare routinely assess cognitive function as part of AWVs (or whenever a cognitive impairment is suspected), identify concerns and have a protocol for referrals and care management. This is especially true for resource-constrained clinical settings, such as Federally Qualified Health Centers (FQHCs) caring for more vulnerable patient populations. Northwestern developed and continues to innovate the NIH Toolbox for the Assessment of Neurological and Behavioral Function . Since 2017, our team has worked closely with primary care practices to develop a brief, technology-enabled, self-administered, EHR-linked cognitive assessment derived from the NIH Toolbox. We also devised a detailed protocol for its use and how results of our test, known as ToolboxDetect, can inform patient care. We propose a large-scale, primary care practice-randomized trial to implement and comprehensively evaluate ToolboxDetect as a standard of care with AWVs, linked to an EHR (Epic). Diverse, academic and community settings are included to optimize future dissemination efforts. Our primary aim is to evaluate the effectiveness of ToolboxDetect, compared to enhanced usual care, to promote timely detection of cognitive decline and its care management. Our secondary aims are to: 2) Disseminate and implement ToolboxDetect among a large Federally Qualified Health Center Network and assess its feasibility and acceptability for use; 3) Investigate the fidelity of ToolboxDetect, and identify any patient, caregiver, healthcare provider and/or system barriers to its optimal, sustained implementation; and 4) Determine costs associated with implementing ToolboxDetect from a primary care perspective.

10. Project Title: A RANDOMIZED CONTROLLED TRIAL OF GERIATRIC EMERGENCY DEPARTMENT INNOVATIONS

Leader(s):   **DRESDEN, SCOTT MICHAEL; HEINEMANN, ALLEN WALTER ; NORTHWESTERN UNIVERSITY AT CHICAGO AHRQ R01HS026489 / (2019 - 2024)**

Core(s):

Geriatric patients use the emergency department (ED) more than any other age group. Once in the ED, geriatric patients have longer stays, receive a greater number of diagnostic tests, and are more likely to be hospitalized than younger adults. ED visits for geriatric patients are sentinel health events. If geriatric patients are discharged, they often return to the ED or are hospitalized and experience declines in health-related quality of life (HRQoL) and disability. If they are hospitalized, they incur increased costs and greater risk for poor outcomes including infections, delirium, and falls. Suboptimal acute care for geriatric patients is a problem nationally, resulting in development of national geriatric emergency department guidelines and endorsement by prominent stakeholder groups. To improve acute care for geriatric patients, Northwestern Memorial Hospital implemented the Geriatric Emergency Department Innovations (GEDI) program. GEDI is an integrated, interdisciplinary approach to ED care for geriatric patients; it applies evidence-based protocols to improve ED care and improve transitions from the ED to the community. The program centers on geriatric nurse liaisons (GNLs) who are ED nurses with additional training in geriatrics and whose time is dedicated to GEDI rather than traditional bedside nursing. When consulted by the ED team, GNLs perform validated assessments and coordinate patient care in the ED, hospital, or outpatient setting. Through this assessment and coordination model, GEDI provides patient-centered care and aims to prevent unnecessary hospitalizations. Though GEDI was built on the best available evidence, and reflects the Geriatric Emergency Department guidelines supported by multiple national stakeholder groups, there are no prospective efficacy studies in the U.S. of ED- based programs for geriatric patients like GEDI. Therefore, GEDI's efficacy has not been tested prospectively. We propose a randomized controlled trial (RCT) to determine the efficacy of GEDI at a high-volume, urban hospital. Additionally, identifying patients most likely to benefit from GEDI is difficult. Available instruments have poor predictive validity for hospitalization, return to the ED, and functional decline. However, the Emergency Geriatric Review and Evaluation Tool (EGRET), which was developed with AHRQ funding, is a promising screener to identify older adults who may benefit from GEDI. A RCT of GEDI will be strengthened by using EGRET to screen geriatric patients at risk of poor outcomes. This study addresses several AHRQ priority populations: women, minorities, inner-city, End-of-Life, low income and the elderly.

11. Project Title: **Technology Facilitated Behavioral Intervention for Depression among Diverse Patients in Ambulatory Oncology**

Leader(s):   **YANEZ, BETINA**
NORTHWESTERN UNIVERSITY AT CHICAGO
NIH R37CA255875 / (2021 - 2026)

Core(s):

Depressionis one of the most common psychological comorbidities experienced throughout the cancercontinuum. Elevated depressive symptoms in oncology patients is a major concern as unmanaged depressive symptoms in cancer patients is associated with poor health-related quality of life (HRQoL), poor adherence to cancer treatments, delayed return to work and baseline function, greater emergency department visits, greater risk of suicide, and higher all-cause mortality. Behavioral interventions for the management of depression are efficacious, but scalability and implementation of these evidence-based interventions in oncology is limited. Health interpretation capture behavioral populations. information technologies (HIT) provide an ideal opportunity t o expedite the administration, scoring, and of depression screening with well-validated, brief and precise measurement tools that can actionable data to screen for depression, and deliver pragmatic and scalable evidence-based interventions that are proven to reduce depressive symptomatology across various other Despite the benefits of these HITs,use of technology-based models to screen and deliver evidence-based behavioral treatments that address the depressive symptoms in cancer remains underdeveloped and poorly implemented. We will evaluate the effectiveness and the implementation of an evidence-based HIT behavioral treatment for cancer patients with elevated depressive symptoms. This HIT treatment combines systematic, electronic health record-integrated screening for depressive symptoms with an individually-tailored HIT interventions to address gaps in the treatment of depression among cancer patients. The study takes place across two distinct health systems in two major metropolitan areas Chicago and Miami (Northwestern Medicine and University of Miami Health System). We aim to conduct a pragmatic Type I effectiveness-implementation hybrid trial of My Cancer Support an evidence-based, tailored behavioral HIT program for the management of elevated depressive symptoms in ambulatory oncology care settings within two large health systems. We will establish the effectiveness of My Cancer Support on depressive symptoms(i.e., primary outcome) and anxiety, HRQoL, and health services use (i.e. secondary outcomes) compared to usual care. We will evaluate the process of implementing My Cancer Support and its impact on patient and system-level outcomes, including reach, adoption, maintenance, and acceptability. Next, we will identify facilitators and barriers to wide-scale implementation of My Cancer Support beyond Northwestern Medicine and University of Miami Health System. Finally, we will explore whether the effects of My Cancer Support vary across SES, language, disease severity, severity of depressive symptoms, recruitment sites, and other patient and clinical characteristics.

12. Project Title: **1/2 + PROMOTE WEIGHT LOSS IN OBESE PAD PATIENTS TO PREVENT MOBILITY LOSS: THE PROVE TRIAL**

Leader(s):   **MCDERMOTT, MARY MCGRAE**
NORTHWESTERN UNIVERSITY AT CHICAGO
NIH UH3HL141729 / (2019 - 2025)

Core(s):

More than 65% of people with lower extremity peripheral artery disease (PAD) are overweight or obese. People with PAD who are overweight or obese have greater functional impairment and faster functional decline than normal weight people with PAD. Walking exercise is first line therapy to improve functional performance in PAD. However, our observational longitudinal data show that overweight and obese PAD participants who combined weight loss with walking exercise had less functional decline than those who walked for exercise but did not lose weight. Therefore, we hypothesize that among people with PAD who are overweight or obese, a weight loss intervention combined with exercise (WL+EX) will improve walking ability more than EX alone. However, effects of intentional weight loss in overweight/obese people with PAD are unknown and may not be beneficial if weight loss exacerbates PAD-related sarcopenia. Behavior change that achieves sustained WL is challenging in older obese people with chronic disease. Therefore, among people with PAD and BMI>28 kg/m2, we will test the hypothesis that WL+EX achieves greater improvement in functional performance than EX alone. Our innovative weight loss intervention uses a group mediated cognitive behavioral framework, connective mobile technology, remote monitoring by a coach, and a calorie restricted DASH-derived OMNIHeart diet. In a seven week pilot study, our intervention achieved mean weight loss of 5.6 pounds and improved the 6-minute walk by 64.1 meters in eight

PAD participants with BMI> 28 kg/m2. Preclinical evidence shows that obesity is associated with impaired limb perfusion. Human evidence shows that obesity is associated with reduced skeletal muscle mitochondrial biogenesis and activity. These obesity related changes exacerbate the pathophysiology of PAD. Therefore, we hypothesize that weight loss will improve walking ability in part by improving calf perfusion, and increasing calf mitochondrial activity. We will randomize 212 participants with PAD and BMI > 28 kg/m2 to one of two groups for 12 months: WL+ EX vs. EX alone. Participants will be randomized from Northwestern University, Tulane University, and the U. of Minnesota. Our primary outcome is change in six-minute walk distance at 12-month follow-up. Secondary outcomes are change in 6-minute walk distance at 6-month follow-up and change in exercise adherence, physical activity, patient-reported walking ability (measured by the Walking Impairment Questionnaire), and quality of life (measured by the SF12 Physical Component Score) at 12-month follow-up. Tertiary outcomes include MRI measured calf perfusion, MRI-measured calf muscle quantity and fat abundance, and diet quality. We will perform calf muscle biopsies in 50 participants to measure mitochondrial biogenesis and activity, capillary density, inflammation, and senescent cell abundance. If our hypotheses are correct, the PROVE Trial will have a major public health impact by preventing functional decline and mobility loss in the large and growing number of people with PAD who are overweight or obese.

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Masters MC, Landay AL, Robbins PD, Tchkonia T, Kirkland JL, Kuchel GA, Niedernhofer LJ, Palella FJ
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Citations: 105 | AltScore: 2.75

37. **Optimizing voice-controlled intelligent personal assistants for use by home-bound older adults.**
O'Brien K, Light SW, Bradley S, Lindquist L
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Citations: 13 | AltScore: 4.75

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Opsasnick LA, Curtis LM, Kwasny MJ, O'Conor R, Wismer GA, Benavente JY, Lovett RM, Eifler MR, Zuleta AM, Bailey SC, Wolf MS
Medicine (Baltimore), 2022 Jun 17, 101(24): e29376
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Citations: 14 | AltScore: 1.85

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Persell SD, Brown T, Doctor JN, Fox CR, Goldstein NJ, Handler SM, Hanlon JT, Lee JY, Linder JA, Meeker D, Rowe TA, Sullivan MD, Friedberg MW
J Gen Intern Med, 2022 Aug, 37(11): 2777-2785
https://doi.org/10.1007/s11606-021-07296-1 | PMID: 34993860 | PMCID: PMC9411452
Citations: 35 | AltScore: 17.25

40. **Survival and Surgical Approach among Women with Advanced Ovarian Cancer Treated with Neoadjuvant Chemotherapy.**
Persenaire C, Pyrzak A, Barber EL
J Minim Invasive Gynecol, 2022 Mar, 29(3): 375-384
https://doi.org/10.1016/j.jmig.2021.09.716 | PMID: 34648931 | PMCID: PMC8918010
Citations: 20 | AltScore: 4.95

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Petrovsky DV, ?o?n LN, Loizos M, O'Conor R, Prochaska M, Tsang M, Hopman-Droste R, Klinedinst TC, Mathur A, Bandeen-Roche K, van der Willik O, Kritchevsky SB
J Clin Transl Sci, 2022, 6(1): e55
https://doi.org/10.1017/cts.2022.1 | PMID: 35754432 | PMCID: PMC9161040
Citations: 27 | AltScore: 43.75

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Polan RM, Barber EL
Obstet Gynecol, 2022 Jun 1, 139(6): 1145-1148
https://doi.org/10.1097/AOG.0000000000004800 | PMID: 35675612 | PMCID: PMC9199588
Citations: 6 | AltScore: 0.5

43. **Association between cystoscopy at the time of hysterectomy performed by a gynecologic oncologist and delayed urinary tract injury.**
Polan RM, Barber EL
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https://doi.org/10.1136/ijgc-2021-003073 | PMID: 34732516 | PMCID: PMC9087478
Citations: 33 | AltScore: 10.15

44. **The Motherhood Penalty in Obstetrics and Gynecology Training.**
Polan RM, Mattei LH, Barber EL

Obstet Gynecol, 2022 Jan 1, 139(1): 9-13
https://doi.org/10.1097/AOG.0000000000004633 | PMID: 34856581 | PMCID: PMC8830705
Citations: 26 | AltScore: 34.15

45. **Blood Pressure and Glycemic Control Among Ambulatory US Adults With Heart Failure: National Health and Nutrition Examination Survey 2001 to 2018.**
Rethy L, Vu TT, Shah NS, Carnethon MR, Lagu T, Huffman MD, Yancy CW, Lloyd-Jones DM, Khan SS
Circ Heart Fail, 2022 May, 15(5): e009229
https://doi.org/10.1161/CIRCHEARTFAILURE.121.009229 | PMID: 35477292 | PMCID: PMC9179200
Citations: 50 | AltScore: 37.65

46. **Associations of Clinical and Social Risk Factors With Racial Differences in Premature Cardiovascular Disease.**
Shah NS, Ning H, Petito LC, Kershaw KN, Bancks MP, Reis JP, Rana JS, Sidney S, Jacobs DR Jr, Kiefe CI, Carnethon MR, Lloyd-Jones DM, Allen NB, Khan SS
Circulation, 2022 Jul 19, 146(3): 201-210
https://doi.org/10.1161/CIRCULATIONAHA.121.058311 | PMID: 35607988 | PMCID: PMC9308688
Citations: 38 | AltScore: 108

47. **Managing Atherosclerotic Cardiovascular Risk in Young Adults: JACC State-of-the-Art Review.**
Stone NJ, Smith SC Jr, Orringer CE, Rigotti NA, Navar AM, Khan SS, Jones DW, Goldberg R, Mora S, Blaha M, Pencina MJ, Grundy SM
J Am Coll Cardiol, 2022 Mar 1, 79(8): 819-836
https://doi.org/10.1016/j.jacc.2021.12.016 | PMID: 35210038
Citations: | AltScore: 29.9

48. **Longitudinal Sedentary Time and Symptoms in Breast Cancer Patients during Chemotherapy Using Ecological Momentary Assessment.**
Welch WA, Solk P, Auster-Gussman L, Whitaker M, Siddique J, Fanning J, Mishory A, Khan S, Santa-Maria C, Kulkarni S, Phillips SM
Med Sci Sports Exerc, 2022 Dec 28, 55(5): 966-974
https://doi.org/10.1249/MSS.0000000000003115 | PMID: 36574735 | PMCID: PMC10106380
Citations: 42 | AltScore: 1

49. **Sleep and gynecological cancer outcomes: opportunities to improve quality of life and survival.**
Zhao C, Grubbs A, Barber EL
Int J Gynecol Cancer, 2022 May 3, 32(5): 669-675
https://doi.org/10.1136/ijgc-2022-003404 | PMID: 35331996 | PMCID: PMC9064983
Citations: 57 | AltScore: 9.1

EXTERNAL ADVISORY BOARD MEMBERS

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RECOGNITION AND AWARDS (2022-2023)

<u>MInjee Kim, MD</u> (2023)

- RCCN Scholar Award
- Nulliparous Pregnancy Outcome Study – Monitoring Mothers-to-be Heart Health Study 2 (nuMoM2b-HHS2) Scholars' Award

MINORITY RESEARCH

General Brief Description of Minority Activities:
Not defined.

Minority Trainee(s):

- Diana Chirinos, PhD, Assistant Professor, Department of Preventive Medicine (Epidemiology)
  Pepper Scholars Program: Differential Associations Between Spousal Bereavement, Physical Functioning, and Health Outcomes Among White and Latino Older Adults
- Emi C. Bretschneider, MD, Assistant Professor, Department of Obstetrics and Gynecology (Female Pelvic Medicine and Reconstructive Surgery (Urogynecology))
  Pepper Scholars Program: Ready for Advances in Bladder health for Older Women (The RAInBOW Study)
- Marquita Lewis-Thames, PhD, Research Assistant Professor, Department of Medical Social Sciences
  Pepper Scholars Program: Designing a Telehealth-Based Tool for Rural Older Adults with Cancer and Cancer-Related Distress: Testing for Usability and Acceptability
- Minjee Kim, MD, Assistant Professor, Department of Neurology
  Pepper Scholars Program: Technology-Enabled Screening Strategy for Obstructive Sleep Apnea (TEST-OSA) in Primary Care Older Patients with Multiple Chronic Conditions
- Prakash Jayabalan, MD, Assistant Professor, Department of Physical Medicine & Rehabilitation
  Pepper Scholars Program: The Development of Novel Therapeutic Walking Exercise Strategies in Sedentary Individuals with Knee Osteoarthritis
- Sadiya Khan, MD MSc, Assistant Professor, Department of Medicine (Cardiology) and Department of Preventive Medicine (Epidemiology)
  Pepper Scholars Program: Prevalence of microvascular dysfunction and association with functional limitation in older adults with chronic obstructive pulmonary disease
- Whitney Welch, PhD, Research Assistant Professor, Department of Preventive Medicine (Behavioral Medicine)
  Pepper Scholars Program: Remote Sensor-Based Frailty Detection in Older Adults

No minority grant information specified.

UNIVERSITY OF PITTSBURGH
Claude D. Pepper Older Americans Independence Center

Susan L. Greenspan, M.D.   412-692-2477   greenspn@pitt.edu
Principal Investigator

Anne Newman, MD, MPH   412-383-1302   anewman@pitt.edu
Co-Director

Bari Guzikowski   412-692-2477   bmg96@pitt.edu
Program Manager

CENTER DESCRIPTION

Gait and balance disorders in older persons are common, disabling and complex. In order to prevent and treat these disorders, a concentrated, multidisciplinary effort to understand causes and consequences, and to develop innovative treatments, is needed. The team of investigators at Pittsburgh offers complementary expertise, outstanding research productivity, and ongoing studies to address this need through a Claude D. Pepper Older Americans Independence Center. This program includes investigators from medicine, bioengineering, rehabilitation, epidemiology/public health, biostatistics, psychology, pharmacology, biology, imaging, informatics, and health services research. Our long range goals are: to address the critical need to improve mobility, balance, and falls risk, both through improved understanding of their causes and through development of preventive and therapeutic interventions.

Our specific aims for the current cycle are to:

1. Promote multidisciplinary research to elucidate the causes, consequences and management of age-related changes in mobility and balance.
2. Further extend our work into two high potential areas: a) translational investigations to examine interactions between multiple systems at the level of molecules, signaling systems, cells and their organelles, and tissues, as they impact mobility and balance in living organisms, and b) impact on individual older adults of novel interventions to enhance mobility and balance.
3. Train young investigators from multiple disciplines to become national leaders in age-related mobility and balance problems in a vibrant, collaborative environment and build a translational sciences workforce through collaborative basic and clinical sciences team mentoring.
4. Serve as a champion and invaluable resource for investigators, research programs, institutions, OAICs and the public in the area of mobility and balance in older adults.

The Program has 7 Cores:

- Leadership/Administration Core
- Pilot Exploratory Studies Core
- Research Career Development Core
- Clinical Populations Outcomes Core
- Integrative Systems Core
- Data Management, Analysis and Informatics Core
- Biology of Mobility and Aging Core

Training support is provided directly to Pepper Scholars and also to trainees in related programs.

Research strategies to achieve OAIC goals:

1. Use Resource Cores to share expertise among projects and investigators.
2. Use pilot and developmental funds to extend existing studies and develop new studies.
3. Promote and reward collaborative multidisciplinary teams of investigators with complementary expertise by prioritizing them for funds and support.
4. Encourage new partnerships with highly productive investigators and programs by offering to partner with our expertise and resources.
5. Reward development of new methods and techniques.
6. Facilitate the use of a common set of core measures of mobility, balance and falls in human studies so results can be merged or compared.
7. Leverage resources by collaborating with other Centers at Pitt, other OAICs, and Centers around the US.
8. Sponsor seminar series to promote general awareness of expertise and resources, review progress in ongoing projects and facilitate new collaborations.
9. Support the new OAIC career development program with salary-funded Pepper Scholars in addition to resource support for Novice, Transition to Independence, and Visiting Scholars, with a focus on multidisciplinary teamwork, thematic knowledge, and specific skills.
10. Promote national discussion through programs at national meetings and other dissemination methods.
11. Provide administrative infrastructure, intellectual leadership, and oversight.

CORES

Leadership and Administrative Core (LAC)

Leader 1:   Susan Greenspan, MD   greenspn@pitt.edu

Leader 2:   Anne Newman, MD MPH   newmana@edc.pitt.edu

The Leadership Administrative Core (LAC) is responsible for the organizational, communication and regulatory functions of the Pittsburgh Pepper OAIC. The LAC receives valuable input and direction from 5 advisory groups including 1) the External Advisory Board (EAB) (national experts), 2) the Institutional Advisory Board (multidisciplinary group of experts on aging from the University and the UPMC health system), 3) the Community Advisory Board (representatives from local health care agencies, IRB, media, and local leaders), 4) the REC Advisory and the PESC Advisory groups (both internal and external experts). These boards provide advice and insight to the Executive Committee composed of leaders and co-leaders of OAIC cores.

The specific aims of the LAC are to:

1. Foster communication and multidisciplinary collaboration among OAIC investigators, cores and projects.
2. Promote awareness and involvement in our work by relevant investigators and research programs in and outside the University of Pittsburgh.
3. Represent the OAIC to the University through the Institutional and Community Advisory Boards.
4. Represent the OAIC to other OAICs and the larger academic, NIH, clinical and lay communities.
5. Through the EAB, maintain independent oversight of OAIC processes, resources and progress.
6. Establish new independent REC and PESC oversight committees as requested by NIA.
7. Provide research oversight and safety monitoring for all OAIC human studies and help establish a Data and Safety Monitoring Board as necessary.
8. Sponsor a Research Seminar series, an Annual Retreat, Workgroups, a publication/communication committee, formal grant reviews, and new partnership initiatives.
9. Increase basic and translational research partnerships.
10. Provide administrative support and manage financial records for the OAIC as a whole.
11. Collaborate outside the Institution on OAIC related themes.

Research Education Component (REC)

Leader 1:   Neil Resnick, MD   resnickn@pitt.edu

Leader 2:   Jen Brach, PhD, PT   jbrach@pitt.edu

The goal of the Research Education Component Core (REC) of the Pittsburgh OAIC is to provide a comprehensive, individualized career development program to prepare future investigators for mobility, balance, and aging research. Our ultimate goal is to develop highly qualified investigators to conduct high quality and high impact research in the field of mobility, balance, and aging and who will become leaders in this field nationally and internationally. We continue to improve our programs with input from our trainees, mentors, Executive Committee, and External Advisory Committee.

Our specific aims of the REC are to:

1. Promote careers in mobility, balance, and aging research among junior investigators at 3 levels:

- Novices: research mentees at the pre-and post-doctoral level
  Goal: submission and funding of their first research award (F series, Foundation, etc.)
- Pepper Scholars: junior faculty with initial expertise who receive OAIC salary support
  Goal: submission and funding of a career or R-type award
- Transition to Independence Investigators: junior faculty with independent career awards
  Goal: submission and funding of an R-type award

2. Foster Trainee success with a comprehensive training program that:

- Prepares trainees to engage in translational teams across basic, clinical, and health services science
- Educates in aspects of basic and clinical research via the Clinical and Translational Science Institute (CTSI) and our complimentary sessions that focus on aging, mobility, and balance
- Creates and monitors individualized teams of experienced mentors
- Offers multidisciplinary research experiences involving OAIC Cores and investigators, as well as retreats, and a peer-led seminar series that includes sessions for manuscript and grant review, career development, and leadership with CTSI
- Sponsors a 2-semester intensive grant writing course resulting in a polished grant proposal
- Uses stipends to protect Scholar time for research and training and provides targeted financial support for initial pilot projects and other opportunities
- Provides individualized advice, feedback, career guidance, and support to trainees and mentors.

3. Manage all aspects of the training program, including promotion, recruitment, selection, scheduling, monitoring, and evaluation of trainees and the program. The REC helps every Scholar complete a Customized Career Development Plan (CCDP) that is used to plan activities and monitor progress.

4. Collaborate with other cores and units within and outside the institution for OAIC related themes.

5. Enrich Scholar training through participation in the OAIC Coordinating Center's Visiting Scholar Program.

Pilot and Exploratory Studies Core (PESC)

<u>Leader 1:</u>   Daniel E. Forman, MD   formand@pitt.edu

<u>Leader 2:</u>   Aditi Gurkar, PhD   agurkar1@pitt.edu

The goal of the Pilot/Exploratory Studies Core (PESC) of the Pittsburgh OAIC is to promote and fund innovative multidisciplinary pilot research in the topic areas of mobility, balance and aging and their interfaces. The expected outcomes for funded pilot studies are their successful completion in a timely manner, that the findings be presented at a national scientific meeting and submitted for publication in the peer review literature. Moreover, the findings from these pilot studies are expected to support the development of mentored career development awards and independent federally funded grant applications.

The specific aims of the PESC are to:

1. Promote innovative multidisciplinary research on mobility, balance and aging.
2. Act as a bridge to foster interactions between the basic geroscience, clinical and community-based research communities.
3. Encourage supplements to leverage ongoing basic, translational, clinical and community-based studies.
4. Promote innovative techniques and methods for research on mobility, balance and aging.
5. Partner with other University of Pittsburgh groups (e.g. Clinical and Translational Science Institute and Aging Institute) that also offer pilot study awards, in addition to the Division of Geriatrics, to increase overall funding for individual pilot projects.
6. Promote, evaluate, and select for funding Pilot projects ($40,000 per year), small REC Pilots (up to $10,000), and Developmental projects ($70,000 over two years).
7. Conduct post-award processes (e.g., monitor adherence to ethics, safety, privacy, tracking of subsequent productivity and other related matters) for pilot and developmental projects.

Biology of Mobility and Aging Core (BMAC)

<u>Leader 1:</u>   Toren Finkel, MD, PhD   FINKELT@pitt.edu

<u>Leader 2:</u>   Stacey Rizzo, PhD   RIZZOS@pitt.edu

Problems with mobility and balance with aging are due to changes in multiple systems that develop due to age-related alterations in basic biological processes. Insights accumulated over the last two decades in the basic biology of aging are poised to be rapidly translated into new interventions to promote a longer healthspan, which depends in large part on maintaining mobility and balance. However, significant barriers must be overcome before the approaches and technologies of basic science can be efficiently translated into clinical practice. While the OAIC partnered over the last 10 years with individual basic scientists

who study aging, there was not yet a critical mass of activity to justify a distinct Pepper Core. With a major new investment creating an Aging Institute dedicated to using biological sciences to advance aging basic discovery and translation, the OAIC now proposes a Biology of Mobility and Aging Core (BMAC). The goal of this new core is to promote both basic-to-human and human-to-basic translation. The BMAC will provide an engine of discovery and innovation to guide and enhance our clinical and translational efforts. Specific emphasis includes using basic science approaches to uncover novel biomarkers and compounds that might aid in the treatment of age-related alterations in mobility and balance. Moreover, the BMAC will assist in the development and characterization of innovative pre-clinical animal models that can be used to mechanistically explore the fundamental basis of age-related changes in mobility, gait and balance.

The specific aims of the BMAC are to:

1. Provide expertise in biomarker development as potential intermediate markers of the aging processes in human studies of aging. This will include the development of novel model systems to accelerate biomarker development.
2. Provide access and guidance to the design and analysis of high throughput screening (HTS) systems and 'omic' technologies for identifying potential molecular targets relevant for mobility, balance and aging.
3. Provide access to and interpretation of various preclinical model systems. This includes cellular (e.g. muscle stem cells), rodent, zebrafish, and drosophila organisms and establish a preclinical phenotyping platform that faithfully reflects age-related mobility impairment in humans to enable translational studies.
4. Support the research training mission of the Pepper Center by enhancing the capacity for Team Science and promoting basic-translational-clinical interactions.

Clinical and Population Outcomes Core (CPOC)

Leader 1:   Steven Albert, PhD, MSPH   smalbert@pitt.edu
Leader 2:   Andrea Rosso, PhD, MPH   alr143@pitt.edu

The Clinical and Population Outcomes Core (CPOC) is dedicated to promoting multidisciplinary research on mobility, balance, and aging through 1) access to human subjects for studies and advice on screening, recruitment, and consent, 2) access to existing data sets from Pitt aging studies for secondary analysis, and 3) resources and space for clinical assessment of mobility and balance. To meet these aims, we provide registries of interested community-dwelling older participants and a Long-Term Care (LTC) Registry of residents from participating institutions, a searchable database on existing Pitt Aging data sets from longitudinal and clinical trial studies, a library of tests and scales with instructions, scoring and advice on implementation, and information on use of our Senior Mobility in Aging Research and Training (SMART) Center space for clinical studies. We successfully launched the Platinum LTC Registry (seniors residing in assisted living and skilled nursing facilities who have consented to research contact). To date, over 40 facilities signed agreements to participate as recruitment sites, and over 400 residents consented to be contacted. Our Community Registry, with over 2500 older

participants, was a key recruitment source for 60 research studies. The CPOC SMART Center provided clinical research space for multiple pilot and external projects. Our Community Advisory Board (CAB) continued to foster community collaboration, stakeholder involvement and feedback on OAIC activities.

Our specific aims of the CPOC are to:

1. Engage older adults from the community and LTC settings in research by expanding large registries of consented and well-characterized older adults accessible to investigators.
2. Provide training to investigators on appropriate contact, screening, and consent strategies for research with older populations.
3. Recruit and maintain a diverse community advisory board of older adults and leaders in aging services to review proposed research and advise the OAIC.
4. Provide access to ongoing and completed Pitt cohort studies, specimens, clinical trials, and existing databases.
5. Provide expertise in clinical assessment methodology by providing a standardized set of forms and instructions to promote a common dataset of core assessments for mobility, balance, and falls.
6. Use noninvasive, portable technology to examine mobility, balance, and physical activity in clinics and in the field through our novel mobile laboratory.
7. Provide access to space and equipment for OAIC-related studies through our SMART Center.
8. Promote dissemination of our findings within and outside the Pittsburgh community.

Data Management, Analysis and Informatics Core (DMAIC)

Leader 1:   Subashan Perera, PhD   pereras@dom.pitt.edu
Leader 2:   Charity Moore Patterson, PhD, MSPH   CGP22@pitt.edu

The overarching goal of the Data Management, Analysis and Informatics Core (DMAIC) is to ensure data and analytic integrity, transparency and reproducibility by continuing to serve as a central source of methodological expertise and a service provider to the researchers of the Pittsburgh Older Americans Independence Center (OAIC). Methodological expertise is most beneficial when provided by a team such as DMAIC familiar with the balance and mobility in aging theme, specialized measures and methods of the OAIC.

Our specific aims of the DMAIC are to:

1. Meet data management requirements of Pittsburgh OAIC PESC, REC, developmental and external projects.
2. Support quantitative and facilitate qualitative analysis needs of Pittsburgh OAIC projects.

3. Provide informatics expertise to Pittsburgh OAIC projects.
4. Support the training mission of the Pittsburgh OAIC with Pepper Scholars and other trainees.
5. Develop new techniques, as wells as novel application of existing methods to address OAIC-related unmet needs and methodological challenges.
6. Collaborate with other cores and units within and outside the institution on OAIC theme-related activities.

Integrative Systems Core (ISC)

Leader 1: Caterina Rosano, MD, MPH   car2350@pitt.edu
Leader 2: Mark Redfern, PhD   mredfern@pitt.edu

Problems of mobility and balance in the aged require multidisciplinary study because they are complex and multifactorial. Advances require integrating expertise and technical resources from biomechanics, physiology, neural control of movement and biology. Thus, the goal of the Integrative Systems Core (ISC) is to provide integrative, multidisciplinary knowledge, skills and techniques that foster an understanding of the biomechanical, structural, functional, physiological and biological influences on age-related mobility and balance.

Our specific aims of the ISC are to:

1. Provide cutting-edge resources and expertise to concurrently study both whole-body as well as multiple systems and physiologic mechanisms affecting mobility and balance during aging, both during study planning as well as during implementation and analysis.
2. Develop and test novel techniques and approaches to address gaps and needs for multi-system evaluation of mobility and balance.
3. Support the training mission of the OAIC by educating and supporting the work of Pepper trainees through workgroups, seminars, "field trips" and active involvement in trainee research projects.
4. Collaborate with other cores and Centers in and outside Pitt on OAIC-related activities.
5. Continuously monitor, evaluate and communicate about Core activities both within and among Core laboratory leaders, as well as with other Pepper Cores, Pepper leadership and NIA.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications
Aimee N. Pickering, MD, MS Assistant Professor / University of Pittsburgh School of Medicine <u>implementation strategy for deprescribing inappropriate medications in older adults with diabetes</u>	2023-2025 / 7 (total) 4 (1st/Sr)
Brendan McNeish, MD Assistant Professor / University of Pittsburgh, Physical Medicine and Rehabilitation <u>aging related structural brain assessment using neuro-imaging</u>	2023-2025 / 10 (total) 5 (1st/Sr)
Nami Safai Haeri, MD Assistant Professor / University of Pittsburgh School of Medicine <u>A Novel Method to Examine Muscle Health in Frail Elderly</u>	2022-2024 / 4 (total) 1 (1st/Sr)
Megan M. Marron, PhD Assistant Professor / University of Pittsburgh School of Public Health <u>Using –omics to better understand the underlying biology of decline in muscle, liver, and physical functioning with aging</u>	2022-2024 / 24 (total) 10 (1st/Sr)
Marcelo Rocha, MD PhD Assistant Professor / University of Pittsburgh School of Medicine <u>Dimethyl-Arginine and Large Vessel Occlusion Stroke in Older Adults</u>	2022-2024 / 28 (total) 7 (1st/Sr)

Past Scholars
Mary Kotlarczyk, PhD, University of Pittsburgh School of Medicine (2017-2020)
Emily Rocha PhD, University of Pittsburgh School of Medicine (2019-2021)
Lena Makaroun MD, MS, University of Pittsburgh/VA Pittsburgh Center for Health (2019-2021)
Samaneh Farsijani, PhD, MSc, University of Pittsburgh School of Medicine (2020-2021)

PILOT/EXPLORATORY PROJECTS (16 Pilot Projects Listed)

1. Project Title: **Medical Marijuana and Chronic Pain in Older Adults**

Leader: **Neelesh NadKarni, MD, PhD, FRCPC; Debra Weiner, MD, FACP**

Background: Challenges with conventional treatments for chronic pain have led to many older adults considering medical marijuana (MM) as a treatment option. Older chronic pain sufferers may be vulnerable to the effects of MM from age-related changes in pharmacokinetic and pharmacodynamic function, and from changes in the brain that control mobility and cognition. Whether potential benefits from alleviation of chronic pain with MM are counteracted by its adverse effects on mobility in older adults on MM is unknown.

Specific Aims: We will compare adults 60 and over who are pain free (PF) to those with chronic pain not on MM (CP), and those with chronic pain on MM (CP-MM) on mobility, cognition, gait-cognitive dual-task measures, mood, anxiety, physical function and quality of life measures. The main hypotheses are that: 1) the CP-MM group will perform the worst on measures of gait speed, physical function, executive function and dual- task gait and cognitive performance (i.e., the interface between gait and cognitive function), and 2) the CP group will perform the worst on other measures of mood, anxiety and quality of life.

Summary of Methods: This pilot will recruit 20 participants in each group, PF, CP and CP-MM. The CP-MM group will be recruited from Solevo Wellness, a Pittsburgh MM dispensary using targeted mailings. We will recruit the PF and CP participants from the Pepper Registry and pain clinics. We will assess mobility performance with the short physical performance battery (SPPB) and the Timed-up-Go. We will assess gait parameters with and without dual tasking on the Gait mat II. We will administer standardized tests of executive function, memory, language and visuospatial function. Accuracy and reaction time will be captured on working memory, response inhibition and motor sequencing tasks performed while standing and while walking (dual-tasking). Mood will be assessed with the PHQ-9 anxiety with the GAD-7, physical function with the late life function and disability index, and quality of life with the EuroQoL. We will also capture details of MM type, blood levels of active MM compounds, dosage, administration, and severity of pain on the BPI.

Future use of data: This data will be used to support a prospective cohort study (R01 application) in response to the FOA from NIA/NIDA (PA-17-196) that will address the relative impact of MM as compared with chronic pain itself on mobility, cognitive function, and other geriatric-specific outcomes in older MM users.

Core Collaborations: CPOC, DMAIC

2. Project Title: **Investigating Biological Aspects of Aging through Molecular Epidemiology: Linking Genes to Physical Function in Older Adults**

Leader: **Adam J. Santanasto, PhD MPH; Joseph M. Zmuda, PhD; Zsolt Urban, PhD; Ryan L. Minster, PhD, MSIS**

Specific Aims: To examine the association of RNA expression profiles of the transforming growth factor-beta (TGF-ß) pathway with baseline and 7-10-year change in physical function among older adults.

Brief Background: The TGF-ß signaling pathway is a strong biological candidate pathway that may negatively impact skeletal muscle and physical function with aging. TGF-ß induces pathogenic tissue fibrosis, negatively regulates skeletal muscle differentiation and repair, and contributes to mitochondrial dysfunction. TGF-ß is also implicated in inducing pathogenic fibrosis, muscle wasting and primary myopathies, all of which can impact physical function.

Methods: We propose to assay the expression of genes involved in the TGF-ß signaling pathway, using a custom-designed TGF-ß pathway expression array. We will examine the relationship between mRNA expression and the Short Physical Performance Battery, a comprehensive lower-extremity performance battery that includes gait-speed, balance and timed chair-rise tests.

Future use of Data: The data generated from the Pepper Pilot will be used in future NIH grant proposals to examine tissue-specific (skeletal muscle) expression of genes involved in TGF-ß signaling and their effect on age-related changes to physical function. Further, this dataset will be integrated with data from PI Dr. Santanasto's K01, which investigates the association of genome-wide genetic markers, circulating TGF-ß, and other biomarkers, to better understanding of biological mechanisms underlying age-related declines in physical function.

Core Collaborations: DMAIC, CPOC

3. Project Title: **Cellular senescence, SASP and Metabolites as biomarkers for early aging**

Leader: **Aditi U. Gurkar, PhD; Susan Greenspan, MD; Neil M. Resnick, MD; Subashan Perera, PhD**

Specific Aims: The aims of the current proposal are to (1) Design assays for measuring senescence and SASP in whole blood/ serum from the Solve-IT study. (2) Perform global metabolomics on serum to quantitate 600+ metabolites and estimate effects of sex, and physical aging using statistical and bioinformatics methods (3) Perform statistical analysis to identify differentiating biomarkers of interest and their co-occurrence patterns. These biomarkers will be selected from the measured metabolites, senescence and SASP markers.

Background: Aging comprises of a diverse array of phenotypes influenced by multiple factors including genetics, epigenetics, environmental influences, diet, exercise and the microbiome. Cellular senescence and senescence associated secretory phenotype (SASP) are known to correlate with age and ablation of such cells drastically improves health span, albeit in model organisms. This hints that cellular senescence can possibly drive aging-related degenerative change. Metabolites are

circulating small molecules that are supremely suited to account for biological aging influenced by a number of these factors. This study will simultaneously identify the metabolite profile, and the immune, as well as senescence markers that collectively play an important role in biological aging.

Methods: Cellular senescence and SASP markers will be measured by ELISA and Luminex based assays from whole-blood and serum samples from the Solve-IT study. Metabolomics profiling will be performed from randomly selected 60 participants. Using statistical and bioinformatic approaches we will analyze (a) which metabolites and combination of metabolites best discriminate the cohorts of interest; (b) which senescence markers and combination of markers best discriminate the cohorts of interest; (c) which combinations of metabolites and senescence markers best discriminate the cohorts of interest. By constructing co-occurrence networks we will identify groups of features/phenotypes that co-occur, potentially suggesting the entities that are be involved in a
biological model for aging.

Future Uses: The assays can be applied to other patient cohorts to determine if the unique signature obtained here significantly correlates with falls, mobility, frailty, critical care patient outcome, risk of aging-related degenerative diseases, healthy aging, etc. In particular, this pilot study will provide critical data for a grant application to fund a larger study to understand the relationship of these measures to outcomes of aging. Our approach has the potential to identify metabolic pathways that may drive cellular senescence, immune system and aging, thus providing a mechanistic insight into healthy aging. This will provide an opportunity to develop novel strategies to modulate aging and simultaneously delay the onset of multiple chronic degenerative diseases.

Core Collaborations: CPOC, DMAIC, BMAC

4. Project Title: **Association of Social Determinants of Health with Functional Status, Mortality, and Healthcare Use in Older Adults Who Survive Critical Illness**

Leader: **Leslie Scheunemann, MD, MPH, Eric Roberts, PhD**

Rationale: More than half of older critical illness survivors develop new or worsened dysmobility and functional impairments. While suspected to influence critical illness outcomes, there is little evidence about how social determinants of health (e.g., income, education, and environmental characteristics such as housing quality, transportation access, and social support) affect functional outcomes and healthcare utilization in this important and currently highly relevant older population.

Approach: This study uses data from the well-established and locally available Health and Retirement Study, which is linked to Medicare claims. It will identify older critical illness survivors, characterize important baseline individual social determinants of health (SDH), and link to their subsequent survival, pre-and post-illness function (including self-reported walking, stair climbing, falls, and activity level), and use of healthcare resources. Aim 1 will examine the relationship between SDH measured the

year prior to critical illness and post-critical illness health outcomes. Aim 2 will assess the relationship between SDH and healthcare utilization.

Relevance to the Pepper theme: Loss of physical function and mobility among older adults after critical illness is highly relevant to the OAIC theme.

Core Collaboration: CPOC (population studies), DMAIC (analysis), includes REC members

5. Project Title:	**Mechanisms underlying changes in inflammation in mobility limited older adults**
Leader:	**Rachel Gottschalk, PhD, Maria Chikina PhD; Co-Is: Drs. Daniel Forman, Anne Newman, Toren Finkel**

This pilot examines gene regulatory networks in macrophages from older adults with impaired mobility and elevated IL-6 levels in the Reducing Inflammation for Geriatric Healthspan Therapy (RIGHT) Study, a clinical trial which will test the effects of an IL-inhibitor.

Significance: Persistent inflammation is associated with aging and the onset and progression of mobility disability and fatigability. Monocytes and macrophages play a pathological role in age-related inflammation and disease,[1,2] and there is substantial person-to-person variation in their gene expression and regulation of inflammatory responses, resulting from age, sex, and genetic factors.This variation is key to understanding mechanisms behind healthy vs non-healthy aging, and how therapies may impact inflammation in mobility limited older adults.

Hypotheses: We expect that 1) inter-person variation in macrophage basal gene expression will predict stimulus-induced macrophage inflammatory responses and 2) these measures will be associated with elevated serum IL-6 and impaired mobility across people.

Approach: (Aim 1) We will utilize pre-treatment blood collected from the RIGHT trial to assess inter-person variation in inflammatory regulatory networks across 50 elderly subjects with high serum IL-6 (>2.5 pg/ml), an inflammatory cytokine associated poor clinical outcomes,[7] and 20 controls (IL-6 <2.5pg/ml). Readouts will include (i) basal serum protein quantification, (ii) macrophage responses to microbial stimuli (inflammatory cytokine output across a range of stimulus concentrations), and (iii) basal and stimulus-induced macrophage gene expression (RNAseq). Using these data and novel computational methods (graphical lasso and causal inference algorithms), we will infer regulatory relationships that govern inflammatory control and identify regulators associated with macrophage responsiveness, elevated serum IL-6, and impaired mobility. (Aim 2) We will analyze a subset of 10 subjects treated with IL-6 inhibitor for 6 months to determine whether serum proteins, macrophage responses, or gene regulatory networks are impacted by therapy.

Innovation: Our preliminary data suggest that person-to-person variation in

inflammatory regulation is most apparent in response to weak stimuli. By using computational and quantitative experimental approaches to elucidate network connectivity and its impact across a broad range of stimulus strengths, this proposal provides a framework for both conceptual and methodological innovation in understanding mechanisms underlying age-associated inflammation.

Core Collaborations/grants: ISC (Dr. Forman's Lab), CPOC (Community Registry), DMAIC (statistical analysis).

Future Proposals: This study will inform a planned R01 grant proposal to further our basic understanding of how gene regulatory networks change with age and impact of IL-6 inhibition.

6. Project Title:	**A lysosomal-based, small molecule approach to prevent and reverse mobility decline**
Leader:	**Emily Rocha, PhD, Stacey Rizzo, PhD; Co-Is: Drs. Toren Finkel and Daniel Forman**

This Pilot leverages the Pitt/UPMC program in drug development to target critical age-related pathways affecting mobility. A small molecule that activates TFEB will be tested, which can lead to Phase I human testing in 18-24 months.

Significance: Aging is the main risk factor for neurodegenerative disease and loss of mobility. Aging lysosomes undergo impaired volume and pH regulation, accumulation of indigestible materials, and reduced functional degradative enzymes. Age-related autophagy-lysosomal dysfunction may be responsible for the observed incidental ?-synuclein pathology that occurs at a frequency of 8-22.5% and up to 34.8% in centenarians; thus may play a role in age-related mobility loss. TFEB is a master regulator of autophagy and lysosomal biogenesis and regulates the expression of Coordinated Lysosomal Expression and Regulation (CLEAR)-network proteins, which include many autophagy proteins. Our data indicates that exposure to a novel, small-molecule (BC18630) prolongs nuclear TFEB activation, and can prevent age-related lysosomal dysfunction, ?-synuclein accumulation, neurodegeneration and loss of mobility.

Hypothesis: Improving lysosomal function using TFEB activator can prevent or delay age-related neuropathology and mobility decline.

Approach: This pre-clinical study evaluates BC 18630 (a small-molecule that selectively prolongs TFEB activation) to 1) prevent the progression of age-related neuropathologies and mobility decline in healthy aging male and female C57BL/6J mice; and 2) attenuate or reverse neuropathology and mobility decline in advanced aged mice. Following baseline assessments of mobility-related phenotypes, BC18630 will be administered via chow to middle aged (6-8 month) and aged (16-18 month) male and female mice for several months and compared to young ~3-4 month vehicle treated sex- and age-matched controls. Based on data in C57BL/6J mice, the dose will be equivalent to 5 mg/kg/day. A battery of behavior tests before and after treatment will assess aging-related gait and motor coordination in addition to hearing, vision, body mass, and frailty index score. Discrete brain regions will be microdissected from the left hemisphere and used for lysosomal enzymatic activity assays. Right hemisphere

regions will be used for histological assessment of autophagy-lysosomal function.

Innovation: This proposal outlines a unique therapeutic strategy to improve lysosomal function and prevent age-related mobility loss that may prevent accumulation of aggregated proteins and delay the onset of mobility disability.

Core Collaborations/grants: DMAIC (statistical analysis), BMAC (Greenamyre), ISC (Forman), REC (Scholar)

Future: This pilot will provide data for a NIA R21 or R01 grant.

7. Project Title:		**The relationship between dietary protein intake, gut microbiome and mobility in older adults**
Leader:		**Samaneh Farsijani, PhD; Co-Is: Drs. Anne Newman and Subashan Perera**

This study builds on the NIA-funded Study of Skeletal Muscle and Mobility in Older Adults (SOMMA), with an add-on study focused on the role of nutrition and the microbiome in influencing muscle health and mobility.

Significance: The imbalanced composition of gut microbiome(dysbiosis), in aging is associated with gait speed and frailty. Protein intake is an important anabolic stimulus for muscle protein synthesis and may influence the gut microbiome, which can in turn affect muscle function and walking ability. Despite emerging evidence supporting the roles of amount, source and pattern of protein intake in promoting muscle health and mobility, associations with age-related dysbiosis are unclear. This study will determine the relationships between dietary proteins and gut microbiome and help inform development of age-specific dietary recommendations to maintain muscle health and mobility by promoting a healthy gut microbiome.

Hypothesis: Higher amount and even within-day distribution of protein intake, as well as higher quantity of plant-based proteins are independently associated with increased diversity of the gut microbiome.

Approach: Two 24-h food recalls, a food frequency questionnaire, and fecal samples (for 16S rRNA analysis) will be collected from 200 SOMMA participants (age ? 70-y) residing in Pittsburgh at baseline, for 80% power with ?=0.05 for detection of R2=0.065 between protein intake measures and microbial diversity.

Innovation: This is the first study to address associations between dietary protein parameters and gut microbiome composition in older adults and will provide preliminary data to test associations with gait speed and mobility in SOMMA.

Core Collaborations/grants: ISC (Forman and SOMMA), DMAIC (analysis), REC (Scholar).

Future: Findings will support Dr. Farsijani's K01 application.

8. Project Title: **Increasing gait automaticity in older adults by exploiting locomotor adaptation**

Leader: **Gelsy Torres-Oviedo, PhD; Co-Is: Andrea Weinstein, PhD, Andrea Rosso, MPH, PhD , Douglas Weber, PhD**

This study integrates the insights of 4 dynamic investigators with complementary expertise in a pilot study of mechanisms and clinical effects of locomotor adaptability training.

Significance: Age-related deficits in locomotor adaptation are common and linked to disability and falls. Older adults are slower at adjusting movements when interacting with a new environment and have difficulty switching motor patterns when transitioning across walking conditions. While locomotor training using split-belt walking (SBW), in which legs move at different speeds, has known efficacy, neither the underlying mechanisms nor clinical relevance of improvements are known.

Hypothesis: SBW-related improvements in locomotor adaptation will translate to increased community mobility activity in older populations by reducing the high cognitive load associated with walking.

Approach: Locomotor adaptation will is studied with a novel SBW protocol. Initial walking automaticity is assessed with wireless functional near-infrared spectroscopy (fNIRS) during dual-task treadmill walking. Mobility performance is evaluated with instrumented walking surfaces and portable sensors recording body motion and muscle activity. Community mobility is assessed with integrated analysis of accelerometry and global positioning system (GPS)-based measures of walking in-home and in the community. We focus on two measures of adaptability: 1) rate at which individuals adapt to SBW and 2) capacity to switch between context-specific walking patterns. We also determine if improving locomotor adaptability changes the neural and cognitive characteristics post-training. We plan for 30 participants for sufficient power.

Innovation. SBW targets locomotor adaptability. We characterize the relation between locomotor adaptability and GPS-based measures of community mobility, and functional gait assessment predicting fall risk.

Future: This will provide needed data for an NIH grant.

Core Collaborations: ISC (Torres-Oviedo and Redfern labs), DMAIC (analysis).

9. Project Title: **Small Pilot for Pepper Scholar: Function, falls and injuries as risk factors and outcomes of elder abuse in the VA**

Leader: **Drs. Lena Makaroun , Debra Weiner, Scott Beach, Ann Marie Rosland**

Significance/Approach: Little is known about physical function and falls as risk factors and outcomes for elder abuse (EA).37-43 With VA administrative data, 2 national cohorts of veterans over age 60 will be compared including one that received services for abuse/neglect and one that did not. Logistic regression and mixed modeling will be used to assess candidate variables including demographics, social status,

physical/cognitive function, falls and injuries. EA will be the independent variable for outcome analyses, and similar statistical methods will be used to explore the association with outcomes, including change in physical/cognitive function, fall and injuries, health service utilization and placement.

Innovation: Exam of a vulnerable population.

Core Collaboration: ISC, PESC, and DMAIC.

10. Project Title:	**Continuous Real-world Sensing of Physical Function in Older Cancer Survivors**
Leader:	**Carissa A. Low, PhD, Grace B. Campbell, PhD, MSW, BSN**

Specific aims: (1) To examine the association between continuous wearable and smartphone sensor data and commonly used clinical measures of physical function in cancer survivors aged 65 and older (2) To develop a preliminary machine learning model using mobile sensor data to differentiate older cancer survivors with impaired physical function, poor performance status, frailty, or history of falls from more physically robust participants. Brief background: Impaired physical function is common among older cancer survivors and is an important predictor of clinical outcomes. Mobile sensors that passively capture continuous objective data provide new opportunities for quantifying physical function in real-world settings during routine daily activities. Summary of methods: We will recruit cancer survivors aged 65 or older (n = 40) to complete a battery of validated performance-based and patient-reported physical function measures. Participants will also collect four weeks of continuous data from wearable devices and personal smartphones that will include physical activity, geographic mobility, sleep, and heart rate. We will evaluate associations between performance-based and patient-reported measures and daily behavioral features and will develop a preliminary model to classify participants into impaired physical function vs. high physical function groups. Future use of data: Data from this project will inform a NIH application assessing physical function longitudinally in a larger sample of older cancer survivors and evaluating the ability of mobile sensing to detect functional decline. This Pepper pilot project will provide important feasibility and effect size data and will help to identify which functional assessments and mobile sensors to use in future work. Core Collaborations: CPOC, DMAIC

11. Project Title:	**The muscle-brain axis: Exploring the effect of skeletal muscle activity on the connectome and transcriptome of aging animals**
Leader:	**Amrita Sahu, PhD**

Aims: The overarching goal of these studies is to test the central hypothesis that skeletal muscle contractile activity promotes a more youthful cognitive connectome (Aim 1) and spatially defined transcriptomic profile (Aim 2), ultimately contributing to enhanced cognitive capacity. Background: Physical activity attenuates age-related declines in neurostructual, neurofunctional, and neuromolecular profile of the brain. However, the mechanisms that underlie this beneficial effect of physical activity on aging brains are poorly understood. Individual approaches of cognitive testing, brain architecture analyses, and neuromolecular probing are often used to understand the aging process within the brain. In order to gain a comprehensive mechanistic understanding of aging brain and its response to physical activity, an integrated approach combining behavioral testing (cognition), connectomics

(neuroimaging), and spatial –omics (neuromolecular) analyses are warranted. Methods: All animal experiments will be performed with prior approval from the Institutional Animal Care and Use Committee of the University of Pittsburgh. Young and aged male C57BL/6 mice will be used in the studies (Young: 3-6 months, Aged: 21-24 months,). For inducing physical activity in animals, mice will be subjected to a neuromuscular electrical stimulation (NMES) protocol to elicit repetitive skeletal muscle contractions. Mice will receive five stimulation sessions over a period of two weeks, with each session consisting of 20 repetitions. Two days after the last session, animals will be subjected to behavioral testing (spatial memory, short-term memory, and motor activity) or neuroimaging (connectomics). After neuroimaging, the brains will be probed for spatial transcriptomic. Future use of data: We anticipate that using this integrated approach we will be able to identify mechanisms that underlie the benefit of skeletal muscle contractile activity on brain health. Findings from this study will lay the groundwork for developing targeted rehabilitation protocols designed to enhance cognitive functioning in an older population. Preliminary results from this study will also be leveraged to apply for larger funding to determine the effect of NMES on cognitive connectome based on sex. Core Collaborations: BMAC, ISC

12. Project Title:	**Interplay between Balance, Gait and Sleep in Older Adults with Glaucoma**
Leader:	**Rakié Cham, PhD, Shachi Tyagi, MD, MS**

Background. Falls are a major health risk for adults with glaucoma. While glaucoma-related changes in vision certainly contribute to falls, other well established risk factors for falls occurring at a greater rate in glaucoma than in older adults need to be considered. Poor sleep, an example of such risk factors, is well documented in glaucoma. In older adults without glaucoma, poor sleep negatively impacts falls risk and postural control, and causes other adverse health outcomes. Yet, we do not know if poor sleep function and disruption in sleep architecture associated with glaucoma, i.e. beyond aging-related symptoms, contribute to the increased prevalence of falls and reduced postural control in this clinical population. The overarching goal of the proposed project is to understand the interplay between sleep and postural control in glaucoma. Specific Aims. Three specific aims will be pursued. In Aim 1, participants with undergo detailed sleep assessments. In Aim 2, the relationship between sleep metrics and postural control function during standing and walking will be examined. In Aim 3, dual-task paradigms will also be used during balance/gait testing to examine attentional influences on postural control. Methods. Adults with advanced glaucoma and controls will participate in the proposed experiments. Our well-established balance/gait assessment protocols including dual-task experiments will be conducted to assess postural control function in various sensory challenging conditions. These protocols probe the ability to integrate multisensory information relevant for mobility through dynamic computerized posturography and gait analyses. In addition, rigorous assessments of sleep will be performed, including validated self-reported measures of sleep function and in-home EEG-based sleep testing. This state-of-the-art sleep assessment technology will provide detailed information related to sleep architecture by recording objective measures of various sleep stages duration. Appropriately constructed mixed linear statistical models will be used to test the hypotheses associated within each aim. The potential mediating effects of sleep on postural control impairments in glaucoma will be of primary interest. Future use of data. The findings can be used to identify specific sleep domains as potentially modifiable risk factors to improve balance/gait and reduce falls-related adverse health outcomes in glaucoma. The data collected

in the proposed project may be used to plan larger-scale intervention studies. Core Collaborations: DMAIC, ISC

13. Project Title: **Continuous Real-world Sensing of Physical Function in Older Cancer Survivors**

Leader: **Low, C; Campbell G**

Specific aims: (1) To examine the association between continuous wearable and smartphone sensor data and commonly used clinical measures of physical function in cancer survivors aged 65 and older (2) To develop a preliminary machine learning model using mobile sensor data to differentiate older cancer survivors with impaired physical function, poor performance status, frailty, or history of falls from more physically robust participants. Brief background: Impaired physical function is common among older cancer survivors and is an important predictor of clinical outcomes. Mobile sensors that passively capture continuous objective data provide new opportunities for quantifying physical function in real-world settings during routine daily activities. Summary of methods: We will recruit cancer survivors aged 65 or older (n = 40) to complete a battery of validated performance-based and patient-reported physical function measures. Participants will also collect four weeks of continuous data from wearable devices and personal smartphones that will include physical activity, geographic mobility, sleep, and heart rate. We will evaluate associations between performance-based and patient-reported measures and daily behavioral features and will develop a preliminary model to classify participants into impaired physical function vs. high physical function groups. Future use of data: Data from this project will inform a NIH application assessing physical function longitudinally in a larger sample of older cancer survivors and evaluating the ability of mobile sensing to detect functional decline. This Pepper pilot project will provide important feasibility and effect size data and will help to identify which functional assessments and mobile sensors to use in future work.

14. Project Title: **A Novel Method to Examine Muscle Health in Community-Dwelling Elderly**

Leader: **Safai Haeri, N**

Background: The assessment of muscle mass in elderly is challenging. This information is important as we try to characterize sarcopenia (loss of muscle) in older adults to improve muscle mass, strength, and function. Although we can measure lean mass by dual X-ray absorptiometry (DXA), DXA is a controversial measure for characterizing sarcopenia and is not well-correlated with strength or function. The deuterated creatine (D3-creatine) dilution method is a novel assessment of total body muscle mass based on the knowledge that nearly all creatine is stored in skeletal muscle, creatine is converted to creatinine at a steady rate, and creatinine is excreted in urine. Muscle mass measured by this method is associated with gait speed, physical function, serious falls and mobility limitation in ambulatory community-dwelling older men. However, the usefulness of this measure has not been established in frail older adults, who have the largest loss of muscle mass and would have the greatest benefits from assessments. Longitudinal measures are also sparse. Rate of muscle loss or gain would be a key determinant for future therapeutic modalities to preserve muscle function and strength in older adults. Aims: Aim 1: Obtain preliminary data on the impact of two different classes of osteoporosis medications on longitudinal changes in skeletal muscle function, muscle strength and lean mass in older adults. Hypothesis 1.1: Older adults on

denosumab (a RANKL inhibitor) will exhibit greater preservation or improvement in lean mass (D3-creatine; primary outcome, whole-body DXA, muscle ultrasound), grip strength and muscle function (Short Physical Performance Battery) over 12 months compared to zoledronic acid (an osteoclast inhibitor). Aim 2: Explore associations between measures of bone mass and skeletal muscle health. Hypothesis 2.1: Measures of bone and muscle health will be associated both cross-sectionally and longitudinally. From previous studies in patients with osteoporosis who took denosumab or zoledronic acid and had their lean mass measured by whole-body DXA, patients who took denosumab, unlike zoledronic acid, preserved their lean mass. Nevertheless, this effect has not been assessed by the D3-creatine method which is a much better surrogate for lean mass compared with the whole-body DXA. This pilot study addresses an important knowledge gap regarding muscle mass assessment in older adults and fits well with the mission of the Pepper OAIC that focuses on mobility, gait, falls and function. Most importantly, for many other Pepper investigators interested in muscle health, this study will lay the groundwork to establish a feasible and novel muscle mass measurement for participants under treatment for osteoporosis. The data will be directly used for sample size and power computations involving Pepper studies that propose to use the measure. Therefore, other investigators who want to use this measurement technique will have it established within the Pepper center. Methods: We propose to perform the D3-creatine test in 20-30 community-dwelling older adults. We have measures of DXA lean mass, grip strength, gait speed and function. In an IRB-approved study, we will perform the D3-creatine method in addition to our standard assessments. Participants will ingest 30 mg D3-creatine, and a fasting spot urine sample will be collected 3-6 days later. D3-creatinine, unlabeled creatinine, and creatine will be measured by liquid chromatography and tandem mass spectroscopy. Total body skeletal muscle mass will be calculated using established algorithms based on the ratio of labeled to unlabeled urinary creatinine. We will repeat the D3-creatine, DXA and function measures, 6 months later to estimate rate of muscle loss. Future Use of Data: These data will demonstrate that this assessment is feasible in older adults, and can be added to 2 other R01-funded ongoing osteoporosis trials. This study will provide preliminary data for a career development award for Dr. Nami Safai Haeri, MD. Finally, if successful, this method will establish a new assessment for many other Pepper investigators with a focus on muscle health.

15.	Project Title:	Interplay between Balance, Gait and Sleep in Older Adults with Glaucoma
	Leader:	Cham, R; Tyagi, S

Background. Falls are a major health risk for adults with glaucoma. While glaucoma-related changes in vision certainly contribute to falls, other well established risk factors for falls occurring at a greater rate in glaucoma than in older adults need to be considered. Poor sleep, an example of such risk factors, is well documented in glaucoma. In older adults without glaucoma, poor sleep negatively impacts falls risk and postural control, and causes other adverse health outcomes. Yet, we do not know if poor sleep function and disruption in sleep architecture associated with glaucoma, i.e. beyond aging-related symptoms, contribute to the increased prevalence of falls and reduced postural control in this clinical population. The overarching goal of the proposed project is to understand the interplay between sleep and postural control in glaucoma. Specific Aims. Three specific aims will be pursued. In Aim 1, participants with undergo detailed sleep assessments. In Aim 2, the relationship between sleep metrics and postural control function during standing and walking will be examined. In Aim 3,

dual-task paradigms will also be used during balance/gait testing to examine attentional influences on postural control. Methods. Adults with advanced glaucoma and controls will participate in the proposed experiments. Our well established balance/gait assessment protocols including dual-task experiments will be conducted to assess postural control function in various sensory challenging conditions. These protocols probe the ability to integrate multisensory information relevant for mobility through dynamic computerized posturography and gait analyses. In addition, rigorous assessments of sleep will be performed, including validated self-reported measures of sleep function and in-home EEG-based sleep testing. This state-of-the-art sleep assessment technology will provide detailed information related to sleep architecture by recording objective measures of various sleep stages duration. Appropriately constructed mixed linear statistical models will be used to test the hypotheses associated within each aim. The potential mediating effects of sleep on postural control impairments in glaucoma will be of primary interest. Future use of data. The findings can be used to identify specific sleep domains as potentially modifiable risk factors to improve balance/gait and reduce falls-related adverse health outcomes in glaucoma. The data collected in the proposed project may be used to plan larger-scale intervention studies.

16. Project Title: **The muscle-brain axis: Exploring the effect of skeletal muscle activity on the connectome and transcriptome of aging animals**

Leader: **Sahu, A**

Aims: The overarching goal of these studies is to test the central hypothesis that skeletal muscle contractile activity promotes a more youthful cognitive connectome (Aim 1) and spatially defined transcriptomic profile (Aim 2), ultimately contributing to enhanced cognitive capacity. Background: Physical activity attenuates age-related declines in neurostructual, neurofunctional, and neuromolecular profile of the brain. However, the mechanisms that underlie this beneficial effect of physical activity on aging brains are poorly understood. Individual approaches of cognitive testing, brain architecture analyses, and neuromolecular probing are often used to understand the aging process within the brain. In order to gain a comprehensive mechanistic understanding of aging brain and its response to physical activity, an integrated approach combining behavioral testing (cognition), connectomics (neuroimaging), and spatial –omics (neuromolecular) analyses are warranted. Methods: All animal experiments will be performed with prior approval from the Institutional Animal Care and Use Committee of the University of Pittsburgh. Young and aged male C57BL/6 mice will be used in the studies (Young: 3-6 months, Aged: 21-24 months,). For inducing physical activity in animals, mice will be subjected to a neuromuscular electrical stimulation (NMES) protocol to elicit repetitive skeletal muscle contractions. Mice will receive five stimulation sessions over a period of two weeks, with each session consisting of 20 repetitions. Two days after the last session, animals will be subjected to behavioral testing (spatial memory, short-term memory, and motor activity) or neuroimaging (connectomics). After neuroimaging, the brains will be probed for spatial transcriptomic. Future use of data: We anticipate that using this integrated approach we will be able to identify mechanisms that underlie the benefit of skeletal muscle contractile activity on brain health. Findings from this study will lay the groundwork for developing targeted rehabilitation protocols designed to enhance cognitive functioning in an older population. Preliminary results from this study will also be leveraged to apply for larger funding to determine the effect of NMES on cognitive connectome based on sex.

DEVELOPMENT PROJECTS (4 Development Projects Listed)

1. Project Title:	**Multi-system measures of mitochondrial dysfunction as early biomarkers of future aging-related mobility impairment**
Leader:	**Sarah Berman, MD, PhD, J. Timothy Greenamyre, MD, PhD, Daniel E. Forman, MD, Caterina Rosano, MD, MPH**
Core(s):	Clinical and Population Outcomes Core (CPOC)
	Data Management, Analysis and Informatics Core (DMAIC)

Significance: Mitochondrial dysfunction in both the brain and periphery occurs with aging. This hallmark of aging is multifactorial and affects muscle-skeletal, central nervous, and cardiovascular systems. The multi-system co-occurrence in heart-brain-muscle systems (HBM) likely influences aging-related healthspan outcome measures including the multidimensional syndrome of frailty. Dr. Greenamyre has shown mitochondrial dysfunction in HBM in animal models of Parkinson's Disease *in vitro* and *in vivo*. However, mitochondrial function in humans has been difficult to measure, particularly in brain. Magnetic resonance spectroscopy (MRS) is able to estimate levels of ATP production via monitoring high-energy phosphates, but resolution in brain is poor. Therefore, correlating mitochondrial dysfunction within each independent component of the HBM system with functional outcome measures has not been possible. The ability to predict mobility impairment by non-invasive biomarkers of mitochondrial function may provide a window for intervention prior to the onset of frailty.

Aims: Our goal is to develop the in-human use of a novel mitochondrial Complex I (Mito-CI) ligand for brain, heart and skeletal muscle using PET imaging to assess mitochondrial function in older adults. Thus, our primary aim is to characterize the pharmacokinetics of 18F-BCPP-EF in human brain, heart and quadriceps and optimize PET data analysis. Our secondary aim is to test the hypothesis that co-occurrence of mitochondrial dysfunction in more than one system plays a synergistic role in the pathogenesis of mobility impairment (e.g. 3>2>1). Conversely, preserved mitochondrial function in any one of these systems may lead to mobility resilience, even in the presence of deficits in the other two.

Approach: The novel PET imaging ligand, 18F-BCPP-EF is a specific ligand of mito-C1 optimized for brain imaging. 18F-BCPP-EF has been successfully utilized to detect mitochondrial dysfunction in animal PD models and has been safely used in preliminary human studies[19] We have established a collaboration with the developer at Hamamatsu Photonics, and we have synthesized and purified the ligand in preparation for human studies at our center. Benefitting from our combined extensive expertise at the University of Pittsburgh in PET radioligand development, in mitochondrial biology, and in geriatric medicine, we propose to perform the first fully dynamic 18F-BCPP-EF PET imaging and analysis in 20 older adults aged >65 free from neurological diseases. Dr. Berman is currently funded to collect PET brain data of mitochondrial complex I in 10 older adults with mobility disorders and 10 age-matched controls. With this DP, we will expand the sample of control participants to 20 (recruited from the Pepper Registry) and add scan time in the cardiac and skeletal muscles (quadriceps). Measures of mobility will also be obtained.

Future Studies: This study will provide proof-of-concept of the utility of this PET ligand in aging, and will serve to inform future larger studies to delineate the mechanisms of frailty and possibly early risk of mobility disability. Imaging Complex I *in vivo* in multiple systems has the potential to 1) provide an early and specific biomarker of mitochondrial dysfunction in multiple systems; and 2) indicate mechanisms underlying the syndrome of physical frailty in aging.

2. Project Title:	**Joint Modeling of Longitudinal and Survival Data for Dynamic Prediction of Mortality Risk with Gait Speed Serially Collected over Time**
Leader:	**Robert Boudreau, PhD, Charity Patterson, PhD, MSPH, Subashan Perera, PhD**
Core(s):	Clinical and Population Outcomes Core (CPOC) Data Management, Analysis and Informatics Core (DMAIC)

Significance: One-time physical performance measures are associated with many future outcomes in older adults. It is not clear how to predict future outcomes when serial measures of performance are available, which is a more realistic situation created by subsequent clinic visits. A prediction of an outcome should be updated with any new information about performance. Short term current vs long term trends, the experience of others who have exhibited similar trends, and how to incorporate those, if useful for prediction, need to be considered. Our prior work has shown decline (improvement) in gait speed is associated with worse (better) survival and rate of decline in gait speed over time is related to brain changes. However, they focused on associations and not individual-specific predictions. We are not aware of any other work that has addressed the problem specific to gait speed in a systematic and integrated way. A survival analysis model with time dependent covariates is not appropriate due to the endogenous nature of serial measurements.

Approach: We propose a novel application of the recently developed joint modeling of longitudinal and survival analysis technique to comprehensively address the question. The method makes use of the distribution of trajectories of all the subjects to better estimate individual trajectories, while allowing the latent local, slope and spline-trended mixed model random effects that characterize the trajectories to be potential predictors of survival risk. The joint distribution of the trajectories and survival model are consequently correlated and model fitting is based on optimizing the joint distribution. The survival component acts as a source of informative censoring and addresses the endogenous quandary discussed above. The model can be applied to make individual-specific short and/or long term mortality and gait speed future-trend predictions with confidence/prediction intervals. The predictions can be based on the actual measurements historically collected during a routine clinic visit and currently available along an individual's trajectory. And predictions are updated over time as new gait speed measurements are obtained. The method has been successfully applied in many other areas of medicine. We will use serial 20m "usual pace" gait speed measures of 3075 older adults in Health ABC (Years 1-6, 8 & 10), and convert them to 4m speeds using a linear or quadratic regression model. Such conversions can be

done with a high R2. We will develop the model using Health ABC data and will include 20 years of mortality data, then independently validate it using the CHS (N =5888) cohort who had annual 15' gait speed assessments and 20 years of mortality data. Briefly, ith participant's survival component of the joint model is given by , where is the true unobserved value of gait speed at time is the history of such information up to time are covariates, and is the baseline hazard function, typically approximated with a piecewise-constant form where 's define a partition of the time scale. The longitudinal component for observed gait speeds is, where and are design vectors for fixed and random effects. The model can be fit using the R package jm.

Innovation: Apart from scientific innovation, we will enlist a graduate student researcher to train and perform analyses (MS/PhD thesis) adding a new core-specific dimension to the OAIC training mission. With CPOC, we will disseminate to put the resulting risk calculator on the Pitt Pepper website and/or create a smartphone app.

Core Collaboration: CPOC and DMAIC. If successful, mobility-predicted risk could be considered a standard outcome to be used across the OAIC studies.

Future Direction: The STAR trial (Irrgang & Patterson, DoD) has serial measurements of quality of life and time to return to duty/activity/work in a knee surgery population presenting an immediate future application related to balance & mobility.

3. Project Title:		**Automated Neighborhood Walkability Audits by Machine Learning**
Leader:		**Andrea Rosso, PhD, MPH, Ervin Sejdik, PhD**
Core(s):		Clinical and Population Outcomes Core (CPOC)
		Data Management, Analysis and Informatics Core (DMAIC)

Significance: In-person environmental audits provide important information on physical barriers to mobility7 but can be time-consuming. Google Street View now provides access to free, online street-level images. We recently used Google Street View's historical images to add environmental data retrospectively to the Health ABC cohort (R21 AG054666-01, PI: Rosso). Use of these images for environmental audits has been demonstrated to be valid and reliable for street-level characteristics.14-19 Because Google Street View images are in the public domain and will not be linked to individual data, this research is not considered human subjects research.

Innovation: No automated methods for environmental features relevant to mobility and falls in older adults currently exist for use in research studies.

Aims: 1) Identify the environmental components most relevant to falls using existing published literature, and 2) Based on findings in Aim 1, develop computer methods to assess these features in an efficient, reliable, and automated way.

Approach: We will develop computer-based, automated methods for auditing Google Street View images for environmental features most relevant to mobility and falls in older adults. We first determine the most relevant environmental features through a systematic literature review. We then use machine learning methods to develop automated auditing processes. Since Google Street View images provide visuals of house exteriors, nature, landscaping, and vehicles on the street20, we can use deep

learning to identify environmental features by looking for key urban design qualities; walkability: imageability, enclosure, human scale, transparency and complexity.21 Prior studies used several methods to detect and estimate pedestrian volume, visual enclosure, automotive vehicles, and curbsides. Since overlapping images are taken from different perspectives and have different levels of color and illumination, deformable part models (DPM) can be used22-27. Each "deformable part" represents an object model by taking on the appearance properties of the object. The deformations are then linked. Histogram of Oriented Gradient (HOG) is also used to capture the image's region's gradient's intensity and direction23,25,26. Algorithms such as the Aggregated Channel Features (ACF) algorithm can increase computational efficiency by large-scale estimating of HOG and then discarding parts in small-scale images23. Artificial Neural Networks (ANN) can be used to analyze color and texture in Google Street View images27. Feature extraction and segmentation can be performed to isolate regions such as the sky, objects that obstruct the view, and other environmental features of interest22. Extracted features from HOG-ACF or ANN can be used for classification using Support Vector Machine, Decision Trees, Adaboost, or other supervised classification algorithms,23,26,27. Convolutional Neural Networks (CNN) may be able to recognize a wide variety of environmental objects that may affect walkability due to CNN's ability in object classification20. However, CNN is a supervised machine learning method that requires a training set of labeled images. Another method is to use a combination of Region Proposal Networks (RPN) and Fast Region-CNN (RCNN)25. RPN is also a convolutional network that can propose areas or regions in the image, while detection of these regions is done by Fast RCNN. The results of the machine learning audits will be validated against human audits.

Core Collaborations: CPOC, DMAIC

Future Uses: These methods would be made available through the CPOC for wide general research use to expand efficient research assessments into community risk factors for any study focused on mobility and falls.

4. Project Title: **Targeting age-reprogrammed activity of methionine and tyrosine metabolism to delay frailty, improve motor function, and suppress age-predicting 'epigenetic clock'.**

Leader: **Andrey Parkhitko, PhD, Stacey Rizzo, PhD**

Core(s): Biology of Mobility and Aging Core (BMAC)

Metabolic reprogramming represents one of the major driving forces in aging and leads to impaired organismal fitness, an age-dependent increase in susceptibility to diseases, decreased ability to mount a stress response, and increased frailty. Although targeting methionine and tyrosine metabolism has been shown to increase lifespan in different species, at present, no data exist to demonstrate their effects on composite measures of health in general and on muscle health in particular. In addition, MetR in human patients has been only tested in the settings of methionine deprivation from food, which is hardly achievable in clinical settings and results in a moderate decrease in plasma methionine, potentially limiting its efficacy.

Rationale: Our preliminary data demonstrate that metabolism in general and methionine/tyrosine metabolism particularly are reprogrammed during aging in Drosophila (Parkhitko et al., 2016; Parkhitko et al., 2019) and (Parkhitko et al., eLife under revision). We also identified two novel anti-longevity genes in the methionine metabolism pathway that can improve the age-dependent decline in climbing activity (indicator of neuromuscular function in flies) and extend health- and lifespan (Parkhitko et al., G&D 2016). Similarly, we demonstrated that aging and mitochondrial dysfunction activate the tyrosine degradation pathway and that downregulation of tyrosine aminotransferase, the first and rate-limiting enzyme in the tyrosine degradation pathway, upregulates the production of tyrosine-derived neuromediators and extends lifespan (Parkhitko et al, eLife, under revision). Both methionine and tyrosine metabolism pathways can be targeted with FDA-approved drugs or drugs that are under current development for human applications. For example, we demonstrated that Methioninase, a bacterial enzyme capable of degrading methionine, efficiently depletes methionine and downstream metabolites (Figure 1) and dramatically extends Drosophila lifespan (Parkhitko et al., Aging Cell, under revision). Recombinant Methioninase has been tested in various cancer models in vivo and was safely used in clinical trials in humans (Agrawal et al., 2012; Chaturvedi et al., 2018; Hoffman, 2015). Cancer patients receiving recombinant Methioninase intravenously had a steady decline in serum methionine levels directly proportional to levels of active enzyme with minimal or no toxicity (Tan et al., 1997). This creates a strong rationale for translating these findings to mammalian systems as anti-aging interventions or for the potential treatment of various age-related diseases.

Approach: We will use either young AD mice or wild-type C57BL/6J mice of different ages: young (4 mo) and old-age (24 mo). We will investigate how manipulations of methionine metabolism via dietary MetR (restricting methionine in mouse food) or enzymatic MetR (feeding mice with Methioninase) or manipulations of the tyrosine metabolism by feeding mice with an FDA-approved drug, nitisinone/orfadin, would affect the frailty index, wheel running, and epigenetic age. To confirm the efficiency of our manipulations and the effect of age, we will measure levels of metabolites from the methionine and tyrosine metabolism pathways in mouse plasma, liver, muscle, and brain. The Frailty Index (FI) is a non-invasive composite measure of health that can assess an effect of treatment on different aspects of healthspan and predict life expectancy and the efficacy of a lifespan-extending interventions up to a year in advance (Sukoff Rizzo et al., 2018), (Schultz, Kane et al., bioRxiv 2019). In addition to the FI, to estimate the potential effects of proposed interventions on lifespan, we will use mouse 'epigenetic clocks' to predict the effects of proposed intervention on biological age and lifespan extension. Through this Developmental Pilot, we expect to test how manipulations of methionine and tyrosine metabolism pathways affect the multitude of parameters relevant to aging in mice, with a special focus on the assessments of motor and fine motor function.

Core Collaborations/ grants: BMAC/ Preclinical Phenotyping Core.

Future Proposals: This pilot project will provide the necessary data for a National Institute of Aging R01 grant proposal. Long-term goals include evaluation of recombinant Methioninase and nitisinone/orfadin for lifespan extension in mice and for the effects on the FI in humans.

RESEARCH (32 Projects Listed)

1. Project Title: **Nitrite Supplementation to Mitigate Fatigability and Increase Function in Long COVID Patients**

Leader(s): **FORMAN, DANIEL E.**
VETERANS HEALTH ADMINISTRATION
VA 1I21RX004409 / (2023 - 2025)

Core(s):

Prevalence of long COVID is surging among Veterans, and Veterans afflicted with this disease typically incur progressive declines in function, diminished quality of life and increased disability. Skeletal muscle pathophysiology has been implicated as a significant determinant of long COVID pathophysiology and clinical declines. Dr. Forman is a cardiologist and geriatrician who is currently engaged in research studying benefits of nitrite supplementation with investigational new drug (IND) nitrite capsule supplements in older adults with sedentariness and/or heart failure. In that work, he is focusing primarily on the utility of nitrites to increase skeletal muscle mitochondrial respiration. Secondarily, he is exploring if mitochondrial respiration changes correlate to changes in physical function. In particular, he is studying if increased serum and skeletal muscle nitrite elevations correlate to improvements in cardiorespiratory fitness (i.e., peak oxygen utilization [VO2]), and to decreased fatigability (i.e., rating of perceived exertion [RPE] during steady-state submaximal [1.5 miles per hour] walking). In this SPiRE application, Dr. Forman proposes to redirect his expertise in nitrite therapeutics to Veterans with long COVID. Nitrites will be administered as nitrate-rich beetroot juice versus nitrate-poor placebo. When beetroot juice is ingested, nitrates are metabolized to nitrite. Compared to IND nitrite capsules, beetroot juice is relatively easier to administer, less expensive, and hemodynamically safer. Whereas serum nitrite levels have not been consistently high in studies of beetroot juice interventions as compared to nitrite capsules, this proposal aims to optimize nitrite levels using 210 ml per day of Beet-It nitrate beverage (James White Drinks Ltd., Ipswich, UK) to provide 16 mmol of nitrate/day for 14 days versus a 210 ml of nitrate- depleted placebo. All participants will also undergo physical therapy. Endpoints in this SPiRE study are oriented principally to physical function. Endpoints (measured pre- and post- the 2-week intervention) include fatigability as well as walking efficiency (VO2/kg) during steady-state walking. Furthermore, traditional functional indices of peak VO2, VO2 at anaerobic threshold, 6-minute walk distance, short physical performance battery, and pulmonary function tests will also be assessed. Nitrite levels (both serologically and in the skeletal muscle itself) will be measured to best ascertain the relationship of nitrite and putative clinical changes. In addition, analyses of skeletal muscle will clarify if nitrite-mediated changes in physical function correlate to changes in skeletal muscle respiration. Overall, this proposal aligns with the Veteran s Affairs Office of Research and Development s commitment to research that helps Veterans affected by COVID-19, and it also aligns with the Rehabilitation Research and Development s mission to maximize Veterans functional independence, quality of life and participation in their lives and community. Dr. Forman anticipates applying the data and momentum from this compelling SPiRE-based analysis to pursue a subsequent MERIT trial that reinforces the value of nitrite therapeutics more definitively for long COVID patients.

2. Project Title: **Leveraging a natural experiment to identify the effects of VA community care programs on health care quality, equity, and Veteran experiences**

Leader(s): **GELLAD, WALID F.; ROBERTS, ERIC T;**
VETERANS HEALTH ADMINISTRATION
VA I01HX003457 / (2022 - 2026)

Core(s):

Background: The Veterans Choice Program and MISSION Act have transformed how VA delivers care by expanding Veterans eligibility to receive VA-funded care from community providers. The effects of this change on the quality and equity of care are unknown. Understanding these effects is critical, given the importance of these programs to VA and the complexity of managing care for Veterans across different health systems. To address this evidence gap, we will use a quasi-experimental regression discontinuity (RD) design and examine outcomes in medically and socially vulnerable subgroups to determine the impact of Choice and MISSION on quality and equity of Veterans health care. To further examine impacts on vulnerable groups, we will analyze disparities in ratings of community care from VA s Survey of Healthcare Experiences of Patients (SHEP). Significance: This proposal addresses cross-cutting HSR&D research priorities, including evaluating the quality and equity of care for Veterans in the context of a key legislative priority for VA: the MISSION Act. We will examine how the effects of receiving community care, and patient experiences with community

care, differ in vulnerable populations, addressing VA priorities related to equity. The project constitutes an advancement in the rigor of research while directly informing ongoing and high priority clinical initiatives within VA. Innovation and Impact: Our project is innovative because it uses an RD design to provide causal evidence about the effects of community care on the quality and equity of outpatient care and prescribing. The project is also innovative and impactful in its attention to subpopulations of socially and medically vulnerable Veterans, including analyses of disparities in community care patient experiences from national survey data. By working closely with operational partners and a Veterans Advisory Board, we will impact VA policy by translating findings into actionable recommendations to improve community care, particularly for vulnerable groups. Specific Aims: (1) Identify the effects of receiving outpatient community care through Choice and MISSION on quality and equity. (2) Identify the effects of community care on the quality and equity of prescribing. (3) Compare Veterans experiences with community care in vulnerable and other Veteran populations. Methodology: We will use an RD design and analyses of both administrative and VA survey data to assess the effects of Choice (all program years) and MISSION (2019-2022) on the quality and equity of Veterans health care. Aims 1-2 will use a quasi-experimental RD design that compares Veterans just above vs. below distance and travel time eligibility thresholds for VA community care in Choice and MISSION. We will study effects of community care use on quality overall and, to evaluate implications for equity, in vulnerable subpopulations defined by the presence of serious mental illness or substance use disorders, complex chronic conditions, low income, and racial/ethnic minority status. Outcome variables in Aim 1 focus on outpatient processes of care (e.g., continuity of care) and outcomes linked to care coordination (e.g., admissions for ambulatory care-sensitive conditions). Outcome variables in Aim 2 focus on prescribing safety and quality (e.g., drug-drug interactions), therapeutic duplication, and refill non-adherence. These analyses use VA Corporate Data Warehouse, Planning Systems Support Group, Medicare, and Program Integrity Tool data. In Aim 3, we will analyze national data from the VA SHEP Community Care survey (conducted among community care recipients) to compare patient-reported experiences with community care among Veterans in vulnerable populations vs. other Veterans. Outcome variables in Aim 3 include 5 domains of Veterans experiences with care coordination, provider communication, and timely access in VA community care. Next Steps/Implementation: Through close partnerships with the Office of Community Care, Pharmacy Benefits Management, Office of Health Equity, and a Veterans Advisory Board, we will rapidly disseminate our findings and translate them into actionable recommendations to improve quality and equity in community care.

3. Project Title: **Identifying Risk and Improving Care for Elder Abuse among Veterans**

Leader(s): **MAKAROUN, LENA**
VETERANS HEALTH ADMINISTRATION
VA IK2HX003330 / (2022 - 2027)

Core(s):

Background. Elder abuse (EA) is the physical, sexual or psychological abuse, financial exploitation or neglect of an adult age =60 years. One in 10 older adults experience EA annually in the US, with many experiencing multiple types. Veterans are at particularly high risk due to the high prevalence of EA risk factors in this population. Experiencing EA is linked to depression, injury, increased healthcare use and mortality, but despite its prevalence and morbidity, fewer than 5% of cases are detected, limiting opportunities for intervention. While screening is a common approach to improving detection of similar conditions, screening tools for EA have not been well validated or widely studied. Furthermore, EA screening may miss important high-risk populations, such as those with dementia, necessitating the development of additional detection strategies that complement screening. This research aims to improve EA risk detection in VA by both evaluating and optimizing current EA screening approaches and by leveraging VA healthcare data to identify Veterans with clinical suspicion of EA who may benefit from further assessment. Significance/Impact. With the growing population of older adults in the US and over 10 million US Veterans age =60 years, improving detection of and interventions for EA is a national and VA public health priority. By improving detection of EA via both better-informed screening and novel data-driven tools, this research aligns with VA HSR&D s priority to improve care for our nation s aging Veterans and their caregivers. Innovation. This research integrates elder abuse and implementation science conceptual frameworks to develop new approaches to improving EA detection. This study will evaluate the test characteristics of the first-ever data marker for EA suspicion using unique VA data elements and will employ innovative data informatics approaches, such as natural language processing (NLP), to address a complex social problem with large health impacts. Specific Aims. Aim 1 is a national assessment of the current landscape of EA screening practices in VA medical centers (VAMCs) and a quantitative evaluation of facility level factors associated with screening. Aim 2 is a quantitative study that will identify the best performing EA administrative marker (AM) in VA data. Aim 3 is a qualitative study that will elucidate opportunities for, facilitators of and barriers to implementation of healthcare-based EA detection programs in VA. Methodology. In close partnership with the VA Office of Care Management and Social Work, Aim 1 will conduct a national survey of VAMCs to assess current practices around EA screening and detection; VA facility-level data will be used to assess structural characteristics associated with screening.

Aim 2 will examine three potential EA suspicion AMs and select the best performing via comparison to a multi-component reference standard consisting of: a) simplified rule-based NLP of progress note content, and b) evaluation of discordance between AMs and NLP through targeted medical record review. In Aim 3, early-, recent-, and non-EA screener sites identified in Aim 1 varying in EA case volume according to the AM selected in Aim 2 will be recruited for in- depth qualitative interviews to elucidate opportunities for, facilitators of, and barriers to EA detection programs in VA. Implementation/Next steps. Findings from this research will be used to derive and validate a novel EA Suspicion Tool (EAST) in VA, then develop and implement a detection approach that improves efficiency and impact by combining improved EA screening with comprehensive EA assessments targeted towards those at highest risk. Candidate. Dr. Lena Makaroun is a geriatrician and Core Investigator at the VA Center for Health Equity Research and Promotion. The goal of this CDA is to gain training and research experience in improving EA detection among older Veterans through in-depth training in: (1) real-world EA evaluation and intervention programs; (2) implementation science; (3) framework-guided qualitative methods; and (4) prediction analytics. This CDA will support Dr. Makaroun s long-term career goal of becoming an independent VA health services researcher focused on improving care delivery, intervention and, ultimately, prevention of EA in older adults.

4. Project Title: TRAINING IN MOLECULAR EPIDEMIOLOGY: LINKING GENES TO PHYSICAL FUNCTION IN OLDER ADULTS

Leader(s):   SANTANASTO, ADAM J
THE UNIVERSITY OF PITTSBURGH
NIH K01AG057726 / (2018 - 2023)

Core(s):   - Clinical and Population Outcomes Core (CPOC)
- Data Management, Analysis and Informatics Core (DMAIC)

Age-related declines in physical function are common and lead to increased health care costs, institutionalization andmortality. As a traditional epidemiologist with unique expertise in skeletal muscle aging and physical function, I haveresearched lifestyle interventions (weight loss, aerobic and resistance training) to prevent age-related declines in physicalfunction. However, lifestyle changes are difficult to adopt, especially for those at the highest risk for functional decline. Toextend the benefits of these interventions, it is imperative to understand biological processes underlying changes in functionwith aging and following intervention. As such, the current proposal will provide the candidate with advanced training inmolecular epidemiology and biology of aging, yield novel insight on the genetic and biological basis of physical functionamong older adults and lay the foundation for future research. Specially, Aim 1 will identify genes and genetic variants forphysical function and changes in physical function with aging. Aim 2 will examine blood RNA expression for componentsof the transforming growth factor beta (TGF-) pathway, which is implicated in muscle dysfunction and pathogenic fibrosis,with physical function and its change with aging. Aim 3 will test if serum levels of TGF- and procollagen type 3 N-terminal propeptide (P3NP - a biomarker of pathogenic fibrosis) are related physical function among older adults. I willleverage robustly collected physical function measures, biological samples, and an ultra-high-density genome-widepolymorphism map from the NIA-funded Long Life Family Study (LLFS), a multi-center study of exceptional aging andlongevity in families and fromThe Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)Consortium. The proposed research and training is very innovative. First, despite being implicated in several age-relatedconditions there have been no human studies that have examined the relationship between TGF- or P3NP and physicalfunction. Further, LLFS has a large number of oldest old , who are understudied and at the highest risk for functionaldecline. There has also been limited research on the genetics of physical function. The proposed career development awardwill provide the applicant with essential new mentorship, knowledge and skills in human genetics and molecularepidemiology including but not limited to blood RNA expression and protein biomarker development (Aim 2 and 3),genome wide association (GWA) and linkage analyses (Aim 1), meta-analysis(Aim 1) and bioinformatics (Aim 1)approaches to follow-up association and linkage analyses. Finally, this award will be critical for facilitating my transitionto an independent research career in aging and molecular epidemiology with a focus on physical function. As anepidemiologist with expertise in both traditional and molecular methods,I will be well-positioned to contribute to theadvancement of the evolving field of GeroScience.

5. Project Title: The relationship between protein intake, gut microbiome, inflammaging and loss of mobility in older adults

Leader(s):   FARSIJANI, SAMANEH
UNIVERSITY OF PITTSBURGH AT PITTSBURGH

NIH K01AG071855 / (2022 - 2026)

Core(s):

This K01 application is for Dr. Samaneh Farsijani to establish a research career in Nutritional Epidemiology and acquire skills to integrate omics (gut microbiome) and non-omics (dietary intake) data towards her long-term goal in Precision Nutrition to develop age-specific dietary recommendations, replacing the current one-size-fits-all approach, to promote healthy aging. The proposal is derived from the candidate s extensive training in nutrition and interdisciplinary research background in biology and epidemiology. The proposed training goals are directed to advance candidate s skills in 1) aging & nutritional epidemiology; 2) advanced biostatistics; 3) gut microbiome; and 4) career development. Acquired skills will be applied toward the proposed scientific goal to determine the relationships between protein intake, gut microbiome, inflammation, and mobility loss in older adults. Aging is associated with inefficient utilization of dietary proteins, due to anabolic resistance, which potentially leads to functional losses. Also, up to 50% of US older adults fail to meet the Recommended Dietary Allowance (RDA) for protein (0.8 g/kg body weight/d). Therefore, a higher protein intake, above the RDA (1.0-1.2 g/kg/d), has been suggested to compensate for changes in protein metabolism and to maintain muscle health in aging. However, this strategy has not been incorporated into dietary guidelines due to inconclusive evidence from small and short- term studies, which were unable to show the underlying mechanisms and causal relationships between protein intake and mobility function in older adults. Gut dysbiosis (i.e., changes in gut microbiome) and inflammaging (i.e., low-grade chronic inflammation in aging) have been linked to frailty in older adults. Since diet plays a key role in shaping the gut microbiome and inflammation, it may be speculated that the effects of protein intake on mobility function are mediated through alterations of dysbiosis and inflammaging. Our central hypotheses are: i) high protein intake reduces the risk of mobility limitation by ameliorating inflammaging; ii) different protein intake metrics are independently associated with gut microbiome and inflammaging; and iii) gut dysbiosis is associated with mobility impairment in older adults. This proposal will leverage data from Health, Aging & Body Composition (Health ABC), and Study of Muscle, Mobility & Aging (SOMMA) cohorts to address three Aims: Aim 1: To simulate a pragmatic clinical trial using the Health ABC cohort to determine i) the effect of protein intake on the risk of mobility limitation, and ii) its causal mediation by amelioration of inflammaging. Aim 2: a) To characterize the associations between different metrics of protein intake (i.e., quantity, source and within-day distribution pattern), gut microbiome composition, and fecal metabolites; and b) to determine the association between gut dysbiosis and inflammaging in SOMMA. Aim 3: To determine the cross-sectional associations between gut microbial composition and fecal metabolites with mobility (i.e., gait speed) in older adults from SOMMA. This project will broaden our insights into the influence of protein intake, as a modifiable factor, on gut microbiome, inflammaging, and muscle health in aging with the ultimate goal to drive age-specific dietary advice.

6. Project Title: **FINANCIAL ASSISTANCE FOR LOW-INCOME MEDICARE BENEFICIARIES: USING NATURAL EXPERIMENTS TO ASSESS EFFECTS ON CARE AND HEALTH OUTCOMES**

Leader(s): **ROBERTS, ERIC T**
THE UNIVERSITY OF PITTSBURGH
AHRQ K01HS026727 / (2019 - 2023)

Core(s): - Clinical and Population Outcomes Core (CPOC)
- Data Management, Analysis and Informatics Core (DMAIC)

PROJECT SUMMARY / ABSTRACT This AHRQ Mentored Research Scientist Career Development Award (K01) for Dr. Eric T. Roberts, anassistant professor of health policy and management at the University of Pittsburgh Graduate School of PublicHealth, will establish Dr. Roberts as a health economist with expertise in health insurance and health carepolicy for aging and low-income populations. Research proposed for this K01 award will harness natural experiments created by eligibility thresholdsand policy variation within Medicare subsidy programs to rigorously evaluate how these programs affectpatients' use of care, access to providers, and health. This project will focus on two subsidy programs forlow-income Medicare beneficiaries: the Medicare Savings Programs (MSPs), which are partial Medicaidbenefits that defray out-of-pocket costs for physician services and inpatient care, and the Part D Low-IncomeSubsidy (LIS), which helps to pay for prescription drugs. Using the Health and Retirement Study linked toMedicare and Medicaid claims, Dr. Roberts will examine how discontinuities in subsidy eligibility affectpatients' use of care including medication adherence, physician visits, and hospitalizations and healthstatus. Dr. Roberts will also examine the relationship between state Medicaid policies specifically, providerpayment rates and rules for recertifying program eligibility with MSP enrollment and patients' access tocare. Evidence generated from this research can guide reforms to increase the benefits of the MSPs and LISto low-income Medicare beneficiaries and to the Medicare program. This project draws on Dr. Roberts' quantitative training, knowledge of Medicare and Medicaid policy, andprior research on health disparities. This work will extend Dr. Roberts' scholarship into

the field of aging whileincorporating methods in pharmaceutical health services research. Therefore, for this K01 award, Dr. Robertswill engage in training and career development activities that focus on acquiring expertise in aging andpharmaceutical health services research. Through mentorship from health services researchers and clinicalexperts, Dr. Roberts will also focus on applying training in these content areas to health policy research. Thistraining plan complements the proposed research and will equip Dr. Roberts to establish an independentresearch program examining policy innovations to improve care for low-income Medicare beneficiaries,quantifying the clinical and economic impacts of policy reforms for patients, payers, and health systems.

7. Project Title: **Human Factors of Aging Program**
Leader(s):   **REDFERN, MARK S**
UNIVERSITY OF PITTSBURGH AT PITTSBURGH
NIH K07AG061256 / (2021 - 2025)

Core(s):

Abstract: The candidate, Mark S Redfern, PhD, is a professor at the University of Pittsburgh with a primary appointment in the Department of Bioengineering, Swanson School of Engineering, and secondary appointments in Otolaryngology, School of Medicine, and Physical Therapy, School of Health and Rehabilitation Science. He is applying for a K07 to establish a new program in Human Factors of Aging to educate and support researchers, clinicians and students focused on improving the lives of older adults. A unique aspect of the curriculum is including design for cognitive decline and Alzheimer s disease through a partnership with Pitt s Alzheimer s Disease Research Center (ADRC). Research often leads to ideas and findings that can have direct application to improve the lives of people of all ages. One limiting step in the translation of these new ideas is the incorporation of human factors in the design. Incorporating the human factors of aging is a critical component of any medical device design for an older population. There are physical (e.g. mobility, dexterity, anthropometry, strength, range of motion), sensory (e.g. vision, hearing, vestibular, proprioception) and cognitive considerations (e.g. memory, executive function, cognitive speed). Translation of ideas for older adults with cognitive decrements and Alzheimer s disease is particularly difficult. The interactions of cognitive decrements with the physical and sensory changes associated with aging require special attention during design that to-date is not addressed. To address this need, Dr. Redfern, in collaboration with the ADRC, will establish a new and novel educational program with a curriculum to bring the necessary knowledge of Human Factors of Aging to the research community. This curriculum will address not only physical and sensory considerations, but also the unique requirements for adults with cognitive decline, and how they interact with other age-related issues. The long-term goal is to improve the development of new medical devices and interventions that are targeted to be used by/with older adults taking into consideration cognitive decline. The specific aims are to: 1) partner with the ADRC to educate clinicians, researchers, and engineers in the human factors of aging to improve the translation of their ideas into effective interventions 2) support investigators with collaborative advising and consultation on special issues in aging-related applications and availability of the Human Factors in Medical Device Laboratory for development and evaluation of medical devices/interventions targeting for older populations; and 3) develop a multidisciplinary community of investigators with interests and expertise in human factors of aging; including experts from the ADRC. Dr. Redfern s background as a senior NIH/NIA researcher, longtime educator in Human Factors/Ergonomics, and positions in academic leadership make him the ideal person to create a sustainable and effective program. The proposed partnership with the ADRC will bring together a unique strength found nowhere else.

8. Project Title: **TELE-RECOVERY: ENGAGING STAKEHOLDERS TO ADAPT AND PILOT TEST A SCALABLE TRANSITIONAL REHABILITATION INTERVENTION FOR OLDER, RURAL ICU SURVIVORS**
Leader(s):   **SCHEUNEMANN, LESLIE PAGE**
THE UNIVERSITY OF PITTSBURGH
AHRQ K08HS027210 / (2019 - 2024)
Core(s):   - Clinical and Population Outcomes Core (CPOC)
- Data Management, Analysis and Informatics Core (DMAIC)

ABSTRACTAccess to high-quality post-intensive care unit (ICU) recovery services is a major problem for thousands ofolder Americans living in rural communities who survive critical illness each year. They and their families oftenexperience uncoordinated care, poor health, reduced independence and quality of life, and high ongoinghealthcare utilization. Any scalable solution will require the flexibility to address multimorbidity, physical, cogni-tive, and psychological dysfunction, caregiver stress, and end-of-life transitions, all of which are common. Toaddress this problem: (1) The principal investigator will acquire new skills that position her as an independentimplementation physician scientist specializing in improving the quality of geriatric critical care in the post-ICUperiod. She will complete a career development plan including didactic courses, experiential research, and in-tensive transdisciplinary mentoring with her team from geriatric psychiatry, occupational therapy, critical care,and biostatistics. It will equip her with expertise in stakeholder engagement, transitional care, rehabilitation,telehealth, and implementation science; (2) The proposed research will develop and pilot test a scalable,stakeholder-informed, evidence-based ICU recovery intervention called TeleRecovery. In TeleRecovery, anurse practitioner and occupational therapist will deliver transitional care, family training and support, andskills-based rehabilitation to rural-dwelling older adults, starting at ICU transfer. From discharge until gradua-tion back to primary care, they will partner with home health providers via telehealth to implement the careplan. Instead of developing TeleRecovery de novo, we will use stakeholder engagement to adapt transitionalcare (Transitional Care Model) and skills-based rehabilitation (Patient-Driven Skills Training) interventions.These interventions have proven success among clinical populations with key similarities to ICU survivors;combining them will comprehensively address rural-dwelling, older ICU survivors complex needs. The firststep in developing TeleRecovery will be semi-structured interviews and focus groups with a full range of stake-holders patients, families, hospital- and community-based providers, and healthcare administrators includingpayers to identify priorities, barriers, and facilitators in delivering ICU recovery care for older ICU survivors.We will integrate results into a model of care delivery that is patient-centered and improves health-system qual-ity, affordability, and access. Second, we will conduct stakeholder workshops, telehealth software modification,interventionist training, and user testing to apply the model from Aim 1 to develop TeleRecovery for rural, olderICU survivors. Finally, we will conduct a pilot study to evaluate its feasibility and acceptability among rural,older ICU survivors. This research will generate: (1) partnerships among institutional leaders in critical care,home health, healthcare administration and finance, rehabilitation, and telehealth to facilitate further research;(2) a pilot tested TeleRecovery intervention that is ready for testing in a clinical trial; (3) an independent imple-mentation physician scientist capable of seeing TeleRecovery through implementation and dissemination.

9. Project Title: **Activity and Participation in Vestibulopathy**
     Leader(s):   **KLATT, BROOKE**
                                   UNIVERSITY OF PITTSBURGH AT PITTSBURGH
                                   NIH K23DC020215 / (2022 - 2027)

Core(s):

Current vestibular rehabilitation intervenes upon vestibular impairments (balance, gaze stability, and dizziness). Activity and participation are reduced in people with vestibulopathy, but are not addressed in vestibular rehabilitation protocols. Approximately 40% of people with vestibulopathy do not fully recover and transition to a state of chronic disability, which often results from reductions in activity and participation, and. Evidence from rehabilitation science within other populations suggest that return to full activity and participation is related to functional mobility status, and also several behavioral, personal, and environmental factors. Similarly, we suspect that cognitive, mood, and personal (confidence, coping, and fear avoidance) factors that are modifiable, may impact activity and participation in people with vestibulopathy. It is also unknown whether improvements in activity and participation are related to remediation of impairments following vestibular rehabilitation. Activity and participation represent important domains to target to optimize outcomes and reduce chronic disability. This career development award will establish Dr. Brooke Klatt as a clinical scientist with expertise in 3 primary domains: (1) cohort design and analysis; (2) qualitative methodology, and (3) complex rehabilitation intervention development and behavioral clinical trial methodology. Dr. Klatt has assembled a multi-disciplinary team of experts in rehabilitation intervention development and implementation (Jennifer Brach, PhD, PT and Elizabeth Skidmore, PhD, OTR/L), activity and participation assessment and epidemiological methods (Andrea Rosso, PhD, MPH), behavioral impacts on vestibular recovery (Jeffrey Staab, MD), and clinical trial methodology (Megan Hamm, PhD and Charity Patterson, PhD, MSPH). Dr. Klatt will conduct a series of studies to develop an enhanced vestibular intervention that will augment current vestibular rehabilitation targeted to improve activity and participation. She will investigate whether impairments (balance, gait, gaze stability, dizziness, cognition, and mood) as well as personal factors (confidence, coping skills, and fear avoidance) are related to activity and participation in people with vestibulopathy (Aim 1), and she will determine if reductions in vestibular impairment is related to improvements in activity and participation (Aim 2). She will use stakeholder input from clinicians and patients to determine the delivery features that show the greatest promise for improving activity and participation in people with vestibulopathy (Aim 3). Dr. Klatt s is plan to develop effective

interventions to enhance current vestibular rehabilitation addresses the NCMRR research priorities to mitigate acquisition of secondary conditions by using a multimodal approach to promote vestibular plasticity and sensorimotor function. The proposed training will be the foundation for a future R01 application examining the efficacy of the enhanced vestibular intervention to improve activity and participation and the quality of life for individuals with vestibulopathy.

10. Project Title: **THE ROLE OF USP30 IN IDIOPATHIC PARKINSONS DISEASE**
   Leader(s):   **ROCHA, EMILY MANGANO**
   THE UNIVERSITY OF PITTSBURGH
   MICHAEL J FOX FOUNDATION MJFF-008849 / (2021 - 2023)
   Core(s):   - Biology of Mobility and Aging Core (BMAC)

Dopamine neurons are highly vulnerable to age-dependent increases in mitochondrial dysfunction, oxidative stress, and protein accumulation due to their high metabolic activity, low antioxidant capacity and post-mitotic nature. Failure to remove these damaged mitochondria will likely lead to a bioenergetic crisis that ultimately contributes to the onset and/or progression of Parkinson s disease. The deubiquitinating enzyme, ubiquitin specific protease 30 (USP30) blocks mitochondrial degradation. In Parkinson s disease, USP30 is increased in dopamine neurons, therefore, blocking USP30 may be neuroprotective by allowing damaged / dysfunctional mitochondria to be degraded. We hypothesize that using targeted genetic technology to block USP30 will allow damaged mitochondria to be removed, and the overall pool of healthy mitochondria to increase. This will enhance dopamine neuron bioenergetics, reduce oxidative stress and promote neuronal survival.

11. Project Title: **BIOBEHAVIORAL STUDIES OF CARDIOVASCULAR DISEASE**
   Leader(s):   **GIANAROS, PETER J**
   THE UNIVERSITY OF PITTSBURGH
   NIH P01HL040962 / (1997 - 2023)
   Core(s):   - Integrative Systems Core (ISC)

ABSTRACTBiobehavioral Studies of Cardiovascular Disease (PO1-HL040962)This Program Project (P01) continuation application focuses on the human brain substrates of behavioral andsocio-environmental influences on cardiovascular disease (CVD) risk in midlife adults. Proposed are 3 Projectsthat are conceptually cross-linked and supported by 3 Core Units. Collaborative investigators representmultiple disciplines, including psychology, neuroscience, biophysics, medicine, psychoneuroimmunology,epidemiology, machine learning, bioinformatics, and statistics. Project 1 aims to elucidate functional andstructural brain phenotypes that predict the multiyear progression of preclinical vascular disease anddysfunction, with a focus on neural circuitries for visceral control that coordinate autonomic, neuroendocrine,hemodynamic, and immune physiology with stress- and emotion-related behavioral processes. Project 2 aimsto establish whether functional characteristics of these visceral control circuits moderate the influences ofstress-related environmental exposures on the progression of preclinical vascular disease and dysfunction,tracking individuals' behavior and cardiovascular physiology in daily life to test a novel neuro-diathesis modelof CVD risk. Project 2 also tests for the first time whether daily life physical activity associates with daily lifestress physiology through its effects neural circuits for visceral control. Project 3 aims extend those of the otherProjects by elucidating the neural and peripheral processes linking physical activity with physiological andpsychophysiological markers of CVD risk (including daily life affect and stress physiology) using anexperimental intervention methodology. These P01 aims are unique in cardiovascular behavioral medicine, andthey will be pursued in the context of multi-component data collection efforts that satisfy all project-specificaims. As a result, the P01 will create new opportunities for integrative and translational science on the humanneurobiology of CVD risk that cuts across multiple methods and levels of analysis. Helping to advance itsparent field, the P01 will generate and disseminate original and expansive public-domain resources and tools tothe broader scientific and clinical communities through comprehensive data and software sharing andeducational objectives. Enabling a precise focus on early CVD etiology, the study cohorts comprise nearly 900midlife adults without clinically apparent CVD, and study methods will include novel combinations ofneuroimaging, ecological momentary assessments of experienced environments, ambulatory hemodynamicmonitoring, autonomic, neuroendocrine, immune, and vascular assessments, laboratory clinical evaluations,hetero-method health behavior assessments, and arterial imaging. The 3 Core Units of this P01 provide forsynergy and inter-project coordination by administrative, data management and participant accrual services;measurement and instrumentation support; and direction in cutting-edge bio-statistical and data-intensive(machine learning) analyses. The present application thus represents a thematic continuation and next-generation extension of translational neurobiological research on CVD by this P01, which was initiated in 1988.

12. Project Title: **RHYTHM EXPERIENCE AND AFRICANA CULTURE TRIAL (REACT)**

Leader(s): **ERICKSON, KIRK I**
THE UNIVERSITY OF PITTSBURGH
NIH R01AG060741 / (2018 - 2023)

Core(s): - Integrative Systems Core (ISC)

Abstract African Americans are almost two times more likely than whites (i.e., Caucasians) to experience Alzheimer'sdisease or other dementias. For those over the age of 65, the prevalence of cognitive impairment is 8.8% in whitesand 23.9% in African Americans. Even in the age range of 55-64, African Americans are 4 times more likely toexperience cognitive impairment than their age-matched white counterparts. Increased risk of dementia amongAfrican Americans may be attributed to lower levels and quality of education, lower socioeconomic status (SES),and higher prevalence of vascular diseases, Type II diabetes, hypertension, and obesity, all of which arerecognized as risk factors for dementia. A critical public health question emerges from these statistics that weintend to address in this proposal: Is there an effective method for reducing or eliminating the race disparitiesin cognitive and brain health Fortunately, physical activity (PA) interventions may be effective at improvingneurocognitive function and reducing risk for dementia. Despite these promising results, prior PA interventionshave had few African Americans making it difficult to stratify results by race to determine whether AfricanAmericans respond to PA in a similar manner and magnitude as whites. In addition, the terms `physical activity'and `exercise' are often considered unpleasant, painful, and fatiguing, which can negatively influence interest,enrollment, and long-term adherence. Methods that increase PA without using the term PA (e.g., dancing) couldbe effective at improving health outcomes while simultaneously having a wider impact on translation and long-term adherence. Here we propose an innovative and culturally sensitive method of increasing PA in older (60-80 yrs) African Americans. We propose a randomized intervention where 180 older African Americans areassigned to either a moderate intensity African Dance group 3 days per week (N=90) or to an AfricanEducation group 3 days per week (N=90) for 6-months. Both before and at the completion of the intervention,we will collect a comprehensive neuropsychological battery and MRI metrics of brain health and function toidentify biological pathways by which PA influences neurocognitive health in an African American population.This proposal has the potential to utilize community-based activities to improve health of older AfricanAmericans. In addition, it could establish a platform (i.e., dance) to implement future interventions targetingminority populations to reduce health disparities. We have three primary aims: Aim 1. Examine whether a 6-month African Dance intervention improves cognitive performance compared to an educational control group.Aim 2. Examine whether African Dance influences brain morphology, task-evoked neural responses, cerebralblood flow, and resting state connectivity. Aim 3. Explore potential physiological and socioemotionalmechanisms of the dance intervention. We will collect measures of physical and psychosocial health such as waistcircumference, blood pressure, blood glucose and lipid levels, mood, anxiety, depression, and loneliness andexamine whether intervention-related changes to these measures mediate improvements in cognitiveperformance.

13. Project Title: **ROLE OF EXTRACELLULAR MATRIX IN AGE-RELATED DECLINES OF MUSCLE REGENERATION**

Leader(s): **AMBROSIO, FABRISIA; LEDUC, PHILIP R ;**
THE UNIVERSITY OF PITTSBURGH
NIH R01AG061005 / (2019 - 2024)

Core(s): - Biology of Mobility and Aging Core (BMAC)

ABSTRACT Skeletal muscle trauma resulting from an injury or surgery often results in significant functional declinesin older adults. These declines are at least partially attributed to failed muscle healing. Muscle regeneration ispredominantly dictated by the action of muscle stem, or satellite , cells (MuSCs), a reserve cell population thattypically demonstrates considerable dysfunction with increasing age. According to the stem cell niche concept, stem cell responses are largely determined by biophysical and biochemical cues that emanate fromthe surrounding microenvironment. Indeed, expanding recognition of the influence of the microenvironment onstem cell behavior has led to a recent surge in the development of bioinspired and engineered extracellularmatrix (ECM) approaches for the treatment of skeletal muscle injuries. Still lacking, however, is an in-depthknowledge of whether and how pathogenic instructional characteristics of the native ECM disrupt MuSCfunction and skeletal muscle regeneration. While it is evident that MuSC activation, self-renewal, proliferationand differentiation are influenced by physical and dynamic niche interactions, a mechanistic understanding

ofthe direct impact of age-related ECM alterations on skeletal muscle regenerative capacity is unknown. The over-arching goal of this project is to test our central hypothesis that age-related biophysicalalterations in the skeletal muscle ECM promotes a fibrogenic conversion in MuSCs, ultimately drivingimpaired skeletal muscle regeneration. Further, we hypothesize that these pathogenic biophysicalchanges may be reverted, at least partially, by mechanical stimulation. To achieve this goal, we willemploy an integrated approach that encompasses cutting-edge super-resolution imaging and 3-D tissueengineering methods to address two specific aims. Aim 1 studies will measure, manipulate, and mimic thebiophysical properties of young and aged skeletal muscle ECM in order to dissect the effect of age-relatedarchitectural and elastic ECM modifications on MuSC fate. Aim 2 studies will identify mechanisms by whichmechanical stimulation modulates biophysical properties of the aged ECM to promote MuSC myogenicity andmuscle regeneration. Successful achievement of these aims will further our understanding of 1) theinstructional capabilities of the native ECM on MuSC lineage specification, 2) how these instructionalcapabilities change over time, and 3) the molecular mechanisms controlling age-related declines in skeletalmuscle regenerative potential. Taken together, successful completion of these studies may provide afoundation for the identification of novel ECM targets in the treatment of skeletal muscle injuries for a geriatricpopulation. More broadly, an improved insight into how age-associated alterations in biomechanical,architectural and dynamic ECM properties direct MuSC function will expand our fundamental understanding ofaging and stem cell biology.

14. Project Title: Comprehensive functional genomic analysis of the multi-disease associated CDKN2A/B locus

Leader(s):   LI, GANG ; FINKEL, TOREN ;

UNIVERSITY OF PITTSBURGH AT PITTSBURGH

NIH R01AG065229 / (2021 - 2026)

Core(s):

ABSTRACT The incidence of cardiovascular disease (CVD), Type 2 diabetes (T2D) and cancers all dramatically increase as a function of age. The underlying mechanisms of these diseases, which vary, are incompletely understood. Genome-wide association studies (GWAS) have identified many SNPs that are associated with these conditions. One of the strongest associations comes from the CDKN2A/B locus on chromosome 9p21.3 which has been associated with multiple age-related diseases, as well as overall human lifespan. Within this 200 kb locus, there are three encoded proteins, p16INK4a, p14ARF and p15INK4b, and one antisense non-coding RNA, the inhibitor of CDK4 (INK4) locus (AS/ANRIL). To date, it has not been firmly established which, if any, of these genes are the risk genes for the associated diseases. There are ~193 disease-associated, noncoding SNPs in linkage disequilibrium (LDs) across this 200 kb region, represented by 18 lead SNPs used for GWAS analysis. While the mechanisms underlying the contribution of these SNPs to specific diseases are not fully understood, a single genetic region associated with multiple different age-related diseases suggests that this locus may modulate these conditions by promoting aging itself, perhaps via induction of cellular senescence as a common mechanism. In this application, we propose to apply an experimental approach using high throughput techniques we have recently developed including Reel-seq and FREP/SDCP-MS, to systematically dissect this locus. We will first identify the disease-associated functional SNPs (fSNPs), as well as the regulatory elements across the 58 kb core region primarily associated with cardiovascular diseases using Reel-seq. Next, we will identify the regulatory proteins that specifically bind to all the fSNPs, as well as the regulatory elements, using FREP/SDCP- MS. A range of relevant cell types related to atherosclerosis will be used to generate the nuclear extract required for our screens. We will demonstrate the role of these regulatory proteins by confirming their direct effects on p16INK4a, p14ARF, p15INK4b and AS/ANRIL expression, and subsequently on cell cycle regulation and cellular senescence. A range of complementary techniques such as RNAi, CRISPR/cas9 gene editing, will be employed. Such analysis will provide the first in-depth understanding of this critical genomic region, as well as a unique strategy to uncover unifying biochemical pathways that simultaneously regulate atherosclerosis, as well as potentially multiple other age-related diseases.

15. Project Title: INVESTIGATION OF BRAIN MECHANISMS INVOLVED IN THE URINARY CONTINENCE MECHANISM ASSOCIATED WITH AGING

Leader(s):   RESNICK, NEIL M.

THE UNIVERSITY OF PITTSBURGH

NIH R01AG065288 / (2020 - 2025)

Core(s):   - Clinical and Population Outcomes Core (CPOC)
                      - Data Management, Analysis and Informatics Core (DMAIC)
                      - Integrative Systems Core (ISC)

PROJECT SUMMARY Prevalent, morbid, and costly ($66 billion/year in 2007), incontinence is a major problem, especially for older adults, in whom the most common type is urgency incontinence (UUI). Generally ascribed to bladder spasms, UUI's actual causes are unknown, and therapy remains inadequate. Recent data suggest that one cause is poor bladder control by the brain. In our recent R01 we used biofeedback (BFB) as a probe to explore this. The exciting findings suggest that one `phenotype' of UUI in older adults seems to be caused by a breakdown in brain control, which can be restored by successful behavioral therapy, while another is refractory. Our proposed new study will explore this further by attempting to differentiate the mechanisms associated with disease and aging. The goal is to identify which brain mechanisms should be suppressed because they are contributing to or causing UUI, which should be enhanced because they are helping to compensate for UUI, and which should be ignored because they are incidental to aging and not related to UUI. Current data suggest that bladder control comprises 3 cerebral circuits that maintain continence by suppressing the voiding reflex in the midbrain. In our UUI phenotype that responded to BFB, the mechanism involved enhancing deactivation of the first brain circuit (medial prefrontal cortex, mPFC) which resulted in less activation of the second circuit (which includes the midcingulate cortex). In the phenotype that was resistant to BFB, no brain changes were seen. Yet, although we have an emerging picture of the brain's role in UUI, we have only rudimentary understanding of what is `normal', i.e. how the brain normally controls the bladder. More relevant, we do not know whether this control mechanism is the same across the lifespan, or if it changes owing to the impact of aging. Thus, our overall aim is to characterize continence control in both young and old people, and examine how changes due to bladder control failure differ in each age group. Our specific aims are to characterize normal voiding in the continent old and young in order to better understand and verify the working model and to use the comparison to older adults with UUI to understand the mechanism of brain failure in these individuals. To address these aims, we will conduct a detailed clinical and neuroimaging study to study 80 asymptomatic women and 80 UUI women, each group divided equally into young (18-45) and old (65+ years). The study will enable us to evaluate the changes in brain structure and function and to identify brain mechanisms involved in continence control, changes due to aging (both benign and contributory to UUI), and changes due to disease. The study will provide the comprehensive data on brain mechanisms involved in the normal continence mechanism in order to better corroborate our working model, understand the aging process, and assess targets for therapy. It will thereby enable scientists to develop novel and more effective new therapies based on the revolution in neuroscience and more hope for UUI sufferers.

16. Project Title: INNOVATIVE APPROACH TO GERIATRIC OSTEOPOROSIS
Leader(s):   **GREENSPAN, SUSAN L**
                        THE UNIVERSITY OF PITTSBURGH
                        NIH R01AG066825 / (2020 - 2025)

Core(s):   - Clinical and Population Outcomes Core (CPOC)
                        - Data Management, Analysis and Informatics Core (DMAIC)

Although close to 85% of residents in long-term care facilities (LTC) have osteoporosis and the risk of osteoporotic fractures is nearly 10 times that of community dwelling elderly, few are treated and studies are scarce. The large pivotal osteoporosis trials in postmenopausal women exclude those who are sedentary, frail or functionally impaired even though this is the group at highest fracture risk. Before a fracture reduction study can be justified in this cohort, an investigation demonstrating efficacy and predictability is a necessary first step. We have previously demonstrated that zoledronic acid (ZOL) can maintain bone mineral density (BMD) and is safe in frail elderly. However a dual action anabolic antiresorptive agent has a distinct advantage to build bone rapidly. The newly approved once monthly dual action romosozumab (ROMO), provides significant improvements in BMD and fracture reduction in 1 year. If ROMO were given prior to a potent antiresorptive medication such as ZOL, this combination (rapid boost over a year with ROMO and maintain integrity 2nd year with ZOL) could provide a novel treatment paradigm in this high risk population. The concern for ROMO is the potential increase risk of cardiovascular events demonstrated in one pivotal study. Before a large fracture reduction trial can be justified in this frail population, a study demonstrating BMD efficacy and safety is imperative. We will test the hypotheses that in frail institutionalized women, one year of ROMO prior to one year of ZOL will 1) be more efficacious compared to one year of calcium plus vitamin D prior to a year of ZOL as demonstrated by improvements in conventional bone density measurements, 2) improve novel measures of bone trabecular microstructure and bone turnover markers, and 3) provide characteristics associated with responders and non-responders. To address these hypotheses, we propose to conduct a 2-year, randomized, double-blind controlled trial to test the efficacy and safety of ROMO (year 1) and ZOL (year 2) compared to calcium+vitamin D (year 1) and ZOL(year 2), in 200 institutionalized frail women age 65+ in LTC.

Safety will be carefully monitored. Serious adverse events (SAE's) will be obtained by a novel electronic alert system that provides real time notifications including ROMO associated cardiovascular SAE's. This study includes innovative features: 1) focus on the neglected LTC population of frail residents in whom we have a track record of successful enrollment, 2) inclusion of a newly approved potent dual action agent feasible in LTC, 3) assessments of bone structure, 4) point of care vertebral fracture images, 5) mobile lab allowing onsite participation, and 6) electronic alerts for real time adverse events. Despite the call by national consensus groups for the past 2 decades to address osteoporosis in frail elderly, trials and treatments are sparse. This study will challenge the current paradigm of avoiding anti-osteoporosis therapy and provide an innovative approach for geriatric osteoporosis, and help target robust responders.

17. Project Title: **ROLE OF LIFESPAN INTERVENTION ON THE REGULATION AND PROGRESSION OF ALZHEIMER'S DISEASE**

Leader(s): **RIZZO, STACEY J**
THE UNIVERSITY OF PITTSBURGH
NIH R01AG067289 / (2020 - 2025)

Core(s): - Biology of Mobility and Aging Core (BMAC)

Project Summary/Abstract Our long-term goal is to identify therapeutic agents that can prevent the pathogenesis of Alzheimer s disease (AD). The number of AD cases is rising dramatically worldwide, and there is an urgent need to develop new therapies that are more efficacious than the four currently approved drugs for AD which provide only modest symptomatic relief. Every clinical trial to date has failed to demonstrate disease-modifying efficacy for AD, which may in part be due to our limited understanding of the mechanisms that precede the pathogenesis of AD, and that are distinct from normal healthy aging. The overall aims of our proposal are to further understand the mechanisms underlying dysregulation of the autophagy-inflammation network that becomes progressively dysregulated with age, and accelerated by pathological conditions. Systemic inflammation is a biomarker of this dysregulation, as exemplified by its prevalence in many aging-related disorders including cardiovascular disease, diabetes, cancers, and neuroinflammation in neurodegenerative disorders such Alzheimer s disease (AD). We hypothesize that mechanisms which drive systemic inflammation are common to both the biology of aging and AD and propose that interventions which target the shared feature of systemic inflammation, via regulation of the autophagy-inflammation network, may have potential as therapeutic agents for the prevention of conversion to disease pathogenesis in AD, as well as improve healthspan and longevity in aging populations. For this proposal we will use a combination of genetic and pharmacological tools to understand which brain specific cell types may be involved in the regulation of the autophagy-inflammation network via both mTOR dependent and mTOR-independent mechanisms that modulate inflammation. Findings from our studies will provide mechanistic insights at a cellular level and innovative therapeutic strategies for further research. Specifically, we will investigate the individual cell types that contribute to the neuroprotective effects of mTOR inhibition in progressive AD, and confirm and extend the data on the beneficial effects of lifespan and healthspan in sporadic AD with prophylactic treatment of rapamycin. Critically, since age and genetics are the leading risk factors for AD, we will evaluate interventions in preclinical model systems that incorporate both aging and genetic risk factors for AD. We will therefore test the role of direct manipulation of AMPK on modulation of lifespan and healthspan in normal aging and in AD susceptible models, and the beneficial role of MAG lipase inhibition in normal healthy aging and in the pathogenesis of AD in comparison to the effects of rapamycin in a mouse model of late onset AD.

18. Project Title: **Supplement to Effectiveness of the On the Move group exercise program to improve mobility in community-dwelling older adults**

Leader(s): **BRACH, JENNIFER S**
UNIVERSITY OF PITTSBURGH AT PITTSBURGH
NIH R01AG071520 / (2021 - 2026)

Core(s):

Effectiveness of the On the Move group exercise program to improve mobility in community-dwelling older adults Gardenia Juarez, a first-generation Hispanic/Latina woman, is a promising rehabilitation science graduate student who is interested in pursuing a career in aging and implementation science research. Supplemental activities will focus on Ms. Juarez s research and career development. These activities will occur under the mentorship of Jennifer Brach, PhD, PT, FAPTA, a successful aging and rehabilitation science research mentor and Principal Investigator of the parent study. The research and career development aims are strongly linked with the activities in the parent grant and supported by the infrastructure and resources of Dr. Brach s research laboratory and her ongoing work with the On the Move (OTM) evidence-based exercise program. The aims of Ms. Juarez s supplemental research project are to 1) identify organizational contextual determinants (barriers and facilitators) to the adoption of OTM and 2) examine the associations of organizational contextual determinants to the acceptability, appropriateness, and feasibility of implementing OTM. Ms. Juarez will obtain robust experience by being a part of a multi-disciplinary research team conducting a large cluster-randomized trial. She will interact with all study investigators (Drs. Beach, Freburger and Weiner) and participate in all research team meetings. Specifically, she will participate in the identification of measures of organizational contextual determinants, recruit and enroll organizations into the study, assist in the interviews and focus groups (including non-adopter organizations), participate in the coding and analyses of qualitative data, and interpretation of the findings. This project will serve as Ms. Juarez s doctoral dissertation with Dr. Brach as the chair of her doctoral committee. She will work with Dr. Brach and her dissertation committee to disseminate her findings at an appropriate scientific meeting and through peer-reviewed publications. Ms. Juarez s career development plan allows her to acquire advanced knowledge in the areas of aging, health promotion, and implementation science and the necessary skills for a career conducting community-based research. Career development goals to be accomplished through Ms. Juarez s graduate training and supported by this supplement include: 1) develop knowledge of aging and health promotion; 2) develop knowledge of implementation science principles; 3) acquire skills in designing and conducting clinical trials; 4) acquire skills in qualitative methodologies; and 5) develop leadership and professional skills important for academia. We anticipate that at the end of this career development plan, Ms. Juarez will have the necessary knowledge and skills to pursue the next phase of scientific training, a post-doctoral fellowship in implementation science or a career as a junior faculty member.

19. Project Title:　　Preeclampsia and the Brain: Small vessel disease and cognitive function in early midlife

Leader(s):　　**CATOV, JANET M; ROSANO, CATERINA ;**
　　　　　　　　　MAGEE-WOMEN'S RES INST AND FOUNDATION
　　　　　　　　　NIH R01AG072646 / (2022 - 2026)

Core(s):

Cerebral small vessel disease (cSVD) predisposes to vascular cognitive impairment and dementia, including Alzheimer s Disease. Preeclampsia (PE), a pregnancy-specific disorder with acute hypertension and placental SVD, is emerging as a sex-specific risk factor for dementia later in life. How PE is implicated in the etiology of dementia is not known. Women with PE have SVD also in other vascular beds, including the brain, after pregnancy and worsening with older age, suggesting this process evolves over time. However, studies on SVD in midlife are sparse. Midlife is an ideal time to assess this risk as PE-differences in cognition are already detectable, and yet there is time to mitigate progression to dementia. Cerebral SVD (cSVD) in midlife may hold the key to understand how PE is implicated in cognitive impairment. Placental SVD, known as maternal vascular malperfusion (MVM) predicts worse short-term pregnancy outcomes. We find MVM and PE combined predict long-term worse maternal vascular health in cardiac, sublingual, and cerebral beds. In our pilot study (n=24) MVM and PE combined predicted lower cerebrovascular reactivity (CVR, an early stage of cSVD), especially in fronto-parietal areas; in turn, lower CVR in these regions was associated with, and appeared to explain, PE-related worse cognition. Importantly, these findings were independent of hypertension, suggesting PE has direct and lasting vascular effects . PE and MVM may be early indicators of a future cerebrovascular phenotype, manifesting in midlife as lower CVR, and may explain how PE affects cognition. We propose to study midlife women with and without prior PE to: 1) Characterize the neural basis of PE-related poorer cognitive performance, 2) Assess whether placental SVD (MVM) predicts cSVD and cognition, and 3) Explore whether sublingual SVD and circulating markers of SVD are markers of cSVD and cognition. We propose a neurocognitive study to capture early stages of cSVD and cognitive status in a racially diverse cohort of 450 women (1:1 PE and non PE) from our ongoing WINDOWS study, mean age=45, 15 years post- pregnancy, 30% black, with existing data on PE, MVM, and sublingual SVD 10 years after pregnancy. We will use our advanced multimodal neuroimaging protocols to quantify cSVD (including CVR, blood flow, connectivity), standardized validated protocols to measure cognition, and non-invasive markers of SVD (sublingual SVD, and circulating biomarker profiles) . Our project is uniquely positioned to identify a previously occult high-risk group that can be identified at delivery by placental pathology, and who may benefit from risk- stratification for dementia, to mitigate or delay disease progression.

20. Project Title: **Longitudinal Examination of Neighborhood Disadvantage, Cognitive Aging, and Alzheimer's Disease Risk in Disinvested, African American Neighborhoods**

Leader(s): **DUBOWITZ, TAMARA ; ROSSO, ANDREA L; TROXEL, WENDY M; RAND CORPORATION**
NIH R01AG072652 / (2022 - 2027)

Core(s):

Project Summary African Americans (AAs) have disproportionately higher rates and earlier onset of Alzheimer s disease and related dementias (ADRD) relative to White Americans. Although prior research has made significant contributions to our understanding of racial disparities in ADRD, we still lack a comprehensive understanding of how the individual lived experience of being AA, including cumulative exposure to structural racism, contributes to elevated ADRD risk and the potential mechanisms underlying those risks. Building on the existing, community-based research infrastructure developed by our team s previously funded studies, we will follow a cohort of residents (n=1133) living in two historically disinvested, predominantly AA communities to understand how dynamic neighborhood socioeconomic conditions across the lifecourse contribute to cognitive outcomes in mid- and late-life adults. This proposal rests on the premise that neighborhood segregation and subsequent disinvestment contributes to poor cognitive outcomes for AAs via factors including a) lower access to educational opportunities and b) higher exposure to race- and socioeconomically-relevant stressors, including discrimination, trauma, and adverse childhood events. In turn, these cumulative exposures foster psychological vigilance in residents, leading to cardiometabolic dysregulation and sleep disruption, which may mediate associations between neighborhood disadvantage and ADRD risk. We also will examine potential protective factors that may promote cognitive health, including neighborhood social cohesion, safety, and satisfaction. The proposed study will leverage our existing longitudinal data on risk and protective factors, biobehavioral mediators, and baseline cognitive assessments, and will include: 1) three waves of cognitive assessments in the full cohort of participants who are 50 years+ (participants who are aged 35-49 years will have two assessments) and clinical adjudication of ADRD in participants who are 50+ (n=906), 2) additional assessments of blood pressure and objective sleep, 3) a comprehensive assessment of life and residential history using the questionnaire from the Health and Retirement Study (HRS); and 4) in-depth qualitative interviews to reveal lifecourse opportunities and barriers experienced by AAs in achieving optimal cognitive health in late life. Understanding how structural racism has influenced the lived experience of AAs including dynamic changes in neighborhood conditions over time is critical to inform multi-level intervention and policy efforts to reduce pervasive racial and socioeconomic disparities in ADRD.

21. Project Title: **Sleep and Bladder Study**

Leader(s): **TYAGI, SHACHI**
UNIVERSITY OF PITTSBURGH AT PITTSBURGH
NIH R01AG076575 / (2022 - 2026)

Core(s):

PROJECT SUMMARY Prevalent, morbid, and costly (=$83 billion/year), urgency urinary incontinence (UUI) is a major problem, especially for older women. With etiology usually ascribed to bladder spasms, the available therapies are bladder-targeted and provide only a modest benefit. Despite inadequate response and poor adherence, there has been little change in therapeutic approach to UUI in decades, and a novel holistic approach to complement or enhance current treatment will have a significant impact on care of those with the debilitating symptoms. UUI has strong bidirectional relationship with poor sleep, a prevalent complaint in older adults. Up to 50% of older adults report poor sleep, which increases the risk of UUI by up to 55% over 5 years. The brain plays a vital role in the continence mechanism and sleep is known to affect the pathways involved in executive continence control. Specifically, sleep loss is associated with hypoactivity in the medial prefrontal cortex (mPFC) a region we have identified to be involved in executive control of voiding, and potential therapeutic response to biofeedback-assisted pelvic floor muscle therapy. Hence, we hypothesize that poor sleep inhibits bladder control as it does with cognitive tasks; and addressing sleep will improve executive control of the bladder complementing concurrent bladder-targeted UUI therapy. Our overall goals are to: (a) assess the additional benefit of behavioral sleep intervention on UUI to the standard of care (3- adrenoceptor agonist mirabegron) providing evidence for assessing and addressing sleep for treatment of UUI, and (b) better understand the brain s role in the effect of sleep on UU providing rationale to investigate other ameliorative brain-based therapies targeting the identified brain

pathways. Specific aims are to examine the effect of adjunctive Brief Behavioral Treatment of Insomnia (BBTI) with the first-line pharmacotherapy: mirabegron on (1) UUI; (2) nocturia; (3) mPFC activity to confirm therapeutic mechanisms by assessing the effect of sleep on currently understood mediators; and (4) durability of therapeutic response. We will randomize 100 women aged = 60 years to receive 8 weeks of either mirabegron alone or mirabegron+BBTI, assessing bladder symptoms, sleep, and functional and structural brain changes pre- and post-intervention. We will also explore the durability of therapeutic response at 6-months post-intervention. The study will provide the first-ever data on a comprehensive multicomponent brain-bladder therapy for incontinence targeting the known brain mechanisms involve in continence control. It will evaluate clinical response and durability of this novel pairing and provide an understanding of the underlying pathways involved in its therapeutic mechanism.

22. Project Title: **Preserving Geriatric Muscle with an Osteoporosis Medication**
Leader(s):   **GREENSPAN, SUSAN L**
                        UNIVERSITY OF PITTSBURGH AT PITTSBURGH
                        NIH R01AG081359 / (2023 - 2028)
Core(s):

Approximately one third of older adults in senior communities fall each year, and falls are the leading cause of morbidity and mortality in this age group. Falls are associated with poor quality of life, disability, and death; the medical cost is over $30 billion annually. Despite these statistics, fall reduction strategies have had limited impact for frail seniors. The most devastating fall-related outcome is a hip or other fracture. Over 90% of hip and nonvertebral fractures occur from a fall, and approximately 85% of long-term care (LTC) residents have osteoporosis. Recently, investigators have reported cross-talk between muscle and bone through mechanical and biochemical pathways. Osteosarcopenia, a newly described geriatric syndrome, involves the coexistence of osteoporosis (low bone mass) and sarcopenia (low muscle mass/function). The coexistence of these conditions puts patients at even greater risk for fall/fracture-related serious adverse outcomes. Denosumab (DEMAB), a medication approved for osteoporosis, acts on molecular targets shared between muscle and bone. In the DEMAB pivotal trial and a meta-analysis in healthy adults, investigators reported a reduction in recalled falls in addition to a decrease in fractures. Therefore, DEMAB has the potential to reduce both falls and fractures in a vulnerable population at high risk for both events. Our goal is to demonstrate efficacy of the novel agent DEMAB to improve or preserve muscle health, strength, mobility and function in frail older adults. If successful, this would lay the groundwork for a larger multicenter trial to examine the dual-action for fall and fracture prevention. To bridge this knowledge gap we propose to conduct a 1-year, randomized, double-blind, active-controlled trial to test the efficacy of DEMAB (expected active muscle agent) versus zoledronic acid (ZOL, muscle control) in 248 underserved, LTC, frail institutionalized men and women (age=65) with osteoporosis. Muscle strength, power, quality, markers, function and bone measures will be collected in a mobile lab. At trial completion, all participants receive ZOL for osteoporosis therapy and to prevent potential bone loss following DEMAB discontinuation. Our objectives include Aim 1: Evaluate efficacy of DEMAB to preserve/improve muscle strength, power, mass and structure. Aim 2: Examine the mechanistic biochemical components of the muscle-bone connection. Aim 3: Explore if the DEMAB effect extends to distal functional outcomes. This study includes a number of innovative features: 1) focus on the neglected LTC population of frail older men and women in whom we have a track record of successful enrollment, 2) inclusion of an approved osteoporosis agent feasible in the LTC setting with a novel focus on muscle strength, power, structure, and function, 3) mobile lab allowing onsite participation, 4) assessment of muscle and bone parameters by portable techniques, and 5) electronic alerts for falls and SAEs. This study will challenge the current paradigm of avoiding anti-fracture/fall therapy in vulnerable fallers and establish the necessary conditions to justify a large trial to maintain muscle and bone health to reduce falls and fractures.

23. Project Title: **THE ASPIROMETER: A NONINVASIVE TOOL TO DETECT SWALLOWING SAFETY AND EFFICIENCY**
Leader(s):   **SEJDIC, ERVIN; COYLE, JAMES ;**
                        THE UNIVERSITY OF PITTSBURGH
                        NIH R01HD074819 / (2013 - 2023)
Core(s):   - Clinical and Population Outcomes Core (CPOC)
                        - Data Management, Analysis and Informatics Core (DMAIC)

ABSTRACTImpaired swallowing (oropharyngeal dysphagia or OPD) causes nearly 150,000 annual hospitalizations andover 220,000 additional hospital days, and prolongs hospital lengths of stay by 40%. OPD risk is typicallyidentified through subjective standard institutional screening (SIS) protocols and those identified throughscreening undergo gold standard imaging testing such as videofluoroscopy (VF). However, SIS methods over-or underestimate risk, and completely fail to identify patients with silent OPD who silently aspirate food intotheir lungs, raising their risk of pneumonia and other adverse events. Pre-emptive detection of silent or near-silent aspiration is essential. Our long-term goal is to develop an instrumental dysphagia screening approachbased on high-resolution cervical auscultation (HRCA) to accurately predict OPD-related adverse events, andinitiate more timely intervention measures to mitigate them. The overall objective here is to develop accurate,advanced data analysis approaches to translate HRCA signals to swallowing events observed in VF images.Our strong preliminary data has led us to our central hypothesis: HRCA coupled with advanced data analyticstools are powerful approaches to automate and improve existing dysphagia screening protocols. The rationaleis that a reliable, robust early-warning instrumental OPD screening approach will reduce adverse events inpatients with silent aspiration/dysphagia, shorten length of stay, reduce cost, and improve patient health.Guided by strong preliminary data, we will pursue the following three specific aims: (1) define HRCA signalsignatures that characterize the entire continuum swallowing safety from unimpaired to severely impaired; (2)translate HRCA swallow signal signatures and equate them to validated measures of swallowing impairment;and (3) prospectively assess the effectiveness of our HRCA system in predicting clinically significant OPD andaspiration in a randomized, controlled trial. Under the first aim, we will collect HRCA swallow signatures fromunimpaired people, and combine and analyze them along with our large database of swallows of people withOPD to characterize the entire range of swallowing function from unimpaired through severe OPD. Under thesecond aim, we will develop HRCA OPD severity cutoffs and match them to gold standard derived OPDimpairment cutoffs to establish HRCA s ability as a diagnostic surrogate that differentiates clinically significantOPD and aspiration from benign swallowing impairments. Under the third aim, we will test HRCA in a clinicalsetting by deploying HRCA with consenting patients, and comparing the accuracy of independent HRCA,independent SIS, and HRCA+SIS to VF data from all participants. The approach is innovative, as it willcombine technology with clinical judgment to shift the OPD screening paradigm and fundamentally improveefforts to reduce morbidity and mortality caused by OPD. Our work is significant, because it will translate to anearly-warning HRCA screening tool that will elevate the current standard of patient care by ensuring thatpatients with OPD are correctly identified before adverse events can occur.

24. Project Title: **THE ROLE OF CALCIUM ENTRY THROUGH THE MITOCHONDRIAL UNIPORTER IN REGULATING CARDIAC METABOLISM AND PHYSIOLOGY**

Leader(s): **FINKEL, TOREN**
THE UNIVERSITY OF PITTSBURGH
NIH R01HL142589 / (2019 - 2023)

Core(s): - Biology of Mobility and Aging Core (BMAC)

The entry of calcium into the mitochondria is fundamentally important in regulating bioenergeticcapacity and modulating cell death thresholds. For nearly fifty years, mitochondria were knownto have a selective calcium-selective pore in the inner mitochondrial membrane. Entry ofcalcium through this pore, often termed the calcium uniporter, was believed to be essential inboosting ATP production by augmenting the activity of multiple calcium-sensitive mitochondrialmatrix enzymes. This increase in mitochondrial calcium therefore allowed for a rapid butregulated increase in mitochondrial ATP under conditions of increased energetic demand. Whileunder these conditions, the entry of calcium appears beneficial, additional evidence suggestedthat excessive calcium entry triggers a mitochondrial cell death program characterized byopening of the mitochondrial permeability transition pore (mPTP). Such situations appear to beparticularly relevant to tissue injury occurring in the setting of ischemia-reperfusion injury. Whileconsiderable electrophysiological, biophysical and physiological data existed on themitochondrial inner membrane calcium pore, its molecular identity remained elusive for over fiftyyears. That situation has demonstrably changed in the last five years with the rapididentification of the components of the inner mitochondrial calcium uniporter complex (MCUC)now known to be composed of at least four proteins. These components include the pore-forming protein MCU, its apparent membrane scaffold EMRE and two calcium-sensitiveregulators MICU1 and MICU2. The molecular identity of the MCUC paved the way for thecreation of mouse models in which one or more component of the complex has been deleted.This, in turn, allows for a more detailed and precise analysis of the physiological role ofmitochondrial calcium in regulating both bioenergetics and cell death. Here, we propose toanalyze the role of the MCUC in basal and stress-induced cardiovascular physiology. Ourparticular emphasis will be on the role of the MCUC in ischemia/reperfusion injury, metabolismand aging. This analysis, we believe, will increase our fundamental understanding of bothmitochondrial biology and cardiac physiology and potentially pave the way for new treatmentstrategies targeting a diverse array of conditions ranging from reperfusion injury to the

age-dependent decline in cardiac function.

25. Project Title: Mapping the cell specific DNA damage-induced molecular and bioelectrical responses in the 3D cardiac unit

Leader(s):   **COHEN-KARNI, TZAHI ; GURKAR, ADITI U;**
CARNEGIE-MELLON UNIVERSITY
NIH R01HL161106 / (2021 - 2026)

Core(s):

PROJECT SUMMARY This project will test the hypothesis that DNA damage in cardiomyocytes activates p53 leading to mitochondrial alterations and secretion of paracrine factors that drive heart failure. The premise for this has been established from our preliminary data and from the work of others. First, DNA damage and activated DNA damage response (DDR) have been observed in cardiovascular disease (CVD) in humans. Second, studies also show evidence that multiple cell types in the cardiac unit, including cardiomyocytes (CM) and cardiac fibroblasts (CF) display markers of DNA damage and cellular senescence in several disease pathologies. Third, we have recently identified that nuclear DNA damage drives dilated cardiomyopathy. Specifically, cardiomyocyte-depletion of the DNA repair endonuclease, ERCC1-XPF in mice, upregulates the DNA damage response gene, p53, and leads to irregular mitochondrial cristae, accumulation of lipids and increased oxidative stress. Additionally, there is an increase in several cardiac failure and senescence associated markers. However, the exact molecular underpinnings and cell-specificity of these DNA damage-induced changes is poorly understood. One barrier to addressing this question in vivo has been lack of appropriate tools, where DNA damage can be introduced in only one cell type (e.g., CM) and its effect on CF and cardiac function can be investigated. Additionally, 2D cell culture and co-culture systems fall short, as they cannot reproduce tissue dynamics present in a cardiac unit. Herein, we have developed several tools enable the study of cell-cell communication of 3D multicellular system. Specific Aim 1 will map the molecular, functional, and architectural changes upon loss of ERCC1 in CM. In this aim, we will test the mechanistic role of p53 and reactive oxygen species on a number of cellular and mitochondrial parameters, as well as cardiomyocyte electrophysiology. Specific Aim 2 will test whether stochastic, spontaneous DNA damage in the CM or CF drives cardiac electromechanical dysfunction in a cell- autonomous or cell non-autonomous manner through a paracrine effect on neighboring cells. Here, we will analyze the pathological secretome upon genotoxic stress, as well as test the role of eliminating senescent cells on cardiac health. This work is technically innovative as it uses a number of unique tools including concomitant optical and bioelectrical measurements in 3D cardiac organoids. These contributions will be significant because DNA damage is unavoidable and intimately linked to cardiac health and disease. Our team is uniquely qualified to perform this work, with expertise in DNA damage/ repair, cellular senescence, nanofabrication, human iPSC- derived cardiac tissue engineering, and data science. This analysis, we believe, will increase our fundamental understanding of the connection between DNA damage and heart disease and potentially pave the way for new treatment strategies.

26. Project Title: Reducing slip-and-fall accidents in the workplace: Role of small-scale roughness of floor surfaces to improve friction

Leader(s):   **BESCHORNER, KURT E; JACOBS, TEVIS ;**
UNIVERSITY OF PITTSBURGH AT PITTSBURGH
Centers for Disease Control and Prevention R21OH012126 / (2021 - 2023)

Core(s):

Project Summary Fall-related injuries burden over 140,000 workers annually, causing significant human suffering and an economic cost of $10 billion in Workers' Compensation. Approximately half of occupational falls are caused by slipping. An under-explored pathway to preventing these slip-and-fall events is to design flooring for workplaces with high friction performance. High-friction flooring prevents the slip events that lead to a fall. Unfortunately, current methods to characterize floor-surface topography are unable to predict friction performance, limiting innovation in this area. In order to catalyze innovation in high-friction flooring, there is a need for improved scientific understanding of the flooring factors that contribute to friction. Our preliminary studies and existing literature suggest that small-scale topography (features at the 1-nm to 1- m scale) is critical for predicting floor performance, but is not measurable using conventional characterization techniques. The purpose of this R21 project is to measure these small-scales of floor-surface topography, and to use them to develop a mechanics-based predictive model for friction. This research is innovative because it will

employ novel experimental methods and analysis techniques that have never been applied to flooring surfaces, and because it will develop a mechanics-based model to predict the relationship between floor structure and friction performance, where prior research has relied solely on empirical correlations. The proposed research will be accomplished through two Aims: Aim 1: Quantify the dependence of shoe-floor friction performance on small-scale topography. This Aim will investigate the ability of small-scale topography to explain variations in shoe-floor friction performance that cannot be explained using current measurement techniques. Then we will test the first hypothesis: Hypothesis 1: Roughness parameters that consider the full range of scales will improve our ability to predict COF values compared with those using just stylus profilometry. Aim 2: Establish a predictive mechanics-based model for shoe-floor friction based on multiscale surface topography. In this Aim, we will develop and validate a multiscale finite element model that captures viscoelastic contributions to friction across all length scales. We will test the second hypothesis: Hypothesis 2: A mechanics-based model using multiscale topography will more accurately predict shoe-floor friction compared with conventional approaches, i.e., statistical models based on stylus profilometry. This research is expected to lead to foundational knowledge and a modeling tool for optimizing high-friction flooring in workplaces. Working with an industry trade group, the Tile Council of North America (TCNA), this research will achieve impact by guiding the evidence-based development of high-friction flooring for workplaces. Thus, the proposed research is expected to achieve impact in improving workplace safety.

27. Project Title: Physical Activity and Dementia: Mechanisms of Action
Leader(s): ERICKSON, KIRK I
UNIVERSITY OF PITTSBURGH AT PITTSBURGH
NIH R35AG072307 / (2021 - 2026)

Core(s):

Abstract Exercise is one of the most promising methods for positively influencing neurocognitive function in late adulthood. Yet, despite this recognition, several major knowledge gaps preclude the ability to broadly prescribe exercise to prevent or treat cognitive impairment. This R35 proposal includes a series of innovative and potentially groundbreaking studies that will contribute to major advancements in the field of exercise and brain health. The studies that we describe in this proposal would be led by several highly promising junior scientists with the support of an experienced and dedicated mentorship team. The conceptual and scientific framework for the hypotheses described in this proposal orbit around three major challenges facing the field of exercise and cognitive aging: (1) We have a poor understanding of the mechanisms by which exercise influences cognitive function in late adulthood, (2) We have a poor understanding of the factors that moderate, or explain individual variation in, the response to exercise, and (3) We do not understand the factors that predict long- term adoption of exercise behavior and how to reduce barriers and enhance incentives for individuals who find it challenging to continue to exercise. Despite the clear benefits of an active lifestyle, most people fail to meet public health recommendations for exercise. The more we know about the factors that predict and enhance long-term adoption of exercise, the more we will know about whether exercise influences incidence of Alzheimer s Disease and best practices for prescribing and maintaining exercise for the prevention and treatment of cognitive impairment. We propose to conduct secondary analysis of banked data from two rigorous and well-controlled supervised exercise randomized clinical trials (RCTs) and to conduct a 3-year follow-up of >570 participants from both of these RCTs of exercise to assess cognitive, cardiorespiratory fitness, and physical activity levels. In particular, we propose to examine whether exercise-induced changes in cardiometabolic and sleep measures mediate exercise-derived benefits to cognitive and brain outcomes. We will also target moderators of exercise including APOE genotype and racial disparities to better characterize which individual difference variables influence the magnitude of effects of exercise on brain health. Finally, we propose a discovery aim that would leverage our rich measurement of participants at the genetic, physiological, brain, cognitive, and socioemotional levels to perform predictive modeling to forecast long-term adoption of exercise (or barriers prohibiting long-term adoption). In short, this research proposal describes a broad and ambitious line of work that will produce groundbreaking and innovative studies to address significant gaps in our understanding of exercise and brain health in late adulthood. The aims target several major AD/ADRD milestones identified by NIH and will position junior scientists in leadership roles to advance the field forward in significant and pioneering ways.

28. Project Title: POPULATION NEUROSCIENCE OF AGING AND ALZHEIMER'S DISEASE (PNA)
Leader(s): ROSANO, CATERINA; GANGULI, MARY ;
THE UNIVERSITY OF PITTSBURGH
NIH T32AG055381 / (2018 - 2023)

Core(s):   - Clinical and Population Outcomes Core (CPOC)
     - Integrative Systems Core (ISC)

Training Grant in Population Neuroscience of Aging & Alzheimer s Disease (PNA) The objective of this new pre- and post-doctoral training program is to train highly talented individuals to pursuesuccessful independent research in the etiology of Alzheimer s Disease and other age-related dementia (ADRD). Eligibleapplicants are PhD graduates or candidates in Epidemiology, Neuroscience, Information Science, Biostatistics,Biomedical informatics and MD/DO graduates with training in Neurology, Psychiatry, Geriatric medicine, and relateddisciplines. We request support for 3 pre-doctoral and 2 post-doctoral positions annually, with a period of training of up to3 years for post-docs and 4 years for pre-docs (up to 5 in some cases). The field of brain aging has profoundly changed because of the collision of two phenomena: worldwide increase ofour aging population, and rapid technological advancements in health measurements in general and in brain science inparticular. Our successes in extending lifespan, with marginal improvements in healthspan, have not only increased thenumber of adults reaching very old ages, but they have also increased the heterogeneity of age-related neurocognitivephenotypes. For these new older adults, there is a very high burden of chronic conditions affecting the central nervoussystem either directly (e.g. stroke) or indirectly (heart conditions, diabetes). Cumulative exposure to chronic conditions,biological ageing, chronological aging and possibly to other life-long environmental factors, interact with each other invery complex ways and are all strong drivers of increased risks of developing dementia. While it is reasonable to expectbrain integrity to decline and dementia rates to increase over time, we cannot assume that chronological years and yearsspent with a disease would have linearly additive effects on brain integrity. Understanding these complex pathways is fundamentally important to conduct rigorous etiological research intocauses and determinants of brain degeneration and dementia. Unfortunately, training and research in the field to date havefocused on dementia as an individual condition, and have mostly considered older age as an homogenous population,while relegating multiple chronic conditions and other health issues as collateral problems , or as completely separateproblems. However, it is clear that to understand these complex issues and improve the brain health of the growingpopulation of elderly living with chronic diseases for a long time, it is necessary to have expertise in diseases of both thebrain/central nervous system and also other organ systems. We are also living through a time of great technologicaladvances in non-invasive and automated methods to measure brain abnormalities, the application of which is providingever more precise phenotypes but also very large and complex datasets. Such data require careful sampling designs andanalytical approaches infused with an understanding of the condition being studied to effectively produce new knowledgeto move research to treatment and prevention. We propose that the successful clinical neuroepidemiological investigatorsof the future must be able to link comorbidities, environmental exposures, lifestyles, genomics, e.g. host susceptibility,with knowledge of modern technology of neurosciences and measurement of brain disease and data science. Our proposed T32 in Population Neuroscience of Aging & Alzheimer s Disease (PNA) merges this gap and aims tocross-train researchers in these inter-related fields. Co-directors Drs. Rosano (Epidemiology) and Ganguli (Psychiatry)have designed a new training formula that benefits from the extensive resources and faculty affiliated with the Schools ofPublic Health (Biostatistics), Medicine (Neurology, Biomedical Informatics), Arts and Science (Neuroscience,Psychology), and Information Science, as well as several University Centers and Institutes: the Alzheimer DiseaseResearch Center, the Center for the Neural Basis of Cognition, the Brain Institute, the Center for Aging, Population andHealth, the Claude Pepper, the Aging Institute. Our curriculum responds to the changing landscape of career pathways, by including: a) foundationalknowledge in data science; b) availability of multi-center and international databases; c) enhanced training incutting-edge multimodal methodologies to measure brain changes with age, including neuroimaging and post-mortemassessments; d) hands-on experiences with internet-based designs for recruitment and data collection. Training in theresponsible conduct of research and efforts to increase diversity are important objectives of the program.

29. Project Title: **NEUROBIOLOGICAL DRIVERS OF MOBILITY RESILIENCE: THE DOPAMINERGIC SYSTEM**

Leader(s): **ROSANO, CATERINA; BOHNEN, NICOLAAS IDA ;**
THE UNIVERSITY OF PITTSBURGH
NIH U01AG061393 / (2018 - 2023)

Core(s):   - Clinical and Population Outcomes Core (CPOC)
     - Integrative Systems Core (ISC)

ABSTRACT In older age, walking becomes slower and less automated, requiring more attention and prefrontal resources.Common causes of age-related walking impairments are cerebral small vessel disease (cSVD) and changes inperipheral systems. We have recently discovered that ~20% of older adults maintain fast gait speed even in thepresence of common locomotor risk factors, thus appearing resilient. Our work suggests that the nigrostriataldopamine (DA) system may be a source of this resilience. We hypothesize that higher nigrostriatal DAneurotransmission drives resilience to locomotor risk factors via higher connectivity with sensorimotornetworks, thus reducing prefrontal-mediated motor control and restoring automated control of walking. Resilience due to the nigrostriatal DA system is a novel and highly promising area of inquiry. Unlike vascularlesions and brain structural impairments, DA neurotransmission is potentially modifiable, thereby offering novelapproaches to reduce age-related walking impairments. Although of substantial potential value to wellbeing inaging, there is a critical gap in knowledge of age-related mobility with simultaneous measures of nigrostriatalDA system, cSVD and peripheral system impairments. Our aims are: AIM 1: Quantify the DA-related contribution to mobility resilience, cross-sectionally and longitudinally.We hypothesize that nigrostriatal DA neurotransmission predicts walking performance, during usual and dualtask conditions and reduces the negative effects of cSVD and peripheral system impairment on walkingperformance. AIM 2: Assess DA-related automated control of walking, cross-sectionally and longitudinally. Wehypothesize nigrostriatal DA neurotransmission acts synergistically with connectivity of sensorimotor networksto predict higher walking performance and lower prefrontal activation while walking. As a first translational step in testing the effects of DA on resilience, we propose to collect pilot data for amechanistic target-engagement study in slow-walking older adults with cSVD and pronounced age-associatedstriatal DA loss. Exploratory AIM 3: To assess the effects of 1 week of L-DOPA administration on connectivityand gait speed as a function of molecular markers of striatal DA release in non-resilient elderly withpronounced age-associated striatal DA losses. This research is innovative in that it goes beyond explaining impairments, to revealing resilience factors andtheir mechanisms as the basis for novel interventions. It has high impact because recent findings suggest thatpharmacological and behavioral interventions can improve DA signaling. Our team has unique expertise in theuse of novel technologies and represents decades as thought leaders in the study of aging, brain and mobility.

30. Project Title: **Defining the impact of stromal aging on ovarian cancer initiation**
   Leader(s):   **COFFMAN, LAN ; BUCKANOVICH, RONALD J; FINKEL, TOREN ;**
   UNIVERSITY OF PITTSBURGH AT PITTSBURGH
   NIH U01AG077923 / (2021 - 2026)

Core(s):

Age is a major risk factor for high grade serous ovarian cancer (HGSOC) with an average age at diagnosis of 63. Ovulation and aging induce inflammatory changes in the fallopian tube microenvironment, the origin of most HGSOC. Over time, cells become senescent and secrete regulatory factors known as the senescence associated secretory phenotype (SASP). SASP-induced changes in the local microenvironment have been implicated in cancer promotion. However, the role of the aging microenvironment in ovarian cancer initiation is unknown creating a major barrier to effective early detection and prevention strategies for this deadly disease. The goal of this proposal is to define the impact of aging on interactions between stromal cells and cancer initiating cells (CIC) that drive ovarian cancer formation. Mesenchymal stromal/stem cell (MSC) are multipotent stromal progenitor cells critical to tissue homeostasis across the lifespan. In cancer, MSCs undergo epigenomic reprogramming to become pro-tumorigenic cancer associated MSCs (CA-MSCs). The pro-tumorigenic CA-MSC phenotype is driven by the activation of the Wilms tumor 1 (WT1) transcription factor. WT1 induces the secretion of CA-MSC derived BMP4 which increases the pool of ovarian CICs. Preliminary data demonstrate that with increasing age, MSCs can express WT1 and adopt a cancer promoting phenotype even before cancer starts. We have termed these cells high risk MSCs (hrMSCs). Preliminary data indicate that hrMSCs (i) recapitulate the CA-MSC phenotype and are enriched in the stroma of pre-malignant epithelial cells, (ii) secrete SASP-like proteins which both induce epithelial cell DNA damage and support the survival of DNA damaged epithelial cells and (iii) support established cancer cell growth. AMP-activated protein kinase (AMPK) may be critical to CA- MSC/hrMSC formation. In a clinical trial Metformin, which increases AMPK, reversed the CA-MSC phenotype in some patients correlating with improved survival. Preliminary data shows a more potent, novel AMPK activator, BC1618, alters the hrMSC secretome. We hypothesize that aging induces epigenetic changes which convert MSCs to hrMSCs and that hrMSCs create a pro-tumorigenic microenvironment that supports the growth of ovarian CICs. Our collaborative team with expertise in aging, stromal stem cells and CICs propose to: 1) Determine the impact of aging on the fallopian tube MSC phenotype and spatial relationship to CICs. We hypothesize that aged MSCs obtain a high risk phenotype through altered DNA methylation and support adjacent CIC formation. 2) Determine the impact of aged hrMSCs on CIC formation and ovarian cancer progression. We hypothesize that aged hrMSCs promote CIC formation and progression via WT1-mediated BMP4 and SASP secretion. 3) Target aging hrMSCs to limit ovarian cancer formation. We hypothesize that the AMPK activator,

BC1618, through altering age-related MSC epigenetic changes, will decrease hrMSC formation and ovarian cancer initiation. This work will broaden our understanding of ovarian cancer initiation by defining the critical role of aging stroma in CIC formation and offer new avenues for early detection and prevention strategies.

31. Project Title: **Generation, Characterization, and Validation of Marmoset Models of Alzheimer's Disease**

Leader(s): **SILVA, AFONSO C; CARTER, GREGORY W; RIZZO, STACEY J; UNIVERSITY OF PITTSBURGH AT PITTSBURGH NIH U19AG074866 / (2022 - 2024)**

Core(s):

PROJECT SUMMARY OVERALL Alzheimer s disease (AD) is a devastating neurodegenerative disorder affecting nearly 6 million Americans and is expected to increase over the next several years. Our limited understanding of the mechanisms that trigger the emergence of AD has contributed to the lack of interventions that stop, prevent, or fully treat this disease. We propose to establish the marmoset as the first primate-specific model to reveal the earliest cellular and molecular events of AD processes and allow charting AD progression from its inception. To do so, we will draw from a self-sufficient and large colony of research marmosets with dedicated veterinary and husbandry teams, state-of-the-art in vivo neuroimaging and molecular assays, and a multidisciplinary team of experts in aging biology, AD genetics and genomics, animal model development and characterization, behavioral and cognitive phenotyping, and marmoset gene-editing technologies. Our proposal s overarching goals are to develop marmoset models of early-onset AD (EOAD) and late-onset AD (LOAD) to enable the investigation of the underlying cellular and molecular root causes of the pathogenesis and progression of AD and support future translational studies. We believe that the simultaneous assessment of genetic, molecular, functional, behavioral, and pathological phenotypes in marmosets will provide translatable knowledge of the origins and progression of AD in human populations. Furthermore, we posit that the comprehensive study of gene-edited marmoset models of AD from neurodevelopment through aging will identify emerging phenotypes that precede frank neuropathology. Our proposal consists of 3 integrated Research Projects that aim to: (1) Conduct characterization and validation of PSEN1 mutations in marmosets as a model for the study of EOAD, and investigate early life molecular determinants of AD disease pathogenesis associated with genetic risk for EOAD; (2) Identify and enhance LOAD-related signatures in outbred and genetically-engineered marmosets; and (3) Conduct a comparative multimodal phenotypic characterization of marmoset models of AD. These projects will be supported by 5 Research Cores focused on project administration, bioinformatics, genetic engineering, multimodal disease characterization, and veterinary and colony management. These supporting cores will integrate marmoset and human genomic signatures and provide data dissemination and resources to the greater research community as part of our commitment to open science, generate novel gene-edited marmoset models of AD, develop optimized protocols for studying disease onset and trajectory in line with clinical protocols, evaluate therapeutic strategies, and provide specialized animal care and support, respectively, allowing complete characterization of the marmoset models. At the conclusion of this project, we will have genetically engineered three AD risk variants into marmoset models, established a disease characterization pipeline for comprehensive phenotyping, and shared these resources with the greater research community.

32. Project Title: **Biospecimen-Core**

Leader(s): **ROJAS, MAURICIO UNIVERSITY OF PITTSBURGH AT PITTSBURGH NIH U54AG075931 / (2021 - 2026)**

Core(s):

ABSTRACT Biospecimen Core: Lung and heart function and aging are major determinants of human health and lifespan, respectively. Combined, lung and heart diseases are the leading cause of morbidity and mortality world-wide (WHO s Global Health Estimates 2020). The Biospecimen Core (BC) will generate high-quality, clinically annotated, and pathologically evaluated specimens from normal human lung and heart (and corresponding vessels and lymph nodes) to provide the fundamental basis for the creation of high-resolution, multi-modal, and multi-dimensional senescence maps. The BC investigators will use their expertise in collecting, processing, annotating, classifying, and distributing tissue samples and primary cells lines for lung and heart senescence mapping. The core will excel in providing already catalogued tissues with as little ischemia-induced artifacts as possible, and meet all legal and ethical standards including broad donor consent. The BC follows NIH/NCI Best Practices for Biorepositories, with standard operating procedures (SOPs) in place

to ensure the highest biospecimen and clinical information quality to meet all legal and ethical standards. The biorepository efforts are approved through OSU, Pitt, and URMC IRB protocols that cover the procurement, processing, and distribution of human biospecimens. The BC will collect whole tissue from humans across the lifespan and will provide whole tissue, precision cut tissue slices (PCTS), and purified cells to the TriState SenNet TMC. Together with the Data Analysis Core (DAC), the BC will use established metadata collection protocols to collect metadata in a consistent and interoperable format.

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Dasgupta P, Frisch A, Huber J, Sejdic E, Suffoletto B
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Citations: 21 | AltScore: 4.35

11. **Establishing Reference Values for Temporal Kinematic Swallow Events Across the Lifespan in Healthy Community Dwelling Adults Using High-Resolution Cervical Auscultation.**
Donohue C, Khalifa Y, Mao S, Perera S, Sejdic E, Coyle JL
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Citations: 34 | AltScore: 0.5

13. **The Association of Mobility Determinants and Life Space Among Older Adults.**
Dunlap PM, Rosso AL, Zhu X, Klatt BN, Brach JS
J Gerontol A Biol Sci Med Sci, 2022 Nov 21, 77(11): 2320-2328
https://doi.org/10.1093/gerona/glab268 | PMID: 34529773 | PMCID: PMC9678196
Citations: 54 | AltScore: 4.25

14. **Modified Application of Cardiac Rehabilitation in Older Adults (MACRO) Trial: Protocol changes in a pragmatic multi-site randomized controlled trial in response to the COVID-19 pandemic.**
Forman DE, Racette SB, Toto PE, Peterson LR, Glynn NW, Pruskowski J, Byard T, Delligatti A, Lolley R, Mulkareddy V, Allsup K, Perera S, Lenze EJ, Rich MW

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Ganz DA, Yuan AH, Greene EJ, Latham NK, Araujo K, Siu AL, Magaziner J, Gurwitz JH, Wu AW, Alexander NB, Wallace RB, Greenspan SL, Rich J, Volpi E, Waring SC, Dykes PC, Ko F, Resnick NM, McMahon SK, Basaria S, Wang R, Lu C, Esserman D, Dziura J, Miller ME, Travison TG, Peduzzi P, Bhasin S, Reuben DB, Gill TM
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Citations: 57 | AltScore: 414.03

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Citations: 25 | AltScore: 243.43

18. **Factors Associated With Cardiac Rehabilitation Participation in Older Adults After Myocardial Infarction: THE SILVER-AMI STUDY.**
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19. **Diabetes Mellitus is Associated with Poor Bone Microarchitecture in Older Adults Residing in Long-Term Care Facilities.**
Haeri NS, Kotlarczyk MP, Perera S, Greenspan SL
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Citations: 29 | AltScore: NA

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Citations: | AltScore: NA

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He Y, Lipa KE, Alexander PG, Clark KL, Lin H
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Citations: 19 | AltScore: NA

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Citations: 17 | AltScore: 8.25

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Citations: 75 | AltScore: NA

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Citations: 115 | AltScore: 10.7

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Patterson CG, Leland NE, Mormer E, Palmer CV
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Citations: | AltScore: NA

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Citations: 1 | AltScore: 17.75

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Qiao YS, Moored KD, Boudreau RM, Roe LS, Cawthon PM, Stone KL, Cauley JA, Glynn NW
J Gerontol A Biol Sci Med Sci, 2022 Dec 29, 77(12): 2507-2516
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Raine LB, Erickson KI, Grove G, Watrous JNH, McDonald K, Kang C, Jakicic JM, Forman DE, Kramer AF, Burns JM, Vidoni ED, McAuley E, Hillman CH
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Citations: 18 | AltScore: 12

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Rocha EM, Keeney MT, Di Maio R, De Miranda BR, Greenamyre JT
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Scheunemann L, White JS, Prinjha S, Eaton TL, Hamm M, Girard TD, Reynolds C, Leland N, Skidmore ER
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Citations: 54 | AltScore: 8.4

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Smagula SF, Biggs ML, Jacob ME, Rawlings AM, Odden MC, Arnold A, Newman AB, Buysse DJ
Psychosom Med, 2022 Sep 1, 84(7): 785-792
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Citations: 50 | AltScore: 0.75

54. **Scientific opportunities in resilience research for cardiovascular health and wellness. Report from a National Heart, Lung, and Blood Institute workshop.**
Taylor HA, Finkel T, Gao Y, Ballinger SW, Campo R, Chen R, Chen SH, Davidson K, Iruela-Arispe ML, Jaquish C, LeBrasseur NK, Odden MC, Papanicolaou GJ, Picard M, Srinivas P, Tjurmina O, Wolz M, Galis ZS
FASEB J, 2022 Dec, 36(12): e22639
https://doi.org/10.1096/fj.202201407R | PMID: 36322029 | PMCID: PMC9703084
Citations: 91 | AltScore: 0.5

55. **\How much desire should I have?\: a qualitative study of low libido in postmenopausal women.**
Thomas HM, Hamm M, Krishnamurti T, Hess R, Borrero S, Thurston RC
J Women Aging, 2022 Sep-Oct, 34(5): 649-657
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56. **Prevalence, Impact, and Trajectories of Sleep Disturbance in Cardiac Rehabilitation: A NARRATIVE REVIEW AND SUGGESTIONS FOR EVALUATION AND TREATMENT.**
Tighe CA, Buysse DJ, Weiner DK, Beehler GP, Forman DE
J Cardiopulm Rehabil Prev, 2022 Sep 1, 42(5): 316-323
https://doi.org/10.1097/HCR.0000000000000694 | PMID: 35522949 | PMCID: PMC9437109
Citations: 80 | AltScore: 5.4

57. **Preexisting frailty and outcomes in older patients with acute myocardial infarction.**
Udell JA, Lu D, Bagai A, Dodson JA, Desai NR, Fonarow GC, Goyal A, Garratt KN, Lucas J, Weintraub WS, Forman DE, Roe MT, Alexander KP
Am Heart J, 2022 Jul, 249: 34-44

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Citations: | AltScore: 14.3

58. **Physical Therapists and Physical Therapist Assistants' Knowledge and Use of the STEADI for Falls Risk Screening of Older Adults in Physical Therapy Practice in the United States.**
Vincenzo JL, Schrodt LA, Hergott C, Perera S, Tripken J, Shubert TE, Brach JS
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Citations: 15 | AltScore: NA

59. **The Inventory of Physical Activity Barriers for Adults 50 Years and Older: Refinement and Validation.**
Wingood M, Jones SMW, Gell NM, Brach JS, Peters DM
Gerontologist, 2022 Nov 30, 62(10): e555-e563
https://doi.org/10.1093/geront/gnab165 | PMID: 34794173 | PMCID: PMC9710241
Citations: 58 | AltScore: 2.75

60. **Benign prostatic hyperplasia/obstruction ameliorated using a soluble guanylate cyclase activator.**
Zabbarova IV, Ikeda Y, Kozlowski MG, Tyagi P, Birder LA, Chakrabarty B, Perera SK, Dhir R, Straub AC, Sandner P, Andersson KE, Drake MJ, Fry CH, Kanai AJ
J Pathol, 2022 Apr, 256(4): 442-454
https://doi.org/10.1002/path.5859 | PMID: 34936088 | PMCID: PMC8930559
Citations: 47 | AltScore: NA

61. **Association of Retail Environment and Neighborhood Socioeconomic Status With Mortality Among Community-Dwelling Older Adults in the United States: Cardiovascular Health Study.**
Zhang K, Lovasi GS, Odden MC, Michael YL, Newman AB, Arnold AM, Kim DH, Wu C
J Gerontol A Biol Sci Med Sci, 2022 Nov 21, 77(11): 2240-2247
https://doi.org/10.1093/gerona/glab319 | PMID: 34669918 | PMCID: PMC9678200
Citations: 34 | AltScore: 3.25

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RECOGNITION AND AWARDS (2022-2023)

Aarohee Fulay, PhD, MPH (2023)

- RCCN Workshop Travel Award for Early Career Investigators on Healthy Aging Through Nutrition

Andrea Rosso, PhD (2022)

- Delta Omega Honor Society Member - Public Health Honor Society

Anne Newman, MD (2022)

- Best Female Scientists in the World 2022 Ranking (Research.com)
- Highly Cited Researcher, 2014-2022, The Web of Science Group, a Clarivate Analytics.

Arjumand Ghazi, PhD (2023)

- Reproductive Geroscience K07 Award

Daniel Forman, MD (2022)

- Michael L. Pollock Established Investigator, American Assoc of CV and Pulmonary Rehabilitation
- Director, American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) Annual Meeting

Daniel Forman, MD (2023)

- Director, American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) Annual Meeting

Fabrisia Ambrosio, PhD, MPT (2022)

- elected to the American Institute for Medical and Biological Engineering (AIMBE) College of Fellows, in recognition of their distinguished and continuing achievements in medical and biological engineering

Lilcelia (CeCe) Williams, PhD, MBA, BSRT(T) (2023)

- 2023 UPMC Rehabilitation Institute Pilot Grant for the School of Health and Rehabilitation Sciences
- abstract has been accepted for presentation at The Gerontological Society of America (GSA) 2023 Annual Scientific Meeting

Neil Resnick, MD (2022)

- 2022 Joseph T. Freeman Award (from Gerontological Society of America)- a lectureship in geriatrics awarded to a prominent clinician in the field of aging, both in research and practice.

Samaneh Farsijani, PhD, RD (2023)

- RCCN Workshop Travel Award for Early Career Investigators on Healthy Aging Through Nutrition

Steven M. Albert, PhD, MS, FGSA, FAAN (2022)

- 2021-22 Fulbright Lecturer/Research Award: "A comparative study of community prevention of disability in older adults: Japan and the U.S."

<u>Susan Greenspan, MD</u> (2022)

- 2022 UPMC Grand Champion for the 14th Annual UPMC Celebrating Senior Champions
- 2021 Excellence in Patient Experience Award (UPMC)

MINORITY RESEARCH

General Brief Description of Minority Activities:
Not defined.

Minority Trainee(s):

- Diana Alvarez-Davidek MD, Novice REC Member
  Age-related mitochondrial decline in lung function
- Gardenia Juarez, Pepper Novice Trainee
  Reducing Fear of Falling and Preventing Falls
- Gelsy Torres-Oviedo, PhD, Pepper REC Transitioned to Independence Trainee
  Increasing gait automaticity in older adults by exploiting locomotor adaptation
- Ikenna D. Ebuenyi, MBBS, PhD , Novice REC Member
  Rehabilitation in the Face of Progressive Decline: Practice and Perspectives
- Lilcelia Williams, PhD, MBA, BSRT(T), Novice REC Member
  She will explore beliefs, values, and perspectives about Mild Cognitive Impairment and associated health care services in black and African American older adults.

No minority grant information specified.

UNIVERSITY OF CONNECTICUT HEALTH CENTER
Claude D. Pepper Older Americans Independence Center

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Center Administrator

CENTER DESCRIPTION

The mission of the UConn Pepper Center is to establish a thriving interdisciplinary research program to promote health, function and independence in old age. The UConn Pepper Center provides numerous resources to catalyze the growth of multidisciplinary, collaborative aging-related research ranging from basic and preclinical to clinical and community-based to population based research in a sustained fashion. Our theme of Precision Gerontology seeks to leverage an understanding of the growing heterogeneity of aging into interventions rendered more effective by being better targeted.

The aims of the UConn Pepper Center are:

- To develop a strong understanding of the multiple facets of heterogeneity aging. With an extensive understanding, we'll be able to develop targeted, precise and effective interventions to improve care provided to aging adults.

- To develop and collaborate with researchers from multidisciplinary teams in order to address questions or problems related to aging from the levels of bench to the bedside and institution to out in a community.

- To foster career development opportunities in an effort to train and collaborate with the next generation of leading geriatric researchers.

CORES

Leadership & Administrative Core (LAC)

<u>Leader 1:</u>	George Kuchel, MD	kuchel@uchc.edu
<u>Leader 2:</u>	Richard H. Fortinsky, PhD	fortinsky@uchc.edu
<u>Leader 3:</u>	Julie Robison, PhD	jrobison@uchc.edu

The Leadership and Administrative Core (LAC) provides the administrative infrastructure and scientific leadership necessary to achieve the overall aims of the UConn Pepper Center. The long-range goal of the LAC is to lead the way in establishing a highly productive research and education program in aging and geriatrics at the University of Connecticut, spanning laboratory, clinical and community, and population-based science collectively guided by the theme of Precision Gerontology.

Research and Education Core (REC)

<u>Leader 1:</u>	David Steffens, MD	steffens@uchc.edu
<u>Leader 2:</u>	George Kuchel, MD	kuchel@uchc.edu

The overarching goal of the Research Education Component (REC) of the UConn Older Americans Independence Center is to cultivate the next generation of investigators and clinician-scientists to become leaders in their career focused on aging with exposure to multidisciplinary translational science, mentorship and expertise in Precision Gerontology. A key component of the Research Education Component (REC) is the Pepper Scholar Program. This program provides financial support, education and training to Pepper Scholars to advance their research careers. Pepper Scholars apply and are chosen as showing particular promise as independent investigators in the field of geriatrics and gerontology. The REC, led by Dr. David Steffens, includes several senior research leaders at UConn who serve as mentors to the Pepper Scholars. The mentors provide each of the scholars with personalized educational opportunities, career development and different networking opportunities in order to facilitate their research interests.

Pilot & Exploratory Studies Core (PESC)

<u>Leader 1:</u>	Lisa Barry, PhD	libarry@uchc.edu
<u>Leader 2:</u>	Rogina Blanka, PhD	rogina@uchc.edu

The UConn Pepper Center Pilot and Exploratory Studies Core (PESC) works to develop and support innovative pilot and exploratory studies that will enhance function and independence in older adults while also advancing knowledge in the field of Precision Gerontology. The PESC provides funding and access to resources offered by each of the UConn Pepper Center research cores, including guidance in research subject recruitment, regulatory and compliance issues, research plan implementation, biostatical considerations, and biomarker analysis. In addition, the PESC provides mentorship and oversight to pilot study investigators to ensure each project is developed and carried out in a timely fashion, and that results are disseminated to optimize scientific impact to the world of aging research.

Biomarkers and Preclinical Research Core (Resource Core 3)

<u>Leader 1:</u>	Laura Haynes, PhD	lhaynes@uchc.edu
<u>Leader 2:</u>	Paul Robson, Ph.D.	paul.robson@jax.org

The UConn Pepper Biomarkers and Preclinical Research Core assists investigators with the expertise and various tools needed to integrate biomarkers, drivers of aging and underlying mechanisms of chronic diseases in humans and animal models in order to promote function and independence in the late stages of life. Resource Core 3 is managed by Whitney Wolf (wwolf@uchc.edu).

Data Resource Core (Resource Core 2)
Leader 1:   Richard H. Fortinsky, PhD   fortinsky@uchc.edu
Leader 2:   James Grady Dr.P.H.   jgrady@uchc.edu

The UConn Pepper Center Data Resource Core (RC2) provides help in the selection and interpretation of geriatric health-related outcome measures; database design; and data collection, management and analysis. Content expertise is available to aid in the selection and interpretation of measures evaluating gait, mobility, affect, cognition, behavior, voiding symptoms, incontinence, body composition, bone density, caregiving, and self-reported quality of life. RC2 team members offer advice and guidance in biostatistics, genetic epidemiology, spatial analysis, computational genomics, and microbiome analysis techniques. Resource Core 2 is managed by Nicole Diggens (diggens@uchc.edu).

Recruitment and Community Engagement Core (Resource Core 1)
Leader 1:   Julie Robison, PhD   jrobison@uchc.edu
Leader 2:   Linda Barry, MD   lbarry@uchc.edu

The UConn Pepper Center Recruitment and Community Engagement Core (RC1) provides expertise in the design and development of recruitment plans and implementation of multidisciplinary complex research projects involving older adults. These efforts address recruitment needs for clinical trials, community-based research and studies with a translational clinical to community and health policy emphasis. The Core also partners with the UConn Health Disparities Institute to ensure research includes and asks questions relevant to communities of color and/or communities most vulnerable to adverse health effects, and to strengthen culturally sensitive approaches in all phases. In addition to these recruitment and community outreach efforts, RC1 also provides regulatory services (e.g., IRB application support) and helps investigators with Human Subjects and Clinical Trials Information grant sections and IRB protocol development. RC1 is managed by Lisa Kenyon-Pesce, MPH (Kenyon-pesce@uchc.edu).

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	**Years / Publications**

Jenna Bartley, PhD
Assistant Professor / UConn Center on Aging, UConn School of Medicine
<u>The Effect of Metformin on Influenza Vaccine Responses in Aged Mice</u>

2022-2024 /
10 (total)
0 (1st/Sr)

With aging, T cells undergo a characteristic shift in naïve/memory phenotype, with decreased proliferation, cytotoxicity, and memory responses. Cellular metabolic pathways, such as mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK), are key regulators of T cell fate and function. Dysregulated metabolism is a hallmark of aging and preliminary studies demonstrate age-related alterations in T cell metabolism, suggesting a link between T cell metabolism and diminished T cell responses with aging. Thus, targeting cellular metabolism may improve overall immune responses and T cell specific responses with aging. Metformin, an FDA approved diabetes drug, modulates mTOR/AMPK to alter metabolism. Further, in young mice, metformin increases CD8 T cell memory formation through AMPK activation and fatty acid oxidation enhancement. In line with the geroscience hypothesis, metformin has been shown to extend lifespan in multiple animal models and reduce all-cause mortality in humans. It is a candidate drug to target the overall biology of aging and the focus of the first large geroscience-guided trial Targeting Aging with Metformin (TAME), making it an ideal intervention to target age-related changes in immune cell metabolism and function. Influenza (flu) is among the leading killers of older adults, yet diminished vaccine responses render them unprotected. Intracellular metabolism modulation has great potential to influence vaccine responses. Inhibition of mTOR with a rapamycin analogue improved flu antibodies and enhanced overall immune function in older adults. Diabetics on metformin have stronger flu vaccine responses than diabetics on other oral hypoglycemics, while incubation with metformin in vitro improved some B cell deficits. More mechanistic studies in murine models would be extremely valuable to inform the design of a larger human clinical trial to investigate the impact of metformin on immune responses in healthy older adults. This study will look to determine the impact of metformin on flu vaccine responses in aged mice, as well as determine the immunometabolic effects of metformin in healthy older adults utilizing cryopreserved peripheral blood mononuclear cells (PBMCs) from a previously completed study (the VEME trial).

- AFAR Reboot The Effect of Metformin on T Cell Metabolism in Healthy Older Adults.
- R21 AG071292 Can Senolytics Improve the Aged Response to Viral Infection?
- R01AR075346 The Mechanistic Effects of a Combined Testosterone Therapy and Exercise Intervention upon Axial Bone and Muscle Post-Hip Fracture
- R33 AG061456 Translational Geroscience Network
- R01 AG051647 Combining Testosterone Therapy and Exercise to Improve Function Post Hip Fracture
- R01 AI173305 Impact of Senolytics on Aged Vaccine Responses

Cristina Colòn-Semenza, PT, MPT, PhD
Assistant Professor / Department of Kinesiology, UConn College of Agriculture, Health & Natural Resources
<u>Peer coaching to improve physical activity in older Latinx adults with Parkinson's disease</u>

2022-2024 /
2 (total)
0 (1st/Sr)

Conservative projections estimate the number of people living with Parkinson disease (PD) will rise to 1.2 million in the United States and 9.3 million in the most populous nations by 2030. This disease disproportionately affects older adults with incidence and prevalence drastically increasing from the sixth to ninth decades. There is also ethnic variation in the incidence of this progressive neurological disorder, with Hispanics experiencing the highest rates in the US. Physical activity not only reduces risk of this debilitating disease but may also reduce disease progression. Therefore physical activity, specifically in the form of physical therapy, is recognized as a critical component of effective disease management. However, Latinx people living with PD, are less likely to receive physical therapy treatment compared to Caucasians. In fact, older Latinx adults without PD have significantly lower rates of physical activity compared with

non-Hispanic whites. Cultural and disease-related barriers compound inactivity and inhibit optimal disease management. The combination of physical therapy and peer support may reduce healthcare disparities for people with PD from under-represented groups. Although little is known about how to increase physical activity in minority populations, older adults from under-represented groups have identified lack of time and motivation, inadequate social support, physical ailments, and chronic health conditions as barriers to physical activity. Facilitators of physical activity noted by older adults from under-represented groups include: receiving positive messages about physical activity from a trustworthy source; making physical activity enjoyable; peer social interaction and support, and competition. Peer support is an obvious facilitator of physical activity. Peers (defined for this study's purposes as Latinx individuals with PD) can address these barriers by sharing knowledge, resources, and friendly competition. Peer interventions for older Latinx adults with PD have not been created to meet the unique needs of this population. This study is a pilot randomized, controlled trial in which 30 Latinx older adults (60 years or older) living with PD will participate in a course of physical therapy via telehealth. Half of the older adults will receive the intervention being that of peer support. If shown to be effective, this intervention could improve disease self-management for those living with progressive neurological conditions from other under-represented groups.

- University of Connecticut, School of Fine Arts, STEAM Innovation grant Movement and Creativity: Improving Gait and Quality of Life in People with Parkinson Disease through Visually Enhanced Gait Training
- Effects of a 6-month intervention with targeted amino acid supplement on Parkinson's disease pathophysiology and symptoms
- Comparison of whey protein and amino acid supplementation on acute symptoms and L-Dopa pharmacokinetics in people with Parkinson's disease
- Peer coaching to improve disease management in older Latinx adults with Parkinson disease: A pilot randomized controlled trial

Roshanak Sharafieh, PhD   2022-2024 /
Assistant Professor / Department of Surgery, UConn School of Medicine   2 (total)
<u>Biomarker Development to Promote Geroscience-Guided Approaches to Chronic   0 (1st/Sr)
Wound Management in Older Adults</u>

The aging population has the highest rate of developing chronic ulcers with the worst outcomes due to poor wound healing. Chronic wounds/ulcers have been largely overlooked with very little advancements in treatment modalities, although more than 15% of Medicare beneficiaries (8.2 million patients) are affected. Costs of wound care for Medicare beneficiaries range from $28-100 billion dollars depending on outpatient and inpatient hospital stays and surgical interventions. The major types of chronic wounds (ulcers) include venous leg ulcers, diabetic foot ulcers and arterial ulcers. Unfortunately, there is very limited understanding of the underlying pathophysiology of these chronic ulcers and no true biomarkers to aid in the diagnosis, prognosis or treatment of Chronic Ulcers in Aging Adults (CUAA). The goal of this project is to explore an association between older adults with poor wound healing and an accumulation of senescent cells at the wound (ulcer) site. Recently, a new class of biomarkers have been discovered utilizing cell-derived extracellular vesicles (EVs), which are lipid bound vesicles secreted by cells into the extracellular space. These microvesicles/exosomes (MVE) are present in biological fluids, including blood. In addition, using extracellular vesicles, identify blood biomarkers in patients with chronic ulcers, to aid in predicting wound progression and defining more effective treatment plans, which will reduce loss of mobility, thereby leading to a higher quality-of-life for these patients.

- 5R21AI151840-02 Using Modified Synthetic MicroRNAs to Control Foreign Body Reactions In Vivo
- 1R43DK123770-01 Development and Validation of Novel Coatings that Extend Glucose Sensor Accuracy and Lifespan in vivo

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Past Scholars

PILOT/EXPLORATORY PROJECTS (3 Pilot Projects Listed)

1. Project Title: **Re-Engaging Black/African American Older Adults During the COVID-19 era: Developing A Community-Based Intervention**

Leader: **Rupal Parekh, PhD (PL) Christine Tocchi, PhD (co-PL)**

The sudden closure of churches and senior centers caused by the COVID-19 pandemic disproportionately impacted the health and well-being of communities of color, particularly Black/African American (BAA) older adults. Prior to the pandemic, these community centers provided social engagement. However, with the closure of these resources, BAA older adults involuntary "disengaged" from activities at these community centers (either no longer attend or utilize the senior centers/churches less frequently than they did prior to the pandemic). This study seeks to better understand the barriers to and facilitators of re-engagement among BAA older adult members who attend churches and/or senior centers, and to determine if mental and physical function are associated with engagement. Findings will help to develop a psychoeducational intervention to encourage engagement in BAAs. To date, two focus groups with church stakeholders were completed and individual interviews with BAA older adults will be conducted in summer, 2023.

2. Project Title: **The Heterogeneity of Vulnerabilities in Aging Cohort (HVAC): A new resource for early biomarker discovery and validation**

Leader: **Laura Haynes, PhD (PL) George Kuchel, MD (co-PL) Co-Investigators: Jake Earp, PhD Oh Sung Kwon, PhD Jenna Bartley, PhD Zhichao Fan, PhD Ming Xu, PhD D. Nehar-Belaid, PhD**

Newly discovered and improved biomarkers are needed to improve understanding of shared biological drivers of healthy aging and to develop geroscience-guided interventions to delay frailty onset in older persons (aged 65 and older). Drs. Earp and Kwon are determining the feasibility and potential future utility of specific biomarkers in aging, frailty, and obesity. They have begun recruitment and they will ultimately have biological data from sex-balanced cohorts of 20 healthy/young, 20 healthy/old, 20 old/frail, and 20 old/frail/obese individuals. Samples will be available for additional investigators to conduct pilot studies focused on immunometabolism, autophagy and mitophagy, p21 senescence markers, and single cell genomics.

3. Project Title: **Apathy: An Early Manifestation of Frailty and Disability in Older Adults with Depression?**

Leader: **Kevin Manning, PhD (PI)**

Dr. Manning's pilot project is evaluating apathy as an early manifestation of frailty and disability in older adults with depression. This approach, which incorporates the assessment of both behavioral and physical measures, may allow for earlier detection of risk factors for disability, with opportunities for initial insights into the role of inflammation and improved targeting of higher risk population subsets. Dr. Manning has recruited 27 individuals (21 not depressed, 3 depressed and 3 depressed/apathetic individual), has started initial assessments and correlational analysis, and study recruitment is ongoing.

DEVELOPMENT PROJECTS (3 Development Projects Listed)

1. Project Title: **Gait Velocity Detection Device for Targeted Recruitment in Geriatric Clinic**

Leader: **Lisa Barry, PhD (PL) Song Han, PhD (Co-I) Jatupol Kositsawat, MD (Co-I)**

Core(s):   Recruitment and Community Engagement Core (Resource Core 1)

Gait speed is often used as an eligibility criterion for and/or a means of stratifying research study participants. The Center on Aging at UConn Health has developed a Radio Frequency Identification (RFID)-based system that offers a feasible and valid means of assessing gait speed in the clinic setting. In addition to being simple, practical, and unobtrusive, this system holds promise as a research recruitment strategy. The objective of this Developmental Project is to use this RFID-based system in the UConn Health geriatrics clinic to expand RC1 recruitment strategies in a novel way. The project will aim to implement a Best Practice Advisory (BPA) in the UConn Health EMR system that indicates if a patient is willing to have contact information added to the Research Volunteer Registry (RVR) so that they may be notified about studies for which they may be eligible. Consequently, following IRB protocol regarding extraction and storage of medical record-extracted data, the medical records of patients who checked "Yes" can be searched to identify individuals who may qualify for a study based on their gait speed. Following implementation of the BPA, the project will evaluate the utility of the RFID-based system as a means of expanding the RVR. We will track the number of patients asked about RVR inclusion and determine the proportion of who opts in/out of joining the RVR through the BPA. This Developmental Project is expected to substantially increase the pool of older individuals who may be willing to participate in research studies.

2. Project Title: **Developmental Project 2 - Analysis of CITE-seq data from metformin study**

Leader: **Duygu Ucar PhD (co-PL), Jenna Bartley (co-PL)**

Core(s):   Data Resource Core (Resource Core 2)

This particular project is a collaboration between the UConn OAIC and The Jackson Laboratory for Genomic Medicine (JAX) in Farmington, CT. Human peripheral blood mononuclear cells (PBMCs) were cryopreserved as part of Dr. Bartley's Vaccination Efficacy with Metformin in Older Adults trial (VEME, PI: Bartley, IND#18974, NCT#03996538, IRB#19-205-2). This clinical trial randomized healthy, nondiabetic/nonprediabetic older adults to metformin or placebo treatment for 20 weeks. To examine the single-cell genomic level changes induced by metformin treatment, CITE-seq was performed on samples prior to and after 20 weeks of metformin treatment. The single cell approach is essential given the remarkable heterogeneity of human blood which increases with aging and, we also believe, with frailty. Such information could help lead to discoveries of risk factors, mechanisms and treatment effects involving metformin. It could also help guide development of interventions targeting shared risk factors, shared mechanisms, or be used in targeting population subsets. The project will explore the role of specific biological hallmarks of aging and determine how metformin treatment, a candidate anti-aging drug, can impact these hallmarks in PBMCs. Sample data will be analyzed from samples generated in the OAIC Developmental Project 3 (DP3) project. PBMC samples will include existing samples from the Vaccination Efficacy with Metformin in Older Adults: A Pilot Study (VEME) (conducted by Jenna Bartley, PhD). Additionally, in future years

prospective samples will be obtained and analyzed as part of the Pilot and Exploratory Project entitled "The Heterogeneity of Vulnerabilities in Aging (HVAC) Cohort: A new resource for early biomarker discovery and validation" (PES3).

3. Project Title:	**Developmental Project 3 - Generation of CITE-seq and scRNA-seq data using samples from metformin study & HVAC pilot cohort**
Leader:	**Laura Haynes, PhD (PL), Duygu Ucar, PhD (Jax GM; co-PI), Jenna Bartley (Co-PI)**
Core(s):	Biomarkers and Preclinical Research Core (Resource Core 3)

This particular project is a collaboration between the UConn OAIC and The Jackson Laboratory for Genomic Medicine (JAX) in Farmington, CT. Human peripheral blood mononuclear cells (PBMCs) are routinely obtained and cryopreserved for future use in many different studies at UConn COA. The single cell approach is essential given the remarkable heterogeneity of human blood which increases with aging and we also believe with frailty. In our aging and flu vaccination studies we have observed major robust changes involving only rare PBMC populations. Such information could help lead to discoveries of risk factors, mechanisms and treatment effects involving metformin and/or flu vaccine. It could also help guide development of interventions targeting shared risk factors, shared mechanisms or be used in targeting population subsets. Samples already collected in Dr. Bartley's Vaccination Efficacy with Metformin in Older Adults study (VEME, PI: Bartley, IND#18974, NCT#03996538, IRB#19-205-2) will be processed for CITE-Seq to interrogate single cell protein level and genomic alterations in nondiabetic older adults due to metformin treatment. Additionally, in future years, PBMCs generated by PESC3, "The Heterogeneity of Vulnerabilities in Aging (HVAC) Cohort: A new resource for early biomarker discovery and validation" will be analyzed via scRNA-seq to interrogate single cell genomic differences due to frailty and obesity in older adults.

RESEARCH (24 Projects Listed)

1. Project Title: **Investigating the Role of p21-Highly Expressing Senescent Cells in Alzheimer's Dementia**

Leader(s): **GASEK, NATHAN**
UNIVERSITY OF CONNECTICUT SCH OF MED/DNT
NIH F30AG081092 / (2023 - 2027)

Core(s):

PROJECT SUMMARY/ABSTRACT Alzheimer s Dementia (AD) is a leading cause of morbidity and mortality that is incompletely understood and lacking effective treatment. Accumulation of senescent cells (SnCs) has recently been implicated in AD pathogenesis and targeted removal of these cells may offer new therapeutic avenues. Cellular senescence is a cell fate defined by stable proliferative arrest, apoptotic resistance, and production of a pro-inflammatory secretome. Though senescence programming can contribute to proper development and regenerative processes, its dysregulation is increasingly linked with disease burden and pathology, including AD. While SnC modulation and clearance is a promising therapeutic target, it is increasingly clear that these cells are highly heterogeneous in their characteristics and function. We recently developed a mouse model to characterize a unique population of SnCs that highly express the cell cycle blockade protein p21 (p21high cells) and demonstrated that these cells play a causal role in age related physical dysfunction and metabolic disease. Furthermore, other literature has implicated clearance of pan-SnCs, which include p21high subpopulations, with cognitive improvements in AD. However, it is unknown if p21high cells make distinct contributions to AD or if their targeted removal can further counteract AD pathology. Therefore, this proposal aims to investigate the specific contributions of p21high SnCs to AD. Preliminary experiments have demonstrated that p21high cells accumulate in the brain of mouse AD models featuring amyloid- plaque. However, it is unknown when these cells begin to accumulate in relation to the underlying disease process and what cell types are undergoing senescence. Therefore, in Aim 1, we will define the precise timeline of p21high cell accumulation in relation to amyloid- plaque deposition (1A) and determine what cell types these represent (1B) by tracking these cells with a transgenic fluorescence reporter system and immunohistochemistry. To understand if these p21high SnCs play a causal role in AD, in Aim 2 we propose to selectively eliminate these cells via an inducible suicide gene to determine if targeted removal of these cells can either prevent (2A) or alleviate (2B) AD associated amyloid- plaque formation and impaired performance on cognitive assays. We will also conduct single nuclei RNA sequencing (2C) on brains with or without p21high cell elimination to assess for changes in AD associated neuro-inflammatory pathways and explore underlying disease mechanisms associated with p21high cells. These aims will help to define the role of p21high SnCs in AD and may serve as a basis for new targeted disease modulating therapy. Furthermore, these results will further implicate p21high cells in age related disease and broaden the field s appreciation of SnC heterogeneity. This work is part of a tailored career development plan at UConn Health that integrates training in aging biology, computational analysis, scientific communication, mentorship, clinical practice, and more to advance my career as a future physician-scientist that studies the drivers of aging.

2. Project Title: **Investigating Cellular Senescence at the Single Cell Level**

Leader(s): **COHN, RACHEL**
UNIVERSITY OF CONNECTICUT SCH OF MED/DNT
NIH F30AG081093 / (2023 - 2027)

Core(s):

Project Summary/Abstract Aging is a key risk factor for chronic disease development which can affect lifespan and quality of life. Cellular senescence has emerged as a potential target to slow down the aging process. Senescent cells are in a state of proliferative arrest and are highly associated with aging and pathological conditions. They accumulate in multiple tissues and secrete pro-inflammatory cytokines and other kinds of molecules that damage surrounding tissues. The markers p16 and p21 (cyclin dependent kinase inhibitors) are commonly used to identify senescent cells, but emerging evidence has shown that these markers are not entirely sensitive or specific markers for senescence. There is currently a lack of understanding of the exact genetic markers that define senescent cells especially on the single cell level. With studies showing that senescent cell clearance can alleviate various diseases associated with aging it is vital to achieve a greater understanding of senescent cell markers so that precision medicine treatments can be designed to more effectively eliminate senescent cells. In this proposal we aim to examine the transcriptome of senescent cells on the single cell level both with aging and senolytic treatment in human adipose tissues. Senescent cells have been demonstrated to accumulate in adipose tissue with aging and chronic disease and with the vast array of cell types present in adipose tissue it makes an excellent model to study specific

cell types and markers associated with senescence. Aim 1 will explore the transcriptome of naturally occurring senescent cell populations in adipose tissue with aging. We will use single nucleus RNA sequencing to capture cell types sensitive to typical single cell dissociation methods and compare the transcriptome differences between cells in aged vs. young tissues. We hypothesize that adipose tissue from older donors will contain more senescent cells and that several novel genetic markers will be identified in these cells. Aim 2 will look at the effects of senolytic treatment on human adipose tissue on the single cell level. Senolytics are drugs that are designed to specifically eliminate senescent cells but we do not know the precise cell types targeted by senolytics. We will use single nucleus RNA sequencing to uncover the transcriptome changes that occur with senescent cell elimination and learn what cell types are removed with senolytic treatment. This project will help advance the field achieving a greater understanding of senescent cell populations in adipose tissue and the markers that define them, which is essential to understanding and potentially treating numerous diseases. Through this fellowship my training will include developing my skills in genetics, aging, computational analysis, communication, presentation, networking, scientific writing, clinical knowledge and mentorship. This training will occur in the environment of UCONN Health as well as the Jackson Laboratory and other research institutions. This work will allow me to take advantage of training opportunities and mentorship to advance my career as a future physician-scientist.

3. Project Title: **The Mito-Frail Trial: Effects of MitoQ on Vasodilation, Mobility and Cognitive Performance in Frail Older Adults**

Leader(s): **KWON, OH SUNG**

UNIVERSITY OF CONNECTICUT STORRS

NIH K01AG080164 / (2023 - 2028)

Core(s):

PROJECT SUMMARY The overarching goal of this proposal is to provide the applicant with selected additional skills required for an applicant to become an independent NIH-funded investigator capable of designing and implementing early phase geroscience-guided clinical trials that have the potential to extend healthy lifespan by targeting biological aging. This custom-designed learning experience will be enhanced by three unique components. First, a Patterson Trust-funded study The Mito-Frail Trial: Effects of MitoQ on Vasodilation, Mobility and Cognitive Performance in Frail Older Adults will provide a research platform. Second, the NIA Translational Geroscience Network (R33 AG061456) and its Facility for Geroscience Analysis has agreed to provide learning experiences and subsidized measurements of biomarkers permitting a much broader and deeper analysis of biological hallmarks of aging. Third, the NIA Geroscience Education and Training Network (R25 AG073119) will permit the candidate to fulfill the requirements for a Certificate in Geroscience at UConn, one of the network's current five sites. Chronic diseases and associated declines in physical and cognitive performance contribute greatly to lost independence with aging. In addition to a lack of effective interventions other than exercise to address either problem, few studies have examined strategies for targeting both conditions in frail individuals who may experience difficulties with both walking and memory. Use of geroscience-guided therapies permits us to target mechanisms shared by aging with chronic conditions for which aging represents a major risk factor. Thus, instead of focusing on one single disease at a time, it may be possible to delay the onset and progression of disability involving multiple functional domains including those caused by Alzheimer's disease and other dementias. We have recently shown that MitoQ, a mitochondria-targeted antioxidant known to improve endothelial function and Nitric Oxide (NO) bioavailability, may also restore impaired flow-mediated vasodilation in frail older adults, enhancing gait speed. In the Mito-Frail study we now wish to explore the hypothesis that MitoQ attenuates aging- related declines in flow-mediated vasodilation involving both peripheral and cerebral blood vessels. At the same time, we will obtain feasibility and pilot data involving measures of physical mobility and cognitive performance that may help us design and power a future clinical trial. Ultimately, we seek to develop strategies for preventing or slowing the progression of Alzheimer's disease and the vascular contribution to dementia. Therefore, Aim 1 will assess peripheral and cerebral NO bioavailability and mitochondrial reactive oxygen species (mtROS) levels in older adults who are healthy, others who are frail with slow walking speed and those who meet criteria for mild cognitive impairment (MCI). Aim 2 will determine whether MitoQ supplementation can improve vasodilation with enhancing cognitive function. The proposed research will provide essential training for the candidate who will establish expertise as an independent NIA-funded investigator conducting cutting-edge translational geroscience research designed to maintain and enhance functional independence in older adults.

4. Project Title: **Targeting Senescence to Improve Frailty in Older Cancer Survivors**

Leader(s): **SEDRAK, MINA S**

BECKMAN RESEARCH INSTITUTE/CITY OF HOPE

NIH K76AG074918 / (2022 - 2025)

Core(s):

PROJECT SUMMARY/ABSTRACT Cancer treatment accelerates aging. In people over 65, accelerated aging may have far greater consequences than in younger adults. One of the most important consequences of accelerated aging is frailty. Frailty is linked to loss of independence, falls, and death. Older cancer survivors develop frailty 2- to 4-fold more frequently and at an earlier age than age-matched controls. Mechanisms underlying frailty are just starting to be understood. One key aging mechanism driving frailty is cellular senescence a state of terminal growth arrest. Senescence is the result of both natural aging and cancer treatment; radiation and chemotherapy both generate senescent cells (Sncs). In pilot biomarker studies, I observed that older survivors treated with chemotherapy (vs. no chemotherapy) have increased T-cell expression of P16INK4a (p16). p16 is an established marker of Sncs. I also observed that the percentage of T-cells expressing p16 correlates with clinical frailty. My findings are consistent with published studies linking p16 and frailty in childhood cancer survivors. Together, these data provide the premise for testing clinical interventions to target and eliminate Sncs in older survivors. Recently, drugs have been discovered that selectively eliminate Sncs senolytics. One such senolytic is fisetin, a natural product flavonoid found in strawberries and other fruits. Because the amount of fisetin varies considerably in food, it is not possible to achieve sufficient levels for eliminating Sncs in a natural diet; however, fisetin is available as a dietary supplement. In preclinical models, fisetin reduces Sncs, inflammation, and frailty. As such, fisetin is now in >10 efficacy trials to alleviate age-related conditions in frail older adults and, so far, has had a favorable safety profile. No trial to date has tested fisetin in frail older cancer survivors. Here, I propose a randomized placebo- controlled trial with multi-modality biomarkers to test the preliminary efficacy, safety, and tolerability of fisetin to improve frailty and reduce Snc burden in frail older cancer survivors. Guided by a firm mechanistic rationale and preliminary data, my overall hypothesis is that fisetin is efficacious (improves frailty), safe, and tolerable in frail older survivors. To test my hypothesis, I will randomize cancer survivors age >65 with diminished gait speed (

5. Project Title: **Targeting Senescence to Improve Frailty in Older Cancer Survivors**
Leader(s): **SEDRAK, MINA S**
BECKMAN RESEARCH INSTITUTE/CITY OF HOPE
NIH K76AG074918 / (2022 - 2025)

Core(s):

PROJECT SUMMARY/ABSTRACT Cancer treatment accelerates aging. In people over 65, accelerated aging may have far greater consequences than in younger adults. One of the most important consequences of accelerated aging is frailty. Frailty is linked to loss of independence, falls, and death. Older cancer survivors develop frailty 2- to 4-fold more frequently and at an earlier age than age-matched controls. Mechanisms underlying frailty are just starting to be understood. One key aging mechanism driving frailty is cellular senescence a state of terminal growth arrest. Senescence is the result of both natural aging and cancer treatment; radiation and chemotherapy both generate senescent cells (Sncs). In pilot biomarker studies, I observed that older survivors treated with chemotherapy (vs. no chemotherapy) have increased T-cell expression of P16INK4a (p16). p16 is an established marker of Sncs. I also observed that the percentage of T-cells expressing p16 correlates with clinical frailty. My findings are consistent with published studies linking p16 and frailty in childhood cancer survivors. Together, these data provide the premise for testing clinical interventions to target and eliminate Sncs in older survivors. Recently, drugs have been discovered that selectively eliminate Sncs senolytics. One such senolytic is fisetin, a natural product flavonoid found in strawberries and other fruits. Because the amount of fisetin varies considerably in food, it is not possible to achieve sufficient levels for eliminating Sncs in a natural diet; however, fisetin is available as a dietary supplement. In preclinical models, fisetin reduces Sncs, inflammation, and frailty. As such, fisetin is now in >10 efficacy trials to alleviate age-related conditions in frail older adults and, so far, has had a favorable safety profile. No trial to date has tested fisetin in frail older cancer survivors. Here, I propose a randomized placebo- controlled trial with multi-modality biomarkers to test the preliminary efficacy, safety, and tolerability of fisetin to improve frailty and reduce Snc burden in frail older cancer survivors. Guided by a firm mechanistic rationale and preliminary data, my overall hypothesis is that fisetin is efficacious (improves frailty), safe, and tolerable in frail older survivors. To test my hypothesis, I will randomize cancer survivors age >65 with diminished gait speed (

6. Project Title: **Combining Testosterone Therapy and Exercise to Improve Function Post Hip Fracture**

Leader(s):   **BINDER, ELLEN F; FISHER, STEVEN R; KIEL, DOUGLAS P.;**
MAGAZINER, JAY ; SCHECHTMAN, KENNETH B.; VOLPI, ELENA
;
WASHINGTON UNIVERSITY
NIH R01AG051647 / (2017 - 2024)

Core(s):

Hip fractures are common among older women and can have a devastating impact on their ability to remain independent. A clinically important functional decline and failure to recover following a hip fracture has been documented as much as a year after the fracture, even among individuals who were functioning at high levels before the event. Age-associated androgen deficiency in women contributes to deficits in muscle mass, strength and power that are common in this patient population before the fracture, and are exacerbated afterward. A pilot study of testosterone (T) supplementation in elderly female hip fracture patients has demonstrated the feasibility of T treatment in this population, and showed gains in lean body mass (LBM) and muscle strength with active drug, compared to placebo. The benefits of exercise in restoring muscle strength and physical function after a hip fracture have been documented. However, it remains unclear whether T treatment can augment the effects of exercise on mobility and patient-reported function, or whether any observed benefits are sustained beyond the period of active treatment. Proposed is a 3-group, multi-center, randomized, placebo-controlled, double-blinded, parallel group clinical trial in frail elderly female hip fracture patients. 300 female hip fracture patients will be enrolled from 6 clinical sites, using objective screening criteria for T deficiency (serum total testosterone level < 30 ng/dl) and physical frailty (Modified Physical Performance Test (PPT) Score < 28). The trial will compare the effects of supervised exercise training (EX) alone, EX combined with T therapy (EX+T) and no EX with placebo T treatment (CON), to ascertain the incremental impact of adding T to ET in older adult women following hip fracture. The 6-month intervention will be followed by a 6-month no-treatment sustainability phase. The primary outcome measure is the Six Minute Walk Distance (6MWD). Secondary outcome measures include: 1) dual energy x-ray absorptiometry (DXA) measurements of whole body and appendicular LBM and bone mineral density of the unfractured proximal femur; 2) maximal skeletal muscle strength (1-RM) for leg extension in both limbs; 3) objective physical performance measures; and 4) self-reported performance of activities of daily living and quality of life, including the Hip Rating Questionnaire (HRQ). We plan to carefully monitor testosterone levels, adverse events, biochemical parameters, and factors related to adherence to the interventions. Information from this study has the potential to alter treatment of hip fracture in older women, a problem that contributes to significant morbidity and mortality, and has a large public health impact. The proposed study is highly aligned with NIA s mission of identifying interventions that target common geriatric conditions, and improve treatment options for older adults with multiple morbidities or risk factors.

7. **Project Title:**   **Detrusor Underactivity as an HCN-mediated Failure of Resilience in**
Aging

   Leader(s):   **KUCHEL, GEORGE A; LEVINE, ERIC S;**
UNIVERSITY OF CONNECTICUT SCH OF MED/DNT
NIH R01AG058814 / (2019 - 2024)

Core(s):

ABSTRACT Detrusor Underactivity (DU) is a voiding impairment due to insufficient bladder muscle effort to ensure timely and efficient bladder emptying. As a disorder of volume management, DU is often associated with incontinence and other urinary symptoms, especially in later life. Despite the term suggesting a bladder muscle disorder, a key characteristic of DU is loss of sensitivity to bladder volume. Like DU, aging is also associated with loss of volume sensitivity. Moreover, aging is characterized by increasing risk of failure to adapt to biologic challenge, i.e. loss of resilience. We therefore propose that DU is not a detrusor disease, rather it is a manifestation of the nonresilient end of the spectrum of bladder sensory changes of aging. In this project we will investigate the role of a pacemaker ion channel in the age evolution of a control mechanism critical to bladder volume sensitivity. We hypothesize that DU is associated with the more severe age- associated changes. This knowledge will allow us to determine the control factors contributing to the loss of successful, resilient aging and the resulting non-resilience manifested as DU. To accomplish these goals will use our established mouse cystometry model to test urinary resilience and define a DU group separate from age groups. Our research methods will include single cell genomic sequencing, electrophysiology, molecular/cellular investigations, and correlative tissue-level experiments in order to address our objective. By taking advantage of the uniquely available combined expertise within the UConn Center on Aging, Neurosciences department, and on-site Jackson laboratory, we will address the goal of identifying DU pathophysiology and contributing to an improved therapeutic model which recognizes DU as an adaptive failure.

8. Project Title: **COVID-FIS: A PHASE 2 PLACEBO-CONTROLLED PILOT STUDY IN COVID-19 OF FISETIN TO ALLEVIATE DYSFUNCTION AND EXCESSIVE INFLAMMATORY RESPONSE IN OLDER ADULTS IN NURSING HOMES**

Leader(s): **KIRKLAND, JAMES L.**
MAYO CLINIC ROCHESTER
NIH R01AG072301 / (2020 - 2025)

Core(s):

ABSTRACT Coronavirus-19 (CoV) can cause physical dysfunction, morbidity, and death from hyper-inflammation, acute respiratory distress syndrome (ARDS), and multi-organ failure, particularly in older or chronically-ill individuals. Across the US, >50% of CoV deaths are in nursing homes and 25-50% of nursing home residents who test positive for CoV die from these complications. Senescent cells accumulate with age and drive frailty and chronic diseases. These cells can acquire a senescence-associated secretory phenotype (SASP) entailing release of many of the same factors as in CoV-induced cytokine storm. We found CoV antigens exacerbate the SASP, SASP factors increase CoV viral entry proteins, and SASP factors impair viral defense mechanisms in non-senescent cells. A coronavirus related to human CoV rapidly kills old but not young mice. We discovered drugs that selectively eliminate senescent cells, senolytics. They alleviate age-related phenotypes and chronic disorders in mice and are now in clinical trials, in which they have been found to reduce senescent cell burden, inflammation, and frailty. We found that Fisetin, a natural product flavonoid, has a favorable safety profile in old mice, monkeys, and elderly humans with multi-morbidity in a trial now underway in which 53 patients have been treated. Fisetin decreased cytokine storm and mortality in mice infected with -coronavirus. An FDA- approved clinical trial of ours has now begun in older hospitalized CoV patients to prevent progression to respiratory failure. Our hypothesis is that targeting senescent cells with Fisetin will delay or prevent complications of CoV infection in those at great risk: elderly nursing home residents. Aim 1 is to test if Fisetin prevents progression of morbidity in nursing home residents with rt-PCR-proven CoV infection but no, mild, or moderate symptoms (WHO/NIH Classification) in a double-blind, placebo-controlled, multicenter clinical trial across nursing homes associated with the NIA-supported Translational Geroscience Network. The primary outcome in men and women age >65 (75 Fisetin-treated, 75 placebo) will be prevention of progression, based on the WHO Ordinal Scale for Clinical Improvement of CoV. Other outcomes will be safety, need for supplemental oxygen, escalation of care, and death. TGN-based nurses/study coordinators with their own PPE will minimize impact on thinly-stretched nursing home staff. Fisetin can be provided to the study subjects in foods and drinks. Aim 2 is to test if Fisetin delays, prevents, or alleviates hyper-inflammation and ARDS/multi- organ failure in CoV-infected elderly nursing home residents. When feasible, we will ascertain if Fisetin decreases SASP factors, senescent cell abundance, and viral entry proteins and reduces: progression to severe or critical CoV, delirium, and hypo-oxygenation. Aim 3 is to test if Fisetin promotes recovery of CoV-infected nursing home residents followed up to 6 months, including antibody response, physical function, and lung fibrosis. This trial will pave the way for more nursing home trials of interventions not only for CoV, but other conditions in the frail elderly. The impact of this clinical trial will extend beyond the current CoV epidemic.

9. Project Title: **Resilience and brain health of older adults during the COVID-19 pandemic**

Leader(s): **LENZE, ERIC J; DINIZ, BRENO SATLER; WETHERELL, JULIE L;**
WASHINGTON UNIVERSITY
NIH R01AG072694 / (2021 - 2026)

Core(s):

Abstract: Exercise and mindfulness are believed to be effective stress reduction interventions, but research to date has not been able to assess their benefits while individuals are coping with a major stressor in real time. The COVID-19 pandemic is an unwanted natural experiment in the deleterious effects of stress especially social isolation (social disconnectedness and loneliness), a stressor particularly strongly associated with the pandemic - on older Americans cognitive and emotional health and risk for Alzheimer s Disease (AD). This project will elucidate whether exercise and mindfulness can mitigate the effects of pandemic stress on cognitive function and emotional health in later life, including neurobiological measures of risk for AD. We will leverage a unique resource: the NIH-funded trial, Mindfulness-Based Stress Reduction and Exercise for Age-Related Cognitive Decline (MEDEX). By leveraging MEDEX and following these participants, who continue to attend

monthly booster sessions of their randomized condition remotely during the pandemic, we will have repeated sets of clinical, cognitive, molecular, and neuroimaging measures covering 7.5 years during the pre-, during-, and post-pandemic period. We can examine intervention effects, as well as individual factors such as resilience, on long-term outcomes. Among other innovative aspects of the project, we will analyze effects on two novel peripheral biomarkers: Senescence-Associated Secretory Phenotype (SASP), which measures mechanisms of biological aging, and plasma amyloid A 42 and A 40, which measure AD risk. In the proposed project, (1) during the pandemic, we will use novel methods such as Ecological Momentary Assessment (EMA) to characterize social isolation both objectively (e.g., number of social contacts) and subjectively (e.g., loneliness), and its biological mechanisms on aging (such as elevations in SASP and plasma amyloid); (2) post-pandemic, we will assess downstream effects on cognitive function, emotional well-being, and brain health, including AD risk, using neuropsychological assessments, EMA, and neuroimaging. Outcomes include (Aim 1) changes in cognitive performance and emotional well-being, and decline in emotional well-being measured by positive and negative affect and sleep quality; increases in biological aging and decreasing A 42/40 ratio in the post-pandemic phase, indicating higher risk of AD; atrophy in hippocampal and prefrontal volume (structural MRI) and reduced global functional connectivity (resting-state fMRI). Modifiers of these effects (Aim 2) include exercise and mindfulness; psychological resilience; COVID-19 exposure; medical morbidities; and APOE genotype. Mechanisms of cognitive, emotional, and brain health changes (Aim 3) include amyloid (A 40 and A 42), SASP, DNA methylation, and cortisol during the pandemic. This project will advance our knowledge of the impact of social isolation and other stressors on older adults, including mechanisms by which these stressors produce deleterious cognitive, emotional, and brain health changes over time, and whether exercise and mindfulness have durable protective effects.

10. Project Title: Validating a 3rd-generation methylation measure of accelerated aging: DunedinPoAm4x

Leader(s): **MOFFITT, TERRIE E; CASPI, AVSHALOM ;**
DUKE UNIVERSITY
NIH R01AG073207 / (2022 - 2026)

Core(s):

We propose to validate and export to the aging field a novel tool to measure a person s pace of biological aging: DunedinPoAm4x. The measure will be useful for basic aging research and also for testing whether an intervention has slowed a person s pace of aging. We began this work under NIA R01 AG032282 (Belsky et al PNAS 2015). Over two decades, we tracked a 19-biomarker panel of the physiological functions of 1,000 individuals born the same year (1972-73) in the population- representative Dunedin Study. Our goal has been to measure, in people the same chronological age, variation in biological aging defined per geroscience theory as: gradual, progressive decline simultaneously affecting multiple organ systems. We tracked declines in the cardiovascular, metabolic, pulmonary, renal, dental, hepatic, and immune functions of participants by repeating biomarkers at ages 26, 32, 38 and 45 years (94% retention). Growth-curve modelling of this one-of-a-kind dataset yielded a pace-of-aging metric that quantified how slowly or rapidly each participant in our cohort had been aging (Elliott et al Nature Aging, 2021). The next stage of the work applied machine-learning to participants age-45 whole-genome DNA methylation data, training an algorithm on the pace-of-aging metric to derive a score called DunedinPoAm4x (Pace of Aging methylation, 4 waves). This technical advance means that a person s pace of aging can be estimated from just a single blood sample, and the metric can be exported to any research sample that has blood methylation data. Previously we had reported validation checks on a preliminary version of DunedinPoAm, up to age 38, showing that people who had faster methylation pace of aging scores subsequently experienced advanced facial age, declines in cognitive and physical functioning, chronic diseases, and early mortality (Belsky et al eLife 2020). Our Aims propose a systematic out-of-sample validation evaluation of DunedinPoAm4x in 19+ data sets, testing its applicability in older adults, young people, race/ethnic groups, and several countries. Each Aim will also test existing leading methylation clocks for comparison. Our overarching hypothesis is that DunedinPoAm4x will characterize biological aging with greater precision than the clocks, and in so doing will bring added information value over and above the clocks. In addition to aim- specific publications, we plan a final, synthesis publication. We will deliver, to basic scientists and intervention researchers, a reliable, valid, open-access measure of how rapidly a person has been aging.

11. Project Title: The Noisy Life of the Musician: Implications for Healthy Brain Aging

Leader(s): **SKOE, ERIKA E**

UNIVERSITY OF CONNECTICUT STORRS
NIH R01AG075271 / (2022 - 2027)

Core(s):

PROJECT SUMMARY Playing a musical instrument is a popular childhood and adult activity with documented health benefits. One of the most provocative, but least understood, proposed health benefits is preserved brain function in advanced age. Playing a musical instrument, however, can also pose significant health hazards, including those that come from routine exposure to noisy (loud) environments. Beyond the risks of hearing loss from loud environments, noise exposure is a significant risk factor for age-related functional declines. While both the benefits and risks of musical training have been widely studied, little attention has been given to their interplay. To understand the mechanisms that mediate the effects of musical training on the human brain, we must develop a more complete accounting of the risk factors that could counteract the benefits of musical training and the degree to which benefits persist in the face of these risks. To more fully harness the therapeutic benefits of music, we also need a better account of whether the benefits persist after a musician stops playing their instrument. These knowledge gaps motivate the proposed work on auditory brain aging, in which lifelong musicians will be compared to controls and to ex-musicians who have not played a musical instrument since childhood. The proposed work is grounded in our published studies of auditory brain aging, and our published and pilot studies on the interplay of musical training and noise exposure on the young adult auditory brain. The proposed work aims (1) to characterize current and lifetime noise exposure from music and non-music activities, (2) to investigate relations among lifelong musical training, lifetime noise exposure, and auditory-brain aging, and (3) to investigate relations between childhood musical training and later-life auditory-brain function. For all three aims, young adults (18- 24 years) will be compared to middle-aged adults (45-60 years). We hypothesize that music, as a form of acoustic enrichment and training, may mitigate the impact of noise injuries and age-related decline by strengthening the neural systems most vulnerable to being compromised. Our methodological approach is innovative, comprehensive, and corroborated by our prior work. We will use a novel combination of personal sound dosimetry and structured interviews to characterize the risk of noise injury. Noise exposure data will be combined with validated methods to study auditory brain aging across multiple neural circuits, using a statistical design that accounts for selection bias and confounding variables such as socioeconomic status and cochlear function. Most studies of human auditory aging focus on older adults (60+ years), with less attention on studying early-stage aging when opportunities for the prevention of functional decline are greater. This motivates our decision to focus on early-stage aging. The outcomes of this work may suggest new approaches to promote healthy brain aging and clinical recommendations about harnessing the therapeutic properties of music training to maximize benefits and minimize hazards. Our multidisciplinary study team has complementary expertise in auditory neuroscience (Skoe), noise exposure (Tufts), biostatistics (Harel), and aging (Kuchel).

12. Project Title: High-resolution single cell profiling of vaccine responsiveness in the elderly

Leader(s):   UCAR, DUYGU
JACKSON LABORATORY
NIH R01AI142086 / (2019 - 2024)

Core(s):

PROJECT SUMMARY The goal of this project is to understand the aging-related genomic and functional changes in immune cells that affect responses to flu vaccination. The declining ability of the aging immune system to mount protective responses to vaccines is a major threat to the health, independence and survival of older adults. Much knowledge into the mechanisms of this decline has been gained from studies focused on one or a few immune cell subsets, or on bulk transcriptomics. However, this work has not produced two critical pieces of information: 1) an integrated view of the collective changes across relevant immune cell populations with aging, and 2) the ability to link specific immune cell subsets with their underlying cellular phenotypes/transcriptional profiles, and to compare these phenotypes and profiles as a function of age and responsiveness to vaccines. Single cell profiling, a term we use to encompass flow and mass cytometry together with single cell RNAseq (scRNAseq), is uniquely positioned to deconvolve immune system heterogeneity and identify novel distinct immune cell subsets in health and disease. Single cell profiling will therefore enable us to resolve the immune cell subset deficits relevant to the elderly immune response to vaccines from PBMCs, a highly heterogeneous starting population of cells, but one that offers the advantages of being clinically accessible, highly representative and ultimately unbiased for the purposes of data generation and analysis. We have shown that we can identify discreet cell-type-specific immune signatures of aging from PBMCs, even when such immune subsets represent a small fraction of the total PBMC pool, and have preliminary single cell profiling data from elderly PBMCs, underscoring feasibility. Here, we will analyze PBMCs at the single cell level from elderly donors before and after vaccination (Aim 1),

and with or without in vitro activation of specific immune subsets (Aim 2), to understand the coordinated transcriptional and functional changes that occur, or fail to, as a function of age and vaccine responsiveness. This proposal builds on our recognized expertise in human immunology and incorporates essential expertise in cytometry and single cell transcriptomic analysis (JAX-GM), and access to elderly cohorts (George Kuchel, UConn Center on Aging). Impact: These studies will yield, with unprecedented resolution, the cell-type-specific immune signatures that distinguish responders to flu vaccine from non-responders, and will provide critical clues into the mechanisms and biomarkers of a successful vaccine immune response. Furthermore, these studies will generate a considerable amount of transcriptional and functional data related to the outputs of key innate immune and T/B-cell subsets involved in the influenza vaccine response of elderly individuals. The data will be an important resource for future studies of the elderly immune system in health and disease.

13. Project Title: Impact of Senolytics on Aged Vaccine Responses
Leader(s):   **BARTLEY, JENNA**
UNIVERSITY OF CONNECTICUT SCH OF MED/DNT
NIH R01AI173305 / (2022 - 2027)

Core(s):

PROJECT SUMMARY Despite widespread vaccination, influenza (flu) remains a leading cause of death among older adults. Vaccination is the most effective way to prevent infectious disease. However, older adults have dysregulated immune responses that reduce vaccine efficacy and leave them at risk for severe infection and death. Older adults have reduced T cell proliferation, impaired B cell responses, and decreased antibody titers following flu vaccination. Current methods to improve vaccine efficacy in older adults target singular deficits in immune responses and fail to completely rescue responses. Vaccination requires a complex coordination of multiple cell types and tissues; thus an approach that targets the overall biology of aging, in line with the geroscience hypothesis, may be more appropriate for improving vaccine protection and immune responses in older adults. Senescent cell accumulation is a hallmark of aging and evident in various tissues with age. Although these cells are characterized by a mostly irreversible state of cell cycle arrest, they remain metabolically active and importantly, secrete a heterogeneous cocktail of inflammatory cytokines and chemokines that contribute to tissue dysfunction and damage that is coined senescence associate secretory phenotype (SASP). Accumulation of senescent cells and SASP create pro-inflammatory environments and have a causal role in many age-related disorders. CD4 T cells and B cells, the main cells responsible for robust vaccination responses, are extremely sensitive to their microenvironments. Thus, we propose that accumulation of senescent cells and their SASP drive diminished vaccination responses with aging. Importantly, drugs that specifically kill senescent cells, termed senolytics, have been developed and require only intermittent administration to eliminate senescence cells and mitigate the SASP. The safety and efficacy of senolytics have been shown in mouse studies and can alleviate a range of age-related diseases. Human pilot studies have supported their safety and clinical utility in certain pathologies. However, the impact of senolytics on vaccination responses in aged populations has not yet been examined. The overall hypothesis in this proposal is that senescent cells and the SASP play a causal role in impaired flu vaccination responses with aging and that pharmacological clearance of senescent cells will improve vaccination responses. We will test this hypothesis by treating young and aged mice with senolytic drugs prior to vaccination. We will utilize two different vaccination methods, recombinant flu nucleoprotein to induce protective immunity and adjuvanted inactivated flu to induce neutralizing immunity, and then infect mice with flu to interrogate both cell-mediated and humoral vaccination responses. Additionally, we will test our hypothesis in human cells by determining how senescent cell conditioned media impact human T and B cells responses in culture. These approaches will allow us to examine the role of cellular senescence in impaired vaccination responses with aging and investigate the translational utility of senolytic drugs as a pre-vaccination adjuvant.

14. Project Title: **THE SENDEP STUDY: LINKING MOLECULAR SENESCENCE CHANGES TO DEPRESSION AND COGNITIVE IMPAIRMENT IN LATE LIFE**
Leader(s):   **DINIZ, BRENO SATLER**
UNIVERSITY OF CONNECTICUT SCH OF MED/DNT
NIH R01MH115953 / (2019 - 2023)

Core(s):

Project Summary Late-life depression (LLD) is a common mental disorder in the elderly, with prevalence rates ranging from 1 to 5%. Recent evidence suggests that LLD is linked to age-related negative health outcomes, such as cerebrovascular disease, increased risk of Alzheimer's disease, vascular dementia, and of premature mortality. The mechanisms of LLD are complex and involve the dysregulation of different biological pathways. Understanding the interplay between the biological changes in aging and depression can provide insight into the mechanisms by which LLD increases the risk of negative health outcomes. This study proposes to evaluate the association of Senescence-Associated Secretory Phenotype (SASP) Index with different clinical phenotypes of aging (i.e., cognitive impairment) and with cellular senescence phenotype (i.e., leukocyte telomere [LT] attrition) in LLD. Finally, we will evaluate the trajectory of changes in SASP, and its relationship with cognitive performance in these individuals. Our hypotheses are that LLD individuals will show a significantly higher SASP index compared to age- and gender-matched never-depressed control subjects. SASP index will be significantly associated with greater cognitive impairment and telomere attrition in LLD subjects. We further hypothesize that an increasing or persistently higher SASP index trajectory will lead to faster cognitive decline among study participants over two years of follow-up. To our knowledge, this will be the first study to examine the association between circulating molecular senescence markers (SASP), a cellular senescence marker (LT attrition), and neurocognitive and clinical characteristics in LLD. Based on the results of this study, we will also be able to identify novel targets for the development of interventions aiming not only the treatment of depression in the elderly but also aiming the prevention of the negative outcomes related to this condition.

15. Project Title: Can Senolytics Improve the Aged Response to Viral Infection

Leader(s):   HAYNES, LAURA ; XU, MING ;
UNIVERSITY OF CONNECTICUT SCH OF MED/DNT
NIH R21AG071292 / (2021 - 2023)

Core(s):

PROJECT SUMMARY Influenza (flu) is foremost among all infectious diseases causing death and disability in older adults, despite widespread vaccination programs. Age-related changes in the immune system contribute to declines in the ability to mount a highly protective immune response following flu infection in both humans and mouse models. With advancing age, we observe slower viral clearance and lingering lung inflammation, which could set the stage for secondary bacterial infection. Importantly, aging impacts almost every aspect of the adaptive immune response including generation of virus-specific CD4 and CD8 T cell effectors and high affinity antibody production. While flu infection is entirely localized to the lungs, functional decrements in skeletal muscle are also observed with upregulation of inflammatory and atrophy genes and downregulation of positive muscle regulators, ultimately resulting in loss of physical function. Importantly, the impact of flu infection on these molecular changes and overall functional declines is more pronounced and prolonged with aging, suggesting decreased physiologic resilience. Even though much research has been done, the ultimate cause of these age-related decrements has not been elucidated. One of the most prominent features of aging is the accumulation of senescent cells and in this project we will explore their role in the age-related changes in response to flu infection. Cellular senescence is characterized by irreversible growth arrest that occurs when cells experience a range of stresses. The number of senescent cells increases with chronological aging, resulting in many age-related pathologies and disease. Factors secreted by senescent cells can also have a direct impact on surrounding cells driving dysfunction and influencing cell subset differentiation. Interestingly, many of these factors are cytokines that are of vital importance for an effective anti-viral immune response. Senescent cells play a causal role in the progression of many age-related disorders, indicating that clearance of senescent cells might slow down the entire aging process. Importantly, we and others have started to develop drugs, which can specifically kill senescent cells (termed senolytics). Intermittent administration of senolytics can alleviate a range of age-related diseases. However, the impact of senolytics on immune system function in aged population has not yet been examined. The overall hypothesis that we will be addressing in this proposal is that senescent cells play a causal role in the age-related impaired response to flu infection. We will test this hypothesis by eliminating senescent cells in aged mice using senolytic drugs. This approach will allow us to simultaneously examine the role of cellular senescence in the compromised immune response and the associated changes in skeletal muscle and declines in physical function during flu infection in an aged mouse model.

16. Project Title: Using Senolytics to Improve Physical Function in Older Breast Cancer Survivors

Leader(s):   SEDRAK, MINA S
BECKMAN RESEARCH INSTITUTE/CITY OF HOPE

NIH R21CA277660 / (2022 - 2024)

Core(s):

PROJECT SUMMARY/ABSTRACT Breast cancer survivors experience steep and rapid declines in physical function within 3 to 12 months after cancer treatment. Cancer treatment impairs cardiovascular, neurologic, and musculoskeletal systems. Normally, these physiologic systems work in concert to enable physical function, and when one system is compromised, other systems compensate. However, when multiple physiologic systems are simultaneously compromised, patients develop impairments in physical function. Breast cancer survivors experience physical functional impairments at an earlier age and 2- to 4-fold more frequently than age-matched persons without cancer. In women over 65, functional decline may have far greater consequences than in younger adults; functional decline in older adults is linked to a loss of independence, disability, and death. No approved mitigating therapies are in place to treat or prevent functional decline. We hypothesize that cancer treatment-related functional decline can be alleviated by targeting fundamental aging processes, such as cellular senescence. Cellular senescence is a state of terminal growth arrest. Senescence results from both natural aging and chemotherapy. Senescent cells (Sncs) secrete proinflammatory factors (senescence-associated secretory phenotype, SASP) that cause tissue damage and age-related dysfunction. In mouse models, Sncs/SASP can be reduced by agents that selectively eliminate Sncs (senolytics). Senolytics alleviate frailty in mice and show promise in humans in multiple ongoing trials; senolytics reduce Snc burden in human fat tissue, decrease inflammation in older patients with diabetes, and reduce frailty in patients with pulmonary fibrosis. However, the ability of senolytics to reduce Sncs/SASP and, ultimately, improve physical function in older breast cancer survivors has not been tested. Our preliminary data provide evidence that older breast cancer survivors treated with chemotherapy (vs. no chemotherapy) have a higher systemic Snc burden (circulating Sncs/SASP markers) and that physical function and systemic Snc burden are linked. We hypothesize that targeting Sncs with senolytics will improve physical function and reduce systemic Snc burden in chemotherapy-treated older breast cancer survivors. We will test this hypothesis in a double-blind, randomized placebo-controlled trial of senolytic therapy vs. placebo in older (age >65) breast cancer survivors (n=44) who are 3 to 12 months post-chemotherapy completion and have diminished gait speed. Our specific aims are to determine the effects of senolytic therapy (vs. placebo) on physical function (Aim 1) and systemic Snc burden (Aim 2). This study will provide preliminary evidence for a large multi-center trial to establish the efficacy of senolytics in frail older breast cancer survivors. If successful, this would fill a crucial clinical need, as these women currently have no pharmacological options for the treatment or prevention of chemotherapy- induced functional decline. Moreover, since senescence underlies many of the mid and late-life chronic diseases, a safe senolytic that improves function would have a major positive impact that will extend far beyond oncology.

17. Project Title: **Geroscience Education and Training (GET) Network**
Leader(s): **KUCHEL, GEORGE A; ESPINOZA, SARA ELYSE; JUSTICE, JAMIE NICOLE; NEWMAN, JOHN C; PIGNOLO, ROBERT JOHN; UNIVERSITY OF CONNECTICUT SCH OF MED/DNT NIH R25AG073119 / (2021 - 2024)**

Core(s):

PROJECT ABSTRACT/SUMMARY Aging is by far the main risk factor for chronic conditions that jointly account for most morbidity, mortality, and health care costs. Geroscience-guided therapies seeking to alleviate such disorders as a group by targeting basic aging processes are now entering early stage clinical trials. The discovery, validation, and implementation into routine clinical care of such transformational therapies will require the creation of a robust and diverse geroscience workforce and training pipeline. The focus of this application is to address manpower, training, and educational gaps that were identified at a 2017 conference on this topic funded by an earlier Geroscience Network R24 grant (AG044396) with findings published in JAGS (Newman et al., 2019). We are now proposing to create the NIA Geroscience Education and Training (GET) Network through the R25 funding mechanism (PAR-20-095) as a complementary sister network to the Translational Geroscience Network (TGN; R33 AG061456), since educational, curricular, and training goals outlined in this proposal were not suitable for inclusion in a R33 grant. More specifically, we are proposing the creation of a network model designed to leverage and integrate relevant expertise, knowledge, and resources across multiple institutions and organizations to address the following Specific Aims: Aim 1: Develop shared geroscience curricula and educational materials initially targeting: 1A. Medical and 1B. PhD students needing foundational geroscience knowledge irrespective of career plans 1C. Geriatric Medicine Fellows who require a deeper level of geroscience knowledge Aim 2: Develop a Certificate in Geroscience Research Program to train the next generation of geroscience researchers by offering multidisciplinary training in geroscience. Track 1 will address the specific training needs of basic scientists Track 2 will focus on clinicians and others conducting human subject research. This cross-institutional program would be accessible to all eligible trainees wishing to pursue a career in geroscience. Aim 3:

Ensure optimal dissemination of the educational materials developed through this award. 3A. Videotaped lectures and other educational materials will be posted on POGOe with feedback surveys 3B. Our longer-range goal is to create a Geroscience Section in UpToDate an evidence-based, continually updated resource to ensure sustainability beyond the life of this NIA award

18. Project Title: **Microbiome Plasticity and Pathogenicity in Older Adults: Baselines and Transitions from Skilled Nursing Care**

Leader(s):   **OH, JULIA S; KUCHEL, GEORGE A; ROBISON, JULIE THOMPSON;**
JACKSON LABORATORY
NIH R56AG060746 / (2019 - 2023)

Core(s):

PROJECT SUMMARY Individuals =65 years of age are the fastest growing demographic in the US. This population is significantly understudied, highly vulnerable to disease and accounts for at least $400 billion in Medicare costs per year. There is critical need for new biomarkers and risk factors that impact geriatric health to better serve this burgeoning population. The microbiome the vast bacteria, fungi, and viruses inhabiting humans has a ubiquitous role in immune homeostasis, metabolism, and pathogen exclusion, but its dysfunction has also been linked to numerous disorders. Given that it can harbor pathogens, virulence and antibiotic resistance genes, and pro-inflammatory stimuli, it is believed that it is an important contributor to geriatric disease. The goal of this proposal is to understand microbiome plasticity of skin, oral and gut microbiomes in older adults who have been living at a skilled nursing facility (SNF) and then transition back to the community because transitions between care settings predisposes older adults to skin, lung, urogenital, and gastrointestinal infections and varied co-morbidities. Two complementary studies are proposed using systems- genomics approaches and longitudinal cohorts in community-dwelling (CD) and SNF-dwelling (SNFD) older adults. These studies will characterize the skin, oral, and gut microbiome dynamics of SNFD and CD cohorts using deep shotgun metagenomic sequencing, which will reconstruct bacterial, fungal and viral strains, as well as functional elements to establish baseline characteristics, stability, and frequency of pathogenicity reservoirs. Aim 1 will establish the existence of population-level differences between microbiome profiles for individuals residing in different SNFs with relative stability of these measures over time. Aim 1 will characterize the microbial dynamics and pathogenicity reservoirs of CD and SNFD older adults, testing the hypothesis that the microbiota of older SNFD adults will exhibit 1) altered diversity, 2) increased pathogenicity reservoirs, and 3) greater instability over time, which are established metrics of reduced gut health. These characteristics will be investigated during the transition from SNFD to CD in Aim 2, with the hypothesis that as older adults transition from SNFs to the community, their microbiomes will increasingly assume features observed among CD older adults. The existence of individual-level microbial plasticity in response to environmental factors will then be established as clinically stable SNF residents transition back to the community. Understanding longitudinal dynamics will provide new insights into the role of the microbiome as a biomarker for transitional outcomes and is the necessary prerequisite for prospective studies investigating the role of the microbiome in adverse events during transition. This proposal s multidisciplinary team has established SNF access, expertise in transition outcomes and geriatric care, clinical study design, and metagenomic sequencing and analyses. The finding this research will generate a new framework for understanding and investigating the geriatric microbiome and its predictive capacity in clinical outcomes.

19. Project Title: **Impact of AD/ADRD on Health-Related Outcomes in a Statewide Population Enrolled in a Publicly-Funded HCBS Waiver Program for Older Adults**

Leader(s):   **FORTINSKY, RICHARD H; ROBISON, JULIE THOMPSON;**
UNIVERSITY OF CONNECTICUT SCH OF MED/DNT
NIH RF1AG069839 / (2020 - 2024)

Core(s):

Project Summary Many states are aggressively reforming their long-term services and supports systems by constraining the growth of nursing homes and expanding availability of home and community-based services (HCBS) through Medicaid waiver programs, which intend to maximize independent living for individuals at risk for nursing home care. Eligibility criteria for Medicaid HCBS waiver programs include financial and health-related factors, the latter which typically include functional and cognitive deficits. Medicaid HCBS waiver program populations of older adults across the states include individuals living at home with and without diagnosed Alzheimer's disease and related dementia (ADRD) as well as with a wide range of cognitive deficits even without a diagnosis of ADRD. ADRD is associated with many adverse health-related outcomes in population-based studies of community-dwelling older adults; however, whether and how ADRD and cognitive impairment severity are associated with adverse outcomes among older adults receiving services from Medicaid HCBS waiver programs is unknown. Little is known about the strength of informal caregiver support systems and their effects on adverse outcomes for older adults with and without dementia in HCBS programs. Success in meeting self-identified goals of care among older Medicaid HCBS waiver participants, and barriers to achieving these goals, have also not been explored in the context of having ADRD. Moreover, how race and ethnicity might modify effects in associations between ADRD, informal support systems, and health outcomes is unknown in this population. We propose to address these important and interrelated knowledge gaps guided by person-centeredness and health disparities conceptual frameworks. We will study a statewide population enrolled in Connecticut's Home Care Program for Elders (CHCPE), the Medicaid HCBS waiver program for older adults. CHCPE has a racially and ethnically diverse population, and State Medicaid policy decision-makers have expressed strong interest in improving dementia care for CHCPE participants. In Connecticut, a person-centered approach to care planning and implementation guides all Medicaid HCBS waiver program policies and practices. Specific aims guiding this study are to, in the CHCPE participant population: Aim 1: Determine how living with ADRD is associated with health service utilization, including emergency department visits, hospitalizations, and post-acute or long-term admission to nursing homes. Aim 2: Determine whether strength of the informal caregiver support system is associated with utilization of all health services under study, according to ADRD status and racial and ethnic group membership. Aim 3: Determine how living with ADRD, and racial and ethnic group membership, are associated with meeting self-identified goals of care and person-centered outcomes based on their HCBS-related experiences. The study team will disseminate findings to state Medicaid officials and other stakeholders concerned with how best to help CHCPE clients living with ADRD avoid or delay adverse health outcomes and achieve self- identified goals of care. Dissemination activities also will include presentations at annual meetings of relevant national professional and scientific organizations, and publications in relevant peer-reviewed journals.

20. Project Title: **Precursors of Suicide in Older Adults Transitioning from Prison to Community**

Leader(s):   **BYERS, AMY LYNN; BARRY, LISA C;**

                 NORTHERN CALIFORNIA INSTITUTE/RES/EDU

                 NIH RF1MH117604 / (2018 - 2023)

Core(s):

PROJECT SUMMARY/ABSTRACT Factors including posttraumatic stress disorder (PTSD), traumatic brain injury (TBI), and depression are associated with an increased risk of developing cognitive impairment and Alzheimer s Disease. Each of these factors is over-represented among persons who are incarcerated. Moreover, incarcerated older adults (age 50 and older) experience early onset chronic conditions and geriatric syndromes at younger ages than the general population (accelerated aging). Yet, while increasing numbers of older adults are released to the community following incarceration, knowledge regarding dementia in this population is essentially non-existent. Using a unique national cohort developed through the parent R01 (MH117604), Precursors of Suicide in Older Adults Transitioning from Prison to Community, our objective in response to this Notice of Special Interest (NOT-AG- 008) is to characterize the burden of Alzheimer s disease (AD) and Alzheimer s disease-related dementias (ADRD) (hereafter also referred to as dementia), and mild cognitive impairment (MCI) and related diseases (e.g., Parkinson s) in older adults with a recent history of incarceration. We propose to determine the occurrence of dementia and MCI and related diseases in a national sample of veterans released from prison in later life (older reentry veterans), including descriptive epidemiology and examination of the clinical course (health care services use, suicide attempt, and mortality) in this vulnerable population. The overarching goals of the parent grant include (1) determining risk and precursors of suicide, death by unintentional injury, and suicide attempt after prison release; and (2) informing the prison-to-community transition by identifying health care use patterns related to outcomes in a highly vulnerable group. The proposed administrative supplement expands these goals specifically to reentry older adults who have AD/ADRD, MCI and related diseases. This research will generate hypotheses regarding unique aspects of the prison environment [e.g., chronic stress, sleep deprivation, sensory deprivation (among those exposed to solitary confinement)] that may contribute to the development of dementia, MCI and related diseases, and provide insight into unique aspects of the clinical course of dementia and related outcomes during the community reentry period stimulating

novel, and important inquiries for future funded research. We will achieve this by leveraging our (parent grant) national cohort of older reentry veterans and determine incidence and prevalence of AD/ADRD, MCI and related diseases overall and by sociodemographic and clinical factors (Aim 1). In addition, among older reentry veterans with AD/ADRD, MCI and related diseases, we will characterize medication and health services use patterns (Aim 2) and evaluate prognostic factors for predicting risk of suicide attempt and mortality, including death by suicide and unintentional injury (Aim 3). Findings from this project will cultivate future research directions and inform stakeholders involved in transition of care planning and suicide prevention in older adults returning from prison to community living with dementia.

21. Project Title: A deep longitudinal analysis of next generation influenza vaccines in older adults

Leader(s):   **UCAR, DUYGU ; GARCIA-SASTRE, ADOLFO ; KUCHEL, GEORGE A;**
JACKSON LABORATORY
NIH U01AI165452 / (2022 - 2026)

Core(s):

PROJECT SUMMARY The WHO estimates that annual epidemics of influenza result in 3-5 million cases of severe illness and 300,000- 500,000 deaths. 90% of influenza-related deaths occur in older adults despite widespread vaccination programs with vaccines tailored for this high-risk group. The estimated effectiveness of the influenza vaccine in the U.S. for the 2018-2019 influenza season overall was 47%, but only 12-13% in older adults. There is therefore an urgent need to understand the mechanisms that are turned on/off in older adults that result in their limited response rate to the most commonly used influenza vaccine, Fluzone High-Dose. There is also a need to understand whether and why next-generation influenza vaccines might be more efficacious. Immunosenescence is known to be associated with declines in optimal B cell and T cell adaptive immunity, however, our overall understanding of the mechanisms of immunosenescence is incomplete. The central goal of this proposal is to understand the mechanisms that lead to a loss of response to influenza vaccine in older adults through establishment of the 3FluAging cohort of healthy older adults who will be vaccinated with three different influenza vaccines three years in a row. We hypothesize that aging impacts specific regulatory mechanisms of humoral immunity to reduce vaccine effectiveness. In Aim 1, we will establish a cohort of 60 healthy older adults (=65yrs) who will sequentially receive three different annual influenza vaccines, with serial blood and microbiome sample collection during three years of follow-up. Participants will undergo regular clinical assessments. In Aim 2, we will decipher the magnitude and immunodominance pattern of the humoral response to influenza virus in healthy older individuals upon vaccination. For each vaccine, we will characterize antibody titer and quality and will define responders and non-responders. In Aim 3, we will characterize the epigenome, transcriptome, cytokine production, and cell proportions of blood leukocytes in vaccinated healthy older participants. We will identify specific (epi)genomic and functional signatures, and their longevity, associated with vaccine response. We will also sequence all participants to uncover the role of genetic variation on influenza vaccine responses. In Aim 4, we will assess the function of T helper cells and antigen presenting cells, specifically dendritic cells, in influenza vaccine responders and non-responders. By identifying responders and non-responders for each vaccine and integrating these data with baseline immune status multi-omic signatures, we will determine which immune features can predict vaccine responsiveness. We expect to identify humoral immunity pathways that are altered in aging that can be used as the basis for designing novel approaches to boost efficacy of the most commonly used, as well as emerging, influenza vaccines.

22. Project Title: NIA AD/ADRD Health Care Systems Research Collaboratory

Leader(s):   **MOR, VINCENT ; MITCHELL, SUSAN L;**
BROWN UNIVERSITY
NIH U54AG063546 / (2019 - 2024)

Core(s):

PROJECT SUMMARY Over five million Americans have Alzheimer's disease (AD) or an AD-related dementia (AD/ADRD). These high- need, high-cost patients are vulnerable to receiving poor quality, uncoordinated care, ultimately leading to adverse health outcomes, poor quality of life, and misuse of resources. As recently concluded by the federally-funded Research Summit on Dementia Care, improving the care of PWD and their CGs is an urgent public health challenge that must be met and informed by high quality evidence. While prior research has elucidated opportunities to improve the care of PWD and their CGs, the adoption of promising interventions has been stymied by the lack of research evaluating their effectiveness when implemented under real-world conditions. Pragmatic clinical trials embedded (ePCTs) in healthcare systems (HCS) have the potential to accelerate the translation of evidence-based interventions into clinical practice. Since its inception in 2012, the NIH Common Fund HCS Research Collaboratory has made pivotal contributions towards advancing the conduct of ePCTs. However, as concluded in a 2017 NIA-sponsored conference, ePCTs conducted with PWD and their CGs have unique considerations that merit specific focus. Thus, the overarching objective of this proposal is to build on the model of the NIH Collaboratory to establish the National Institute on Aging (NIA) AD/ADRD Research Collaboratory, co-led by the multiple principal investigators (MPIs), Drs. Vince Mor (Brown University) and Susan Mitchell (Hebrew SeniorLife (HSL)) and co-administered by their respective institutions. The Aims are: 1. To establish the infrastructure of the AD/ADRD Collaboratory, 2. To develop and disseminate guidelines for the conduct of all aspects of ePCTs among PWD and their CGs in partnership with HCS, 3. Enhance research development and investigator capacity to conduct ePCTs in PWD and their CGs within HCS, and 4. To disseminate knowledge and best practices to engage stakeholders in this research. Accomplished investigators from across the nation will lead the following Working Group Cores: 1. Technical and Data (B), J. Bynum, MD, MPH; 2. Regulation and Ethics (C), J. Karlawish, MD; 3. Design and Statistics (D), H. Allore, PhD; 4. Pilot Studies (E), A. Brody, PhD, RN; 5. Patient and CG Reported Outcomes (F), L. Hanson, MD, MPH; 6. Dissemination and Implementation (G), L. Gitlin, PhD/J. Gaugler, PhD; 7. HCS (H): E. Larson, MD, MPH, and Training (I): C. Callahan MD/A. Torke MD. An Administration Core (A) will integrate all critical functions across the Collaboratory. IMPACT: There is an urgent need to improve care provided by HCS for PWD and their CGs. ePCTs conducted are ideally-suited to test the effectiveness of interventions aimed at improving their health outcomes but require specific expertise, methodology, data sources, and industry partnerships. The knowledge, investigative experience, collaborations, and evidence generated by an AD/ADRD Collaboratory has the potential to transform the delivery, quality, and outcomes of care for Americans from all backgrounds with AD/ADRD and their CGs.

23. Project Title: **The KAPP-Sen Tissue Mapping Center Collaborative**
Leader(s): **KUCHEL, GEORGE A; GAROVIC, VESNA D; MUSI, NICOLAS ; ROBSON, PAUL ;**
UNIVERSITY OF CONNECTICUT SCH OF MED/DNT
NIH U54AG075941 / (2021 - 2026)

Core(s):

PROJECT SUMMARY OVERALL This proposal seeks to establish the KAPP-Sen Tissue Mapping Center Collaborative (TMC) as part of the Cellular Senescence Network: Tissue Mapping Centers effort {RFA-RM-21-008). Our application represents a multidisciplinary collaborative effort involving six leading institutions and aging research programs working together to characterize the distribution and biological heterogeneity of senescent cells in different healthy human tissues in full alignment with the objectives of the Cellular Senescence Network {SenNet). KAPP-Sen brings together skills, resources and perspectives needed to address Sen-Net goals in the framework of the healthy human Kidney. Adipose tissues, Pancreas and Placenta. Given our ability to obtain full thickness skin tissues from individuals providing KAPP samples, we may explore the possibility of future collaborative studies with TMCs selected for their major focus on skin. Our six collaborating institutions located in Farmington. CT (UConn Health, Jackson Laboratory for Genomic Medicine), Boston {Brigham & Women's Hospital, Joslin Diabetes Center), Rochester. MN {Mayo Clinic) and San Antonio. TX {UTHCSA) have all been carefully selected for their essential and unique individual contributions to the field and this effort. Our objectives will be achieved through the following aims: Aim 1 : Coordinate research activities across KAPP-Sen TMC Collaborative sites in support of Sen-Net goals towards mapping cellular senescence and its associated secretory phenotype in the healthy human kidney, adipose tissues, pancreas and placenta. Aim 2: Obtain tissues from healthy kidney transplant donors {kidneys, fat, skin), C-section pregnancies {placenta, cord, fat, skin), outpatient healthy donor biopsies {fat, skin), beating heart brain dead donors {full pancreas) and IIPD/Prodo {dispersed pancreas). Aim 3: Generate highest quality data pertaining to cellular senescence including scRNA-Seq, snRNA-Seq, spatial transcriptomics, immunohistochemistry and Telomere-associated DDR foci {TAFs) in all tissues Aim 4: Perform high level integrative data analysis required for the creation of aUases of human cellular senescence in collaboration with other TMCs, CODDC and NIH staff.

24. Project Title: **Bio-Analysis Core**
     Leader(s):   **KUCHEL, GEORGE A**
                          UNIVERSITY OF CONNECTICUT SCH OF MED/DNT
                          NIH U54AG075941 / (2021 - 2026)

Core(s):

The KAPP-Sen Tissue Mapping Center (TMC) Biological Analysis Core will be responsible for generating high-resolution and high-content datasets to define senescent cells and their microenvironment in aged non-diseased human tissues, and measure how such cells compare across a range of ages. We will utilize state-of-the-art single cell technologies on dissociated tissues and on intact tissue sections to study this biology. We will coordinate with our KAPP-Sen Biospecimen Core to obtain high-quality human normal kidney, pancreas, placenta, and adipose tissue. By employing unbiased, sequencing-based, single-cell resolution methods, we will generate high-content spatially resolved data to enable the identification of senescent cells. We will work with our KAPP-Sen Data Analysis Core to discover comprehensive mRNA biomarkers for human senescent cells. A selection of target epitopes derived from these biomarkers will be detected within tissue sections at high resolution (1 m) utilizing a highly multiplex antibody imaging approach. Additional tangential experiments in human tissues and ex vivo and induced pluripotent stem cell (iPSC) models will further inform and validate senescence signatures, and identify associated epigenomic features, within intact human tissues. The Biological Analysis Core will achieve its objectives through the following Aims: Aim 1. To establish optimal tissue dissociation and preparation techniques to implement both dissociative and spatially-resolved single-cell transcriptome methods for the identification of senescent cells in human tissues. Aim 2. To scale and standardize the pipeline to generate high-quality, high-resolution, and high-throughput datasets and construct maps of cellular senescence in the four target tissues. Aim 3. To identify mRNA biomarkers of human senescent cells and construct and apply a multiplex antibody panel derived from these. Aim 4. Leverage ex vivo human models to further characterize the functional features of senescent cells. Together, this analytic approach will define the comprehensive tissue signature of senescence at 1 m resolution and begin to uncover the molecular foundations of the senescent cell and its response to therapy. In addition, the data set generated will provide insight into senescence-associated secreted proteins that may inform the design of blood biomarker of senescence. Altogether, our approach and its associated tools will be applicable across a wide array of human tissues types.

PUBLICATIONS

2023

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    Front Immunol, 2022, 13: 1006710
    https://doi.org/10.3389/fimmu.2022.1006710 | PMID: 36119079 | PMCID: PMC9473698
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    Citations: 5 | AltScore: 191.118

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RECOGNITION AND AWARDS (2022-2023)

<u>Cristina Colón-Semenza, PT, MPT, PhD</u> (2023)

- 2022 National Institute on Aging, Research Centers Collaborative Network, Early Career Investigator Travel Award
- 2023 University of Connecticut, College of Agriculture, Health & Natural Resources, Justice, Equity, Antiracism, & Inclusion award.
- 2023 American Physical Therapy Association, Academy of Leadership & Innovation, Social Responsibility award for poster presentation.

<u>David Steffens, MD</u> (2022)

- 2022 Distinguished Life Fellow of the American Psychiatric Association
- 2023 UConn Health Chapter of the Alpha Omega Alpha Honor Medical Society

<u>George Kuchel, MD CM, FRCP, AGSF, FGSA</u> (2022)

- Co-Mentor, Po-Jung Chen, DDS, MDS, MDentSc, John Haddad Young Investigator Award, ASBMR
- Elected Member, The Academy for Health and Lifespan Research
- 2023 Institute for Collaboration on Health, Intervention, and Policy (InCHIP) Excellence in Faculty Mentoring Award

<u>Jacob Earp, Ph.D</u> (2023)

- 2022 Selected for the National Coordinating Center for Older Adults Independence Centers Early Career Visiting Scholar Exchange Program
- 2023 Selected for the National Institute of Aging's Butler Williams Scholar Program

<u>Julie Robison, PhD</u> (2023)

- Southern Gerontological Society: The Gordon Streib Academic Gerontologist Award.

MINORITY RESEARCH

General Brief Description of Minority Activities:

General Brief Description of Minority Activities:

Project # 1

Rupal Parekh, PhD, Assistant Professor , UConn School of Social Work; Christine Tocchi, PhD, UConn School of Nursing (co-PL)

Re-Engaging Black/African American Older Adults During the COVID-19 era: Developing A Community-Based Intervention

The sudden closure of churches and senior centers caused by the COVID-19 pandemic has disproportionately impacted the health and well-being of communities of color, particularly Black/African American older adults. Prior to the pandemic these community centers provide social engagement by

As churches and senior centers have reopened and resumed their services, African American older adults have either completely become disengaged or utilize the senior centers/churches less frequently than they did prior to the pandemic. This study will develop a psychoeducational intervention to add

Project # 2

Cristina Colòn-Semenza, Assistant Professor Department of Kinesiology, UConn College of Agriculture, Health & Natural Resource

Peer coaching to improve physical activity in older Latinx adults with Parkinson's disease

Conservative projections estimate the number of people living with Parkinson disease (PD) will rise to 1.2 million in the United States and 9.3 million in the most populous nations by 2030. This disease disproportionately affects older adults with incidence and prevalence drastically increasing from the sixth to ninth decades. There is

Physical activity not only reduces risk of this debilitating disease but may also reduce disease progression. Therefore physical activity, specifically in the form of physical therapy, is recognized as a critical component of effective disease management. However, Latinx people living with PD, are less likely to receive physical therapy t

Minority Trainee(s):

● Cristina Colòn-Semenza, Assistant Professor Department of Kinesiology, UConn College of Agriculture, Health & Natural Resources
Dr. Colòn-Semenza is a physical therapist whose current research career is focused on improving motivation and engagement with exercise and physical activity in the management of neurological disease and disorders. In January 2022, Dr. Colòn-Semenza was named as a UConn Pepper Scholar. In addition, she recently received a

Minority Grant(s):

1. **Project Title:**   **Cardiac Dysfunction in Older Sepsis Survivors**
   Leader(s):   **MANKOWSKI, ROBERT TOMASZ**
       UNIVERSITY OF FLORIDA
       American Heart Association (AHA) 18CDA34080001 / (2018-2021)

   As a result of sepsis, approximately 30% of older Americans (age >65 years) have elevated levels of systemic inflammation at discharge from the intensive care unit (ICU) and die from cardiovascular (CV) events, including congestive heart failure, within 12 months. Although recently improved implementation of evidence-base high-risk new population for cardiac disease and death within 12 months post-sepsis. Cardiac dysfunction after discharge (i.e., impaired cardiac contractility) that may lead to cardiomyopathy and heart failure after sepsis, however, has not been characterized in this high-risk population. Novel measures of myocardial contractility the infrastructure of the NIH-funded project (P50GM111115202) at the University of Florida that is currently successfully enrolling and following sepsis patients for up to 12 months. For the proposed pilot study, we will perform biventricular myocardial contractility analyses and peripheral blood analyses for pro-inflammatory cy and help develop anti-inflammatory interventions to lower the CV risk in older sepsis survivors. (AHA Program: Career Development Award)

2. **Project Title:**   **Role of PFKFB3 in peripheral artery disease**
   Leader(s):   **RYAN, TERENCE**
       UNIVERSITY OF FLORIDA
       American Heart Association (AHA) 18CDA34110044 / (2018-2021)

   Peripheral artery disease (PAD) is a leading cause of atherosclerotic cardiovascular disease death which is estimated to affect more than 20% of individuals older than age 60 (~200 million people worldwide). PAD is defined as a blockage in the peripheral arteries which results in decreased blood flow to the lower legs. Patients w interventions aimed to improve blood flow to the leg, but mortality rates in PAD remain high (50% within 10 years of diagnosis). The low success rate of PAD therapies indicates that restoration of blood flow alone is not sufficient to rescue the limb, implying that factors other than limb perfusion regulate the limb's response to i systemic glycolytic flux display complete protection from ischemic muscle necrosis; (ii) among the genes responsible for elevated glycolytic flux, PFKFB3 is required for ischemic protection; and (iii) PFKFB3 protein expression is decreased in severe PAD patients. Based on these discoveries, we hypothesize that glycolytic met through metabolomics/proteomics experiments. This work will advance fundamental knowledge on ischemic cell metabolism, develop novel gene therapies, and offer mechanistic insight applicable to multiple diseases and tissues.

3. **Project Title:**   **Calf Muscle Mitochondrial Dysfunction and Impaired Autophagy in Peripheral Artery Disease**
   Leader(s):   **LEEUWENBURGH, CHRISTIAAN**
       UNIVERSITY OF FLORIDA
       American Heart Association (AHA) 18SFRN33900136 / (2018-2022)

   Lower-extremity peripheral artery disease (PAD) results in ischemia-reperfusion-induced oxidative stress in calf skeletal muscle and reduced skeletal muscle metabolic activity, but the specific mitochondrial defects and their association with functional impairment and decline in people with PAD are not established. In this basic transport chain (ETC) proteins have greater damage, resulting in poorer ETC function in PAD compared to those without PAD. In Aim 1B, we will investigate the D-loop region of mtDNA involved in regulating mtDNA replication, to determine if the increased mtDNA abundance in PAD is due to oxidative stress. Aim 1C will i of >0.20 between their legs. We will determine whether: a) the leg with lower ABI (more ischemia) has greater mitochondrial abnormalities than the leg with higher ABI (less ischemia); b) mitochondrial abnormalities are associated with greater functional impairment and faster functional decline in PAD participants; and c) PAD associated with skeletal muscle pathophysiologic changes in PAD. Results are expected to identify new potential targets for interventions that may improve functional performance and prevent functional decline in PAD. (AHA Program: Strategically Focused Research Network)

4. **Project Title:**   **Longitudinal Modeling and Sequential Monitoring of Image Data Streams**
   Leader(s):   **QIU, PEIHUA**
       UNIVERSITY OF FLORIDA
       National Science Foundation 1914639 / (2019-2022)

   In imaging applications related to earth and environmental monitoring, manufacturing industries, medical studies and many others, collected image data are often in the form of data streams in the sense that new images are acquired sequentially over time. In such applications, one fundamental task is to monitor the image sequen distributed freely for convenient use by practitioners. A web portal will also be developed for individual researchers to try the proposed methods. The PI plans to integrate the research results into educational activities, including the development of new curriculum modules, the mentoring of Ph.D. students, and outreach to local h model for describing observed images in a given time interval is flexible, and its estimation procedure has the edge-preservation property while removing noise. It can accommodate both geometric misalignments among observed images and spatio-temporal data correlation in the observed image data. The proposed image monit

5. **Project Title:**   **FLUAD? vs. Fluzone? High-Dose Study**
   Leader(s):   **SCHMADER, KENNETH**
       DUKE UNIVERSITY
       Centers for Disease Control and Prevention 200-2012-53663 / (2016-2021)

   The objective of this randomized controlled clinical trial is to compare the reactogenicity, safety, and effect on functional status and quality of life in older adults of the high dose influenza vaccine (Fluzone?) versus the MF-59 adjuvanted influenza vaccine (FLUAD?). In this randomized safety trial of 757 older adults (adjuvantec acceptable option to prevent influenza in older adults.

6. **Project Title:**   **Mitochondrial Function in Postmortem Muscle**
   Leader(s):   **SCHEFFLER, TRACY**
       UNIVERSITY OF FLORIDA
       United States Department of Agriculture 2017-67017-26468 / (2017-2021)

   Our goal is to understand how mitochondria influence postmortem metabolism and tenderization, in order to optimize meat quality and value. Living muscle relies primarily on mitochondria and aerobic metabolism for energy; ATP is necessary for muscle contraction and relaxation, and to fuel active transport and maintain ion g and result in pH declining to a final or ultimate pH (pHu) near 5.6. At this point, ATP is exhausted and no longer generated, and rigor is complete and additional ATP is not generated by metabolism. The rate and extent of metabolic processes postmortem significantly impact water holding capacity, color, and protease-mediated t properties influence mitochondria function and integrity. Our objectives are to evaluate changes in mitochondrial function in oxidative and glycolytic muscles during the first 24h postmortem determine mitochondrial function in oxidative and glycolytic muscles under pH and oxygen tension conditions that simulate postmortem n

7. **Project Title:**   **Identifying Genes That Regulate Mitochondrial Positioning at the Synapse During Aging**
   Leader(s):   **HAN, SUNG MIN**
       UNIVERSITY OF FLORIDA
       American Federation for Aging Research (AFAR) AGR00015406 / (2019-2021)

   A decline in the functions of the nervous system is a hallmark of aging, and can lead to many age-related changes in balance, mobility, hearing, vision, smell, and taste. The function of the nervous system depends on the maintenance of synapses-the special contact area where neurons communicate with other neurons. Many lines mediate mitochondrial positioning at synapses and how aging affects this regulation remain unclear. Our goal is to uncover the underlying mechanisms that regulate mitochondrial positioning and function at the synapse during the aging process. My proposed aims are based on my hypothesis that mitochondrial localization at the mitochondrial localization at the synapse, we have established an innovative visual genetic screen for assessing mitochondrial distribution in the AIY interneuron of Caenorhabditis elegans. We anticipate that these screens will identify novel molecules that regulate mitochondrial targeting or anchoring at the synapse. As evidence understanding the maintenance of synaptic function in aging and other neuronal diseases associated with abnormal mitochondrial positioning and function.

8. **Project Title:**   **The Impact of Reactogenicity of the Recombinant Zoster Vaccine on the Physical Functioning and Quality of Life of Older Adults**
   Leader(s):   **SCHMADER, KENNETH**
       DUKE UNIVERSITY
       Glaxo Smith Kline GSK Zoster 063 / (2017-2019)

   Herpes zoster and its related complications are associated with significant medical burden, which negatively affects quality of life and daily functioning of older patients. The recently licensed recombinant zoster vaccine (RZV) offers high efficacy but is associated with local and systemic reactions. This study assessed the impact Functioning scale scores from pre- to post-RZV dose-1 were observed over a 7 day period post-vaccination.

9. **Project Title:**   **CEREBRAL NETWORKS OF LOCOMOTOR LEARNING AND RETENTION IN OLDER ADULTS**
   Leader(s):   **CLARK, DAVID J**
       VETERANS HEALTH ADMINISTRATION
       VA I01RX003115 / (2019-2023)

   Aging often leads to substantial declines in walking function, especially for walking tasks that are more complex such as obstacle crossing. This is due in part to a lack of continued practice of complex walking (sedentary lifestyle) combined with age-related deficits of brain structure and the integrity of brain networks. Neuroreha is a need for research to develop strategies for enhancing motor learning of walking (?locomotor learning?) in order to improve the effectiveness of neurorehabilitation. The objective of this study is to use non-invasive brain stimulation to augment locomotor learning and to investigate brain networks that are responsible for locor proposed study is designed to address this gap. Our pilot data from older adults shows that prefrontal transcranial direct current stimulation (tDCS) administered during learning of a complex obstacle walking task contributes to multi-day retention of task performance. In the proposed study we will build upon this pilot work by c with individual differences in baseline and practice-induced changes in brain measures (working memory, gray matter volume, task- based prefrontal activity, and brain network segregation). Specific Aim 3: Investigate the extent to which tDCS modifies resting state network segregation. We anticipate that prefrontal tDCS will a

10. **Project Title:**   **EXPLORING THE EFFECTS OF EXERCISE TRAINING ON PTSD SYMPTOMS AND PHYSICAL HEALTH IN OLDER VETERANS WITH PTSD**
    Leader(s):   **HALL, KATHERINE SHEPARD**
        DURHAM VA MEDICAL CENTER
        VA I01RX003120 / (2020-2024)

    Posttraumatic stress disorder (PTSD) is prevalent among military Veterans, and affects over 30% of older, Vietnam-era Veterans. These servicemembers have endured nearly 40 years with these symptoms, and as a result, have significantly poorer health, higher rates of chronic disease and obesity, and an excess mortality rate 3 pilot studies of exercise and PTSD have been published, and all suffer a major limitation: a singular focus on outcomes ?above the neck.? These studies do not report the impact of exercise on physical health- and mobility-related outcomes that contribute to long-term impairment and disability in Veterans with PTSD. There hav group (HA-ATC). This study will be a randomized controlled trial of a 6-month, supervised exercise program among 188 Veterans ?60 years of age with PTSD at the Durham VAHCS. Participants will be randomly assigned to Supervised Exercise or HA-ATC. The exercise arm will include 3 weekly exercise sessions, each one packets, email newsletters, webinars, and group video telehealth sessions. Participants in the Exercise intervention arm will receive an individualized exercise prescription based on the individual?s exercise history, current exercise capacity, personal preferences, and current health status. This will be a multicomponent program primary outcome for this study will be PTSD symptoms assessed with the CAPS-5. Physical function, another outcome of primary interest will be measured objectively with a Physical Performance Battery. This test battery assesses aspects of daily function including balance (single leg stance), gait speed (4 meter walk), and ch Mixed linear models will be used to compare outcomes for the two study arms.

11. **Project Title:**   **AEROBIC EXERCISE AND COGNITIVE TRAINING IN OLDER ADULTS**
    Leader(s):   **NOCERA, JOE ROBERT**
        VETERANS HEALTH ADMINISTRATION
        VA IK2RX000744 / (2012-2018)

providing spiritual healing, health-related education, social interaction and activities and political activism. With the closure of these resources, African American older adults involuntary disengaged their involvement. Previous research shows such disengagement is associated with a decrease in quality of l
ress the needs and concerns of African American older adults as a means of preventing or reducing depressive symptoms and physical disability.

also ethnic variation in the incidence of this progressive neurological disorder, with Hispanics experiencing the highest rates in the US.

reatment compared to Caucasians. In fact, older Latinx adults without PD have significantly lower rates of physical activity compared with non-Hispanic whites. Cultural and disease-related barriers compound inactivity and inhibit optimal disease management.

Pre-K Scholar Career Development Award.

d ICU care has resulted in decreased early hospital mortality in older adults, many survivors become chronically critically ill (CCI) with persistent inflammation and fail to recover. CCI patients are defined as patients who remain in the ICU for more than 14 days with organ failure, in contrast to those who experience rapid recovery (RA
by speckle-tracking echocardiography can detect clinically meaningful dysfunction undetectable by conventional echocardiography (i.e., ejection fraction). Therefore, we propose an observational pilot study to test our central hypothesis that the persistent systemic inflammation that occurs in CCI patients following sepsis is associated v
tokine levels in a subset of older (>65 years) sepsis patients (CCI=40 and RAP=40) enrolled in the parent P50 study at discharge (RAP) or at day 14 in ICU (CCI) and 3 months after sepsis onset. This research project is in close alliance with the mission of the American Heart Association because of the high risk of cardiac events and de

with PAD present clinically with symptoms ranging from mild discomfort to unbearable ischemic rest pain and gangrene. Recent clinical work has demonstrated that patients with similar limb blood flow can have markedly different symptoms, suggesting that the patients' response may be dependent on genetic mechanism(s) regulating tl
ischemia. This proposal seeks to address this knowledge gap by advancing the fundamental knowledge on ischemic cell metabolism in both skeletal muscle and endothelial cells, with a long-term goal of developing novel therapies to improve ischemic outcomes in PAD and other ischemic disease. This proposal focuses on the role of gly
abolism, driven by PFKFB3 expression, regulates muscle cell survival and angiogenesis in ischemia. We will test this hypothesis using the following: Aim 1 will determine if loss of PFKFB3 expression increases ischemic pathology; Aim 2 will determine if overexpression of PFKFB3 is protective against ischemic injury; and Aim 3 wil

science research study of Northwestern Universitys Strategically Focused Research Network (SFRN), we will delineate the specific mitochondrial abnormalities in calf muscle of people with PAD. In Aim 1, we will analyze calf-muscle biopsy specimens stored at Northwestern from 75 well-characterized people with and without PAD. .
investigate whether autophagy, the process that removes damaged mitochondria is incomplete in PAD. In Aim 2, we will analyze calf-muscle biopsies collected in the SFRNs population/epidemiology study (PI Greenland). This project will recruit 50 participants with PAD and 50 without PAD and follow them longitudinally with baseli
participants have more adverse changes in their muscle at 2-year follow-up than non-PAD participants. In Aim 3, we will analyze calf-muscle biopsies from the NICE trial (PI McDermott) to determine whether the NICE Trial interventions significantly increase activity of pathways involved in mitochondrial biogenesis and metabolic h

ce to see whether the underlying longitudinal process of the observed images changes significantly over time. This project aims to develop novel and effective statistical methods for answering this question. Because of the wide applications of image sequence monitoring, this project will have broader impacts on society through its applic
igh schools students for after-school activities to raise their interests in data modeling and scientific research, and contribute to the workforce development in Science, Technology, Engineering and Mathematics. This project aims to develop a flexible longitudinal modeling approach and an effective sequential monitoring scheme for ana
oring approach can account for dynamic longitudinal patterns of the observed image data streams. To this end, image pre-processing, including image denoising and image registration, will be performed properly before image monitoring. The proposed methods will consider both cases where the observation times are equally or unequall

l inactivated influenza vaccine, trivalent [aIIV3], 378; high dose inactivated influenza vaccine [HD-IIV3], 379), the proportion of participants with moderate-to-severe injection-site pain (primary outcome) was not higher after aIIV3 than HD-IIV3. No vaccine-related serious adverse events occurred. Post-vaccination HRQOL impact wa

radients. In fact, mitochondrial density varies in muscle cells and is a key factor influencing energy producing capacity. At slaughter, exsanguination eliminates the blood supply to muscle cells, and oxygen is no longer delivered to mitochondria for oxidative phosphorylation. Anaerobic glycolysis predominates in the postmortem period;
enderization of meat. Because the oxygen supply to muscle is removed at harvest, the contribution of mitochondria to postmortem metabolism and meat quality has been largely disregarded. However, the role of mitochondria in cellular function and homeostasis is multifaceted and extends beyond ATP production. Our overall objective
muscle assess mitochondrial respiration and postmortem metabolism in longissimus muscles with varying mitochondrial content.

s of?evidence suggest that the function and structure of synapses change with aging. At the synapse, mitochondria remain tightly packed to supply adequate energy and maintain calcium homeostasis. These mitochondrial functions are required to support synaptic function. Despite clear evidence supporting the important role of mitochon
synapse is actively regulated by currently unknown molecules in response to local demand for mitochondrial support and function. We will apply our expertise in cell biology and our novel imaging approaches to discover short- and long-term changes in mitochondrial behavior at synapses in a wide range of genetic backgrounds in respo
supporting the strength and feasibility of this approach, our unsaturated pilot screens have already identified several mutants with abnormal mitochondrial targeting to the synapse. Successful completion of the proposed research will substantially increase the knowledge base of how synaptic mitochondria respond to aging. We expect tl

of RZV on the quality of life and daily functioning of 400 older participants. Grade 3 reactogenicity occurred in 9.5% of participants and was associated with a transient clinically important decrease in SF-36 Physical Functioning score (affecting activities such as walking, carrying groceries, climbing stairs) and the EQ-5D-5L on Days

bilitation can contribute to recovery of lost walking function in older adults, but major and persistent improvements are elusive. A cornerstone of neurorehabilitation is motor learning, defined as an enduring change in the ability to perform a motor task due to practice or experience. Unfortunately, in most clinical settings, the time and co
motor learning in mobility-compromised older adults. We have shown that frontal brain regions, particularly prefrontal cortex, are crucial to control of complex walking tasks. Our neuroimaging and neuromodulation studies also show that prefrontal cortex structure and network connectivity are important for acquisition and consolidatio
conducting a full scale trial that also investigates mechanisms related to brain structure, functional activity, and network connectivity. We will address the following specific aims: Specific Aim 1: Determine the extent to which prefrontal tDCS augments the effect of task practice for retention of performance on a complex obstacle walkin
ugment retention of locomotor learning, and that our data will provide the first evidence of specific brain mechanisms responsible for locomotor learning/retention in older adults with mobility deficits. This new knowledge will provide a clinically feasible intervention approach as well as reveal mechanistic targets for future interventions

times higher than the general population. Clearly PTSD is more than just a psychological disorder. There is evidence to suggest that the pathway from PTSD to poor health is mediated by behavioral risk factors, such as exercise. Structured exercise is a highly effective, pluripotent strategy for the prevention, treatment, and management c
e been no studies of exercise and PTSD done in older adults, representing a significant research gap. This research examines a wellness-based approach to promoting health in older Veterans with PTSD, targeting exercise, a major modifiable risk factor. The objective of this study is to compare the impact of a supervised exercise progran
lasting approximately 60 minutes, led by an exercise specialist. The HA-ATC will receive a health education program and materials modeled on the 10 KeysTM to Healthy Aging curriculum and the National Council on Agings Aging Mastery Program. The HA-ATC will include an 8-week face-to-face group program followed by 4 mc
that includes a selection of 8 to 12 strengthening, balance, and flexibility exercises targeting the major muscle groups as well as primary joints. Participants will also be instructed in endurance exercise, including treadmill walking or recumbent bicycle. The exercise protocol will consist of a 5-10 minute warm-up, followed by a series of
air stands (# in 30 seconds). Aerobic endurance, the investigators primary functional outcome, will be assessed with the 6-minute walk test (6MWT). Secondary outcomes include depression, sleep, and cognitive function. Outcomes will be assessed at baseline, 3 months, and 6 months. Assessments will be repeated 12 weeks post-interve

ife and negative mental and health outcomes.

P). Due to persistent inflammation, we believe that older CCI patients represent an extremely
with impaired myocardial contractility over 3 months after sepsis onset. We will capitalize on
aths among older adults after sepsis. A future long-term study may help predict heart failure

e limbs response to decreased blood flow. The current treatments for PAD include surgical
olytic metabolism in the ischemic limb based on the following discoveries: (i) mice with elevated
l identify novel metabolic targets/pathways regulating ischemic pathology in human PAD samples

Aim 1A will test the hypothesis that mitochondrial (mt)DNA regions that encode the electron
e and 2-year follow-up biopsies. Of those with PAD, 30 will have an Ankle-Brachial Index (ABI)
ealth, compared to placebo. This projects overall goal is to identify specific mitochondrial defects

ations in different disciplines and areas. Open source R packages will be developed and
lyzing image data streams, and study their statistical properties. The proposed longitudinal
y spaced.

s similar between aIIV3 and IIV3-HD groups. From a safety standpoint, aIIV3 or HD-IIV3 is an

breakdown of glycogen generates lactate and H+, which accumulate in postmortem muscle
is to define how postmortem conditions and inherent muscle metabolic and contractile

dria at synapses, and the effect aging has on synaptic function, the molecular mechanism(s) that
onse to aging and acute mitochondrial stressors. To reveal new mechanisms that mediate
is research to have widespread implications in the neurobiology of aging, particularly in

1 and 2 post-first vaccination. No clinically meaningful reductions in mean SF-36 Physical

ost demands of delivering a sufficiently intensive motor learning intervention is not feasible. There
of new motor skills. However, a major gap exists regarding learning of walking tasks. The
g task. Specific Aim 2: Determine the extent to which retention of performance is associated
s to enhance locomotor learning and rehabilitation.

of chronic physical and psychological health conditions in older adults. To date, only a few
n on PTSD symptoms and related health outcomes versus a healthy aging attention control
nthly sessions, the latter of which will be further supplemented with mailed informational
progressive aerobic and strengthening exercises, and will end with a 5 minute cool-down. The
ntion (9 months) to examine whether any observed exercise intervention effects are maintained.

DESCRIPTION This proposal, 'Aerobic Exercise and Cognitive Training in Older Adults', is resubmission for a Career Development Award- Level 2 with Dr. Joe R. Nocera as the Principal Investigator and a mentoring team of Drs. Bruce Crosson, Ron Shorr, Marco Pahor and Michael Marsiske. Dr. Nocera received his under...of Florida. Dr. Nocera then received a CDA-1 aimed at studying the effects aerobic exercise on executive language function in older adults. It was hypothesized, and demonstrated in the preliminary CDA-1 work, that the robust documented benefits of aerobic exercise on cognition could carry over to more specific executive lan...the purpose of designing interventions aimed at improving function and quality of life in older veterans. Specific training components in the proposal include; skills in cognitive neuroscience with specific training in cognitive aging, measurement, neuroanatomy, and basic imaging approaches. Additionally, the proposal is desig...the generalizability of the cognitive training. Importantly, this study wil focus on older veterans at-risk for mobility disability. This area is of particular importance for he VA system, considering a large percentage of veterans are entering old age and therefore likely to suffer from age-related cognitive decline and mobility disab...training arm will consists of a popular commercially-available brain fitness program that has demonstrated specific cognitive improvements and high adherence. Ultimately, this investigation will substantially advance the development of treatments for cognitive impairment because these goals explore an intervention that may p

12. Project Title: ROLE OF MICRORNAS ON AGE AND CONTRACTION-INDUCED SKELETAL MUSCLE GROWTH

Leader(s): RIVAS, DONATO A

TUFTS UNIVERSITY BOSTON

NIH K01AG047247 / (2015-2020)

DESCRIPTION (provided by applicant): The age-associated loss of skeletal muscle mass and function (sarcopenia) is associated with substantial social and economic costs. The plasticity and adaptability of skeletal muscle to contraction (i.e. resistance-exercise) is a fundamental physiological event leading to larger and more r...from young and older men, I identified ten specific miRNAs as important regulators of muscle plasticity (Plasticity Related miRs [PR-miRs]) leading to the transcriptional response to exercise and lean mass in young and older men. However, the precise mechanisms underlying the expression of PR-miRs on age-related changes...aging and sarcopenia in response to anabolic stimulation (AIM 1). Mechanistically determine the extent to which manipulation of PR-miR levels in vitro, in human primary myocytes, can reverse anabolic resistance observed with age and sarcopenia (AIM 2) and the effect of altering PR-miRs levels on skeletal muscle growth a...molecular biologist, Dr. Laurence Parnell a computational biologist and authority in gene and miRNA expression analysis, Dr. Thomas Gustafsson a physician-scientist and clinical researcher and Dr. Thomas Travison an expert in biostatistics. The mentorship team has a variety of know-how in every facet of this project includi...development plan will facilitate a transition to an independent research career.

13. Project Title: PHARMACOLOGICAL MANAGEMENT OF PAIN IN ALZHEIMER'S DISEASE AND RELATED DEMENTIA

Leader(s): WEI, YU-JUNG

UNIVERSITY OF FLORIDA

NIH K01AG054764 / (2017-2022)

Summary: My career goal is to become an independent geriatric pharmacoepidemiologist with expertise inpharmacotherapy quality measurement and outcomes evaluation in the fields of pain and aging. The clinicalfocus of my research has centered on the management of multi-morbidity in older adults and particularly, theinter...hasattempted to establish the effect of adequate pain control on preventing mental health (MH) disorders. Thegoal of my K01 proposed research is to provide preliminary data that improve our understanding of currentpain medication prescribing and potential discrepancies between practices and pain guidelines, and toformulate...validating MDS-based pain, depression, and behavioral symptoms against medical records at two nursinghomes (Aim 1). With the nationally representative Medicare-MDS data, we explore the quality ofpharmacological pain management and its determinants among ADRD and non-ADRD residents with non-cancer pain (Aim...(Aim 3). This project is well tailored for me to apply the knowledge and skills that will beobtained from training activities with my Primary Mentor, Dr. Almut Winterstein (pharmacoepidemioloy, qualitymeasurement and outcome assessment) and Co-Mentors: Drs. Roger Fillingim (pain), Marco Pahor (aging),Babette Brumba...ADRD. The results from this line of research are expected to lead to better pharmacological painmanagement and improved pain and health outcomes in older adults with cognitive impairments.

14. Project Title: THE AMPK/ULK1/P27KIP1 AXIS REGULATES AUTOPHAGY AND CELL SURVIVAL IN AGED SATELLITE CELLS

Leader(s): WHITE, JAMES P.

DUKE UNIVERSITY

NIH K01AG056664 / (2017-2022)

a. Project summary/abstract:Sarcopenia is the age-related loss in skeletal muscle mass and strength; it leads to a host of co-morbiditiesincluding loss of physical function and overall resilience. One such perturbation in persons with sarcopenia isthe diminished ability to regenerate muscle after injury. Muscle stem cells, referred t...AMPK/ULK1/p27Kip1 pathway withadvanced age. This award period will investigate the role of the AMPK/ULK1/p27Kip1 pathway in thephenotype of satellite cell aging in both human and mouse models. In Aim1, we will test the hypothesis thatactivation of AMPK and its downstream targets ULK1 and p27Kip1 regulate t...test the hypothesis thatAMPK/ULK1/p27Kip1 signaling will regulate the beneficial effects of caloric restriction on aged satellite cells.Together, the experiments in this proposal will test the hypothesis that the AMPK/ULK1/p27Kip1 pathway isimpaired in aging satellite cells resulting in a reduction in autophagy and susceptibl...progress towardindependence. The research and career development plan detailed in this proposal will be conducted with ateam of outstanding mentors. Dr. William E. Kraus, a professor at the Duke Medical School is an establishedexpert in clinical exercise studies and muscle/satellite cell biology; he will serve as the primary ...as anindependent investigator.

15. Project Title: DEPRESCRIBING CENTRAL NERVOUS SYSTEM MEDICATIONS IN HOSPITALIZED OLDER ADULTS

Leader(s): PAVON, JULIESSA M

DUKE UNIVERSITY

NIH K23AG058788 / (2019-2024)

This K23 Career Development Award in Aging focuses on the development of Dr. Juliessa Pavon, a hospital-based geriatrician, and on reducing central nervous system (CNS) medication use in hospitalized older adults.Dr. Pavon?s long-term goal is to improve the resilience of older adults against the acute stressors ofhospitali...anxiolytics and 60% to opioids during their hospital stay. De-prescribing is a systematic process oftapering or reducing medications. Interventions to facilitate de-prescribing that target specific medicationclasses, like CNS medications, or specific populations, like those with existing cognitive impairment, have notbeen well-stu...will inform the epidemiology of the problem and identify target populations forrecruitment. Aim 2 will use qualitative methods to examine barriers and facilitators of hospital de-prescribing.Results will inform the intervention delivery strategies best suited to facilitate CNS medication de-prescribing ina well-tolerated, feasible ...optimal delivery strategy for safely de-prescribing. During this K23 grant period, Dr.Pavon will also complete additional training in Markov modeling statistical techniques, interventiondevelopment, health informatics, and leadership. Dr. Pavon?s mentor team will provide scientific support withexpertise in aging, pharmacology...hospitalization.

16. Project Title: METABOLOMIC & RADIOGRAPHIC MARKERS OF FRACTURE RISK AMONG OLDER ADULTS WITH DIABETES

Leader(s): LEE, RICHARD H.

DUKE UNIVERSITY

NIH K23AG058797 / (2018-2023)

ABSTRACTAmong its medical complications, type 2 diabetes mellitus in older adults is associated with atwo-fold increase in the risk of hip and other low-trauma bone fractures. Paradoxically, thisincreased risk occurs despite a higher average bone mineral density. This increased fracturerisk is likely multifactorial, stemming ...fracture risk. The objective of this application is to develop and evaluateradiographic and laboratory biomarkers of fracture risk among older adults with diabetes,utilizing biomechanical and translational measures. The proposed research has the followingaims: 1) Determine the association between metabolomic profiles and incr...understanding the interaction of chronic medical conditions onthe bone health of older adults, focusing on diabetes. Dr. Lee is a dual-trained Geriatrician andEndocrinologist with expertise in metabolic bone disease. The primary training goals of thisproposal include the following: 1) Develop laboratory and analytical skills in tr...significant source of morbidity and mortality amongan increasing proportion of older adults.

17. Project Title: INVESTIGATIONS OF BOTANICALS ON FOOD INTAKE, SATIETY, WEIGHT LOSS, AND OXIDATIVE

Leader(s): ANTON, STEPHEN D

UNIVERSITY OF FLORIDA

NIH K23AT004251 / (2009-2014)

DESCRIPTION (provided by applicant): My training to date has provided me with a solid understanding of the behavioral, psychosocial, and environmental factors that contribute to eating behavior and weight management; however, my understanding of physiology and the biological mechanisms regulating eating behavior an...research investigating alternative and adjunctive treatments involving behavioral for age-related metabolic conditions (obesity, type 2 diabetes). My immediate career goals are to 1) obtain a R01 grant to further examine the potential effects of different doses of the selected botanical compounds on food intake, body weight, and...that botanical compounds have in affecting food intake, neuroendocrine signals, satiety, weight loss, and oxidative stress levels. Study 1 will investigate the effects of two promising botanicals (garcinia cambogia derived hydroxycitric acid, and glucomannan) on food intake, satiety, and weight loss using a double-blind, placebo ...(i.e., DNA and RNA oxidation). PUBLIC HEALTH RELEVANCE: Botanicals represent important sources of potential new adjunctive therapies for obese and insulin resistant individuals and may enhance the health benefits of weight loss interventions by reducing systemic oxidative stress levels.

18. Project Title: NEURO-INFLAMMATION IN POSTOPERATIVE COGNITIVE DYSFUNCTION: CSF AND FMRI STUDIES

Leader(s): BERGER, MILES

DUKE UNIVERSITY

NIH K76AG057022 / (2017-2022)

This is a K76 Beeson career development award for Dr. Miles Berger, a geriatric neuro-anesthesiologist with a focus on postoperative cognitive disorders. Each year >16 million olderAmericans undergo anesthesia and surgery, and up to 40% of these patients developpostoperative cognitive dysfunction (POCD), a syndrome of ...inflammationcauses POCD, but little work has directly tested this theory in humans. Our preliminary datastrongly suggest that there is significant postoperative neuro-inflammation in older adults whodevelop POCD. In this K76 award, we will prospectively obtain pre- and post-operative cognitivetesting, fMRI imaging and CS...link(s)between these processes and postoperative changes in AD pathology, in line with the NationalInstitute of Aging?s mission to understand aging and fight cognitive decline due to AD. During thisK76 grant period, Dr. Berger will also complete an individually tailored MS degree in TranslationalResearch that will include tr

19. Project Title: NORTH CAROLINA DIABETES RESEARCH CENTER

Leader(s): NEWGARD, CHRISTOPHER B

WAKE FOREST UNIVERSITY HEALTH SCIENCES

NIH P30DK124723 / (2020-2021)

PROJECT SUMMARY/ABSTRACT ? METABOLOMICS CORE Comprehensive metabolic analysis, or ?metabolomics?, is a technology that defines the chemical phenotype of living systems. Given that metabolic fluxes and metabolite levels are downstream of genomic, transcriptomic, and proteomic variability, metabolomi...rigorous and reproducible fashion. The DMPI Metabolomics Core Lab has a long history of collaborative research and has established a strong and reliable infrastructure for conducting measurements for investigators at Duke and at outside institutions. Thus, it is well poised to become the NCDRC Metabolomics Core. While D

20. Project Title: PICS: A NEW HORIZON FOR SURGICAL CRITICAL CARE

Leader(s): MOORE, FREDERICK A

UNIVERSITY OF FLORIDA

NIH P50GM111152 / (2014-2019)

DESCRIPTION (provided by applicant): Despite 30 years of intensive research, morbidity and mortality of sepsis in surgical intensive care unit (ICU) patients remain unacceptably high. Although recent advances in early ICU care have reduced in-hospital mortality, with the aging population a new epidemic of chronic critical i...least in part, by dysregulated myelopoiesis and expansion of myeloid-derived suppressor cells (MDSCs), aggravated by aging and largely driven by acute kidney injury (AKI), resulting in imbalance of angiogenic and anti-angiogenic factors. This Sepsis and Critical Illness Research Center (SCIRC) application comprises four p...ICU patients and what are the long-term cognitive and functional consequences? #1b) Can novel biomarkers predict, early, which patients will develop CCI, and, later, which CCI patients will have morbid long-term outcomes (i.e., PICS)? #2) Is PICS inherently driven by dysregulation in myelopoiesis and inappropriate MDSC...reduce inflammation, and alter the trajectory of CCI away from the PICS phenotype? We will study 400 surgical ICU patients who develop sepsis for at least one year, and use murine models of chronic polymicrobial sepsis for mechanistic studies and interventional methods. We recognize that no single therapeutic intervention ...understood and novel therapies developed.

21. Project Title: ADAPTABILITY AND RESILIENCE IN AGING ADULTS (ARIAA)

Leader(s): BARTLEY, EMILY J.

UNIVERSITY OF FLORIDA

NIH R00AG052642 / (2016-2021)

Growing evidence supports the presence of dysregulated pain modulation in older adults, an effect which may heighten age-associated risk for chronic pain. While persistent pain is common in older adults, chronic low back pain is the leading cause of disability in this population and results in significant impairments in psychos...fostering adaptive physiological and affective responses to pain. Given this, capitalizing on positive resources is a promising target for enhancing pain adaptation, and is especially salient to older adults given the burden of high-impact pain in this group. Therefore, the overall goal for this mentored career development applicatio...and assessment of psychosocial and biological (i.e., inflammatory, neuroendocrine) markers associated with pain and resilience; and 3) augment training in the design, implementation, and analysis of randomized clinical trials. The proposed study is delineated into two phases. Study 1 (K99 Phase) will examine associations am...effects on pain modulatory function and patterns of pain- evoked recovery in physiological and affective systems, and will establish whether a resilience-oriented intervention confers benefits in psychosocial and physical functioning in older adults with chronic low back pain. The proposed career development plan extends from

22. Project Title: AGING IN 1000 HEALTHY YOUNG ADULTS: THE DUNEDIN STUDY

Leader(s): MOFFITT, TERRIE E ; CASPI, AVSHALOM ;

DUKE UNIVERSITY

NIH R01AG032282 / (2009-2020)

DESCRIPTION (provided by applicant): Declining fertility rates, aging of the baby-boomers, and increasing life expectancy are leading to population aging. As the population ages, this increases the public-health burden of age-related conditions, such as cardiovascular disease, type 2 diabetes, and dementia. Treating un-prevent...the first half of the life course. Consequently, new interventions aiming to prevent age-related diseases will have to be applied to individuals while they are yet young, before they reach midlife. Translation of basic-science gerontology discoveries into interventions for young humans is lacking because virtually nothing is know...linkage to nationwide administrative records (health, welfare, finances). We propose to administer a full-day data-collection protocol to the 1004 living members of the birth cohort. To assess each cohort member's pace of biological aging we will: (a) measure biomarkers across multiple organ systems, and (b) statistically mode...support future interventions to slow aging, prevent age-related disease, and improve the quality of longer lives.

23. Project Title: ESTROGEN AND COGNITION OVER THE LIFESPAN

Leader(s): FOSTER, THOMAS C ; KUMAR, ASHOK ;

UNIVERSITY OF FLORIDA

NIH R01AG037984 / (2010-2023)

AbstractSex differences are evident in vulnerability to age-related cognitive decline and diseases of aging. Estradiol(E2) is protective against neurodegenerative diseases, including Alzheimer?s disease, implicating sexhormone effects on sex differences in vulnerability. However, obstacles to sex steroid treatments includedeclosin...receptor(NMDAR)-mediated synaptic transmission examined several days after treatment. Aim 1 will test thehypothesis that E2 treatment, several days prior to testing, specifically influences NMDAR-dependentepisodic memory, such that it can rescue an age-related decline in episodic memory examined on the watermaze and...E2 treatment will promote antioxidant enzyme activity, reduce oxidative stress, andminimize redox-mediated decrease in CaMKII activity and NMDAR function. Further, following closing of thetherapeutic window (i.e. for animals in which E2 does not rescue cognition and NMDAR function), E2treatment will not promote an...particularly in gene body regions (introns), and specific to CpG,relative to non-CpG methylation sites. The proposed studies will employ a powerful combination of behavioraltests that are sensitive to NMDAR function, patch-clamp recording of NMDAR synaptic responses, measuresof oxidative stress and enzyme activity, tra

graduate degree (B.A., 2001) from the University of California, Los Angeles. He completed his graduate degrees in Kinesiology from the University of Nevada, Las Vegas (M.S., 2004) and the University of Georgia (Ph.D., 2007). Following completion of his terminal degree, Dr. Nocera earned a post-doctoral fellowship under a Nation... language functions. Concurrently, the CDA-1 was designed to increase Dr. Nocera's understands of cognitive neuroscience thus bridges the gap between cognitive functions and Dr. Nocera's previous education emphasis of physical function in older adults. The general purpose of the career development in this CDA-2 application is to furth... ...ed to develop Dr. Nocera's skills in clinical/translational research necessary for high-quality clinical trials research. The purpose ofthe CDA-2 study will build on the CDA-1, which demonstrating an improvement in cognitive function via aerobic exercise, by adding a cognitive training component that will be done immediately followin... ...ility. To address our research question 60 older veterans (age 65-89) will be randomized to one of two 12-week intervention groups: 1) Cognitive Training alone (CT) or 2) Aerobic Exercise + Cognitive Training (AE+CT). The aerobic exercise arm of the study will follow the same format shown to improve a broad range of executive fu... ...potentially have pervasive effects on patient quality of life from a cognitive as well as a physical standpoint. Concurrently, this proposal will provide Dr. Nocera with the skill necessary to grow into a successful, independent VA Research.

obust skeletal muscle. However, muscle growth in response to resistance exercise (RE), like other anabolic stimuli, is attenuated in older adults The cause of aberrant muscle adaptation with aging is complex. Recent work has revealed a novel role for small non-coding RNAs, called microRNAs (miRNA) in the regulation of gene express... ...in muscle anabolism and sarcopenia are currently unknown. Thus, the overall objective of this K01 application will be to determine the mechanistic role(s) of these PR-miRs in skeletal muscle adaptation to anabolic stimulation in 1) healthy young, 2) sarcopenic older and 3) age- and functionally-matched non-sarcopenic older males an... ...d development (AIM 3). This project will improve our understanding of the molecular mechanisms that contribute to the loss of skeletal muscle and eventually leading to the development of drug therapies for the treatment of sarcopenia in the ever growing aging population. The mentorship team includes, Dr. Roger Fielding, a leader in... ...ng, conducting human clinical trials and skeletal muscle biology, computational biology and genomics and molecular biology and mechanisms. The proposed career development plan includes research-oriented and didactic training at Tufts University, Boston University and the Karolinska Institute in Stockholm,Sweden. The pursuit of...

...play of mental and physical disease and its treatment. One example of combination of health problems iselderly patients who live with Alzheimer's disease and related dementia (ADRD) and also suffer from chronicpain. To date, data on quality of pain medication prescribing and the sequelae of poor pain control in patientswith ADRD a... ...hypotheses for future research regarding the role of pain control in reducing MH problems in ADRD.We propose a longitudinal design using 4 years (2011-2014) of Medicare 5% sample whose billing records arelinked to nursing home resident assessment data (Minimum Data Set, MDS, 3.0). Because it is unclearwhether MDS 3.0 can... ...2). The quality will be examined based on five common clinical standards--pain medicationselection, pain medication scheduling, pharmacological prevention of drug adverse event, contraindicatedmedication use, and overall pain control. We then explore the extent to which pain control is associated with adecreased risk for select MH... ...k (advanced methods for longitudinal data), and Laurence Solberg (clinical geriatric care andassessment). For further guidance, I enlist the expertise of Dr. Siegfried Schmidt in the field of pain medicineand Dr. Steven DeKosky in ADRD. This K01 award will provide protected time for me to receive trainingneeded to prepare an R01 gr...

...to as satellite cells, arerequired to activate, proliferate and differentiate to regenerate muscle and restore physical function. Agedsatellite cells are slower to activate upon injury; susceptible to apoptosis; and less efficient in repairing injuredmuscle. The AMPK/ULK1/p27Kip1 pathway appears critical for successful transition from quiesce... ...the autophagy/apoptosis decisionin aged satellite cells. We will use molecular assays to rescue the functional loss of this pathway in aged cellsand return proliferative capacity. In Aim 2, we will test the hypothesis that exercise, a physiological inducer ofAMPK and autophagy, stimulates the AMPK/ULK1/p27Kip1 pathway, thereby enha... ...ity to apoptosis. Keyaspects of Dr. White's career enhancement will be: to learn how to coordinate clinical exercise trials; to trainin methods of satellite cell isolation and metabolic analysis, especially in the context of the aging organism.The training program will entail dedicated internal and external scientific presentations; pertinent co... ...mentor. Drs.Kenneth Schmader, Deborah Muoio (Duke) and Amy Wagers (Harvard) will serve as co-mentors; they willfacilitate training in aging biology, cell metabolism and aging stem cell biology, respectively. The environmentat the Duke School of Medicine is ideal for the research and training activities outlined in this proposal. Th...

...ration. She has built her research program on investigating hazards of hospitalization, and a majorthreat is high-risk medication exposure. Sub-optimal CNS medication use during hospitalization is a keymodifiable risk factor for poor health outcomes; common classes include opioids, anxiolytics, anti-depressants,antipsychotics, and hyp... ...died in the inpatient setting. This gap represents a key opportunity to reduce potentiallyinappropriate CNS medications and their debilitating side effects in vulnerable patients--in line with the NationalInstitute of Aging?s priorities to improve medication use in older adults. Dr. Pavon?s K23 award proposes todevelop and pilot test a de-p... ...manner. Aim 3 will develop and pilot test a multi-component hospital-based de-prescribing intervention that uses health informatics for content delivery, and provider behavior change andpatient activation strategies. This work will advance understanding of 1) which patients and CNS medicationclasses to target for de-prescribing interve... ...r, hospital medicine, and research methodology. This career developmentplan will give Dr. Pavon the skills in conducting intervention development studies within the hospital setting.This training and resulting data will establish Dr. Pavon as a strong candidate for an R01 intervention designedto facilitate de-prescribing of CNS medicati...

...from metabolic dysfunction that results in both increasedfalls risk and decreased bone strength. However, fracture risk stratification currently is limitedlargely to bone density testing and clinical risk tools that do not perform adequately for adultswith diabetes. Because bone is both a metabolic and structural tissue, metabolomics andbiom... ...ident clinical fractureamong older adults with diabetes; 2) Compare geometric and biomechanical measures at thefemoral neck and intertrochanteric region among older adults with diabetes, with and without hipfracture. This application builds upon the prior published work and clinical expertise of thePrinciple Investigator, Dr. Richard... ...translational sciencethat will be used in the development and evaluation of clinical biomarkers, including ?omicstechnologies; 2) Acquire principles and skills in biomechanical engineering and materialsscience to integrate with clinical and epidemiological analyses. By integrating biomechanicalengineering and metabolomics approaches...

...d body weight remains to be improved. Therefore, I seek to increase my knowledge of the physiological aspects of age-related metabolic conditions, and the potential role botanical extracts may have in affecting physiology, eating behavior, body weight, and oxidative stress levels. This knowledge, coupled with my previous training, wi... ...oxidative stress levels and 2) increase my understanding of the effects that botanicals have on physiological processes related to food intake. My long-term career goal is to become an independent investigator focused on developing safe and effective alternative or adjunctive interventions involving natural compounds for the treatment o... ...controlled design. Based on the findings from study 1, the botanical with the most significant effects on food intake will be used in a 24-week, placebo controlled calorie restricted weight loss trial. In addition to body weight, this trial will examine the effects of the selected compound on: 1) food intake, 2) self-reported satiety, 3) postpra...

...postoperative thinking and memorydeficits. Although distinct from delirium, POCD (like delirium) is associated with decreased qualityof life, long term cognitive decline, early retirement, increased mortality, and a possible increasedrisk for developing dementia such as Alzheimer?s disease. We need strategies to prevent POCD,but first... ...F samples in 200 surgical patients over age 65. This will allow us toevaluate the role of specific neuro-inflammatory processes in POCD, its underlying brainconnectivity changes, and postoperative changes in cerebrospinal fluid (CSF) Alzheimer?sdisease (AD) biomarkers, such as the microtubule-associated protein tau. This project wil... ...aining in immunology methods, fMRI imaging, cognitive neuroscience,geroscience, and physician leadership. This career development plan will give Dr. Berger thetransdisciplinary skills to pursue his longer term goal of improving postoperative cognitive functionfor the more than 16 million older Americans who have anesthesia and s...

...ics provides a highly integrated profile of biological status. As such, it has unique potential for discovery of biomarkers that predict disease incidence, severity, and progression, and for casting new light on underlying mechanistic abnormalities. Metabolomic analyses are challenging, however, due to the complexity inherent in measuring... ...uke has world-renowned facilities for metabolomics, its use by diabetes investigators outside of Duke (such as WF and UNC researchers) has been limited by bottlenecks, particularly in the analysis and interpretation of data, which the NCDRC seeks to address by establishing the NCDRC Metabolomics Core with support from Research...

...illness (CCI) has emerged and its progression into what we call the persistent inflammation, immunosuppression and catabolism syndrome (PICS) has unacceptable morbid long-term consequences. Our overarching hypothesis is that PICS is now a predominant clinical trajectory in the surgical ICU patients after sepsis, and is the greatest... ...rojects and five cores drawn from two colleges (Medicine and Public Health and Health Professions) and eight University of Florida Health departments (Surgery, Medicine, Anesthesiology, Biostatistics, Molecular Genetics and Microbiology, Aging and Geriatric Research, and Physical Therapy) and will address the following question... ...expansion, promoting persistent inflammation, immunosuppression and catabolism?; #3) Does AKI, through dysregulation of anti-angiogenic and angiogenic cytokines, drive the expansion of MDSCs, inflammation, and anti-angiogenesis?; and #4) Does CCI contribute significantly to muscle atrophy, especially in mechanically ventilat... ...will prevent PICS, but the SCIRC's overall goal is to understand the prevalence and pathogenesis of this new syndrome at a mechanistic level. Only through multi-disciplinary translational research by basic and clinical scientists with diverse expertise in critical care medicine, physical therapy, immunology, molecular, and unde...

...social and physical functioning. Given reports of suboptimal treatment of pain in older adults, improvements in pain management in this cohort are of critical importance. Resilience is characterized as a dynamic process resulting in positive adjustment and adaptation after exposure to adversity. The benefits of resilience in health-related... ...on (K99/R00) is to fill this knowledge gap and characterize resilience mechanisms associated with adaptive pain modulatory capacity in older adults with chronic low back pain. Primary training goals for the current application are to: 1) develop a comprehensive knowledge base in biopsychosocial processes of aging and enhance training... ...ong measures of resilience, biological markers of inflammation and neuroendocrine activity, and pain modulatory capacity in older adults with chronic low back pain. Increased knowledge and understanding of the resilience pathways that promote adaptability to pain will allow for the development of a targeted resilience intervention dur... ...n the PI's prior work on affective regulation and mechanisms of vulnerability in chronic pain, and will forge a path towards understanding and investigating psychological therapies of resilience that improve pain and disability in older adults.

...nted diseases in late life has proven costly and ineffective. It is now known that potentially preventable risk exposures and physiological causes of age-related disease emerge in childhood. This recognition lends new scientific significance to studies that have followed cohorts from childhood. It is also now known that the pathogenesis of... ...rn about the process of biological aging during the first half of the life course. This prompts our proposal to study the pace of biologicalaging from the twenties forward. We will use the Dunedin Multidisciplinary Health & Development Study, a longitudinal study of a birth cohort now entering its fifth decade. This study combines meth... ...l correlated change in these biomarkers assessed at ages 26, 32, 38, and 45 years. We will describe individual variation in the pace of aging, plus its developmental origins, genomic signatures, functional consequences, and economic costs. We will identify attributes that set apart individuals whose bodies are months or years younger than...

...g of the therapeutic window observed as decreased effectiveness of E2 treatment with advanced age.The goal of the proposed research is to provide an understanding of the mechanisms for E2 effects onmemory and the closing of the therapeutic window. Closing of the therapeutic window is marked by a decreasein E2-responsive transc... ...novel object recognition tasks. Aim 2 will test the hypothesis that E2 effects on memory andNMDAR function are mediated by reversal of NMDAR hypofunction, mediated by redox regulation ofphosphatase/kinase activity, similar to that previously described in aging males. Thus, it is predicted that priorto closing of the therapeutic wi... ...tioxidant enzyme activity or reduce oxidative stress, and the NMDAR responseand CaMKII activity will be decreased due to an oxidized redox state. Aim 3 will test the hypothesis that age-related changes in transcriptional responsiveness to E2 are due, at least in part, to epigenetic regulationthrough DNA methylation. It is predicted that... ...scription, and DNA methylation.

al Institute of Health T32 training grant within the Department of Neurology at the University
er and more substantially develop Dr. Nocera's understanding of cognitive neuroscience for
g the aerobic exercise. It is hypothesized that the aerobic exercise will potentiate and increase
nctions in older adults in previous research as well as our CDA-1 pilot work. The cognitive

ion. Using an integrated bioinformatics analysis of protein-coding gene and miRNA array data
d females. This will be accomplished by determine the differences in expression of PR-miRs with
aging research and muscle biology, Dr. Kenneth Walsh, a cardiovascular researcher and leading
the specific aims of the research project, the multidisciplinary mentorship team and the career

re scarce. Studies investigating these associations are limited by small sample size, and none
accurately detect patients with pain and MH disorders, we first conduct a feasibility studyof
disorders, including depression, behavioral symptoms, anxiety, and sleepdisorders in ADRD
ant application to examine pain medication practices and their impact on healthoutcomes in

nce to entryinto the cell cycle. Our preliminary data identify perturbations in the
ncing proliferation andmetabolic function in aging murine and human satellite cells. Aim 3 will
ursework/workshops in stem cell biology and aging; and intensive career mentorship to ensure
hisaward will provide Dr. White with optimal training to ensure an outstanding start to his career

otics. Our preliminary data suggests that nearly 40% of hospitalized older adults areexposed to
rescribing intervention that is informed by a theoretical model of behavioralchange. Aim 1 results
entions, 2) whether there are unique barriers to de-prescribing in thehospital setting, and 3) the
ons for the nearly 1 in 2 older adults that will experience exposure toa CNS medication during

echanical analyses would be particularly useful for developing and assessing newmeasures of
ee, and provides him additional research skills to assist withhis career development goal of
with epidemiologic research to identify new markersof fracture risk, this application addresses a

ll provide an ideal foundation from which I can build a unique and independent line of
f obesity and other metabolic conditions. The proposed line of research will explore the role
ndial neuroendocrine signals (i.e., CCK, GLP-1, insulin, and leptin), and 4) oxidative stress levels

, we need to understand what causes it. A dominant theory holds that brain
ladvance understanding of neuro-inflammatory processes in POCD and clarify the potential
urgery each year.

; large numbers of intermediary metabolites with diverse chemical properties in a quantitatively
n Navigators.

, near-term clinical challenge in surgical ICUs. We further hypothesize that PICS is caused, at
s in four projects: #1a) What is the incidence and early risk factors for CCI in septic surgical
ed patients' diaphragms and extremities, and will resistance exercise improve muscle strength,
standing of muscle, kidney, and aging physiology, can CCI progression into PICS be

unctioning are manifold, and recent evidence suggests that resilience plays an important role in
t in the assessment and treatment of older adults; 2) increase knowledge in the understanding
ing Study 2 (R00 Phase). This phase will provide the opportunity for examining intervention

age-related diseases involves gradually accumulating decline in organ systems, beginning in
ds of demographic/economic surveys, clinical- quality health assessments, biobanking, and
a their chronological age. The proposed work will improve knowledge by generating findings to

ription and an inability of E2 treatment to enhance N-methyl-D-aspartate
ndow (i.e. in animals in which E2 treatment improves cognition and increasesNMDAR function),
decreased responsiveness of E2-sensitive genes will beassociated with DNA hypermethylation,

24. **Project Title:** NEURAL SIGNATURES OF HEALTHY AND UNHEALTHY AGING

    Leader(s): HARIRI, AHMAD R ; MOFFITT, TERRIE E ;

    DUKE UNIVERSITY

    NIH R01AG049789 / (2015-2020)

DESCRIPTION (provided by applicant): Declining fertility rates, aging of the baby-boomers, and increasing life expectancy are leading to population aging. As the population ages, this increases the public-health impact of age-related conditions, such as cardiovascular disease, type 2 diabetes, and dementia. Treating un-preven now known that the pathogenesis of age-related diseases involves gradually accumulating damage to organ systems, beginning in the first half of the life course. Of these organ systems, the central nervous system is integral, prompting our proposal to add neuroimaging to the Dunedin Multidisciplinary Health & Development S birth cohort. Our proposed neuroimaging protocol will measure individual variation in brain function, structure, and connectivity. We focus on the hubs of four neural circuits and the core behavioral capacities each supports: (1) the amygdala and emotion/threat, (2) the ventral striatum and motivation/reward, (3) the hippocamp necessary to prepare for successful aging. Aim 3 tests if neural measures are related to the accelerated pace of biological aging. The proposed work will improve knowledge by generating findings about the neural correlates of age-related diseases and successful healthy aging. These findings are expected to support preventing d

25. **Project Title:** EPIGENETIC MECHANISMS PROMOTING LONGEVITY

    Leader(s): KRAUS, VIRGINIA

    DUKE UNIVERSITY

    NIH R01AG054840 / (2018-2023)

AbstractCirculating small regulatory RNAs (sRNAs) are short non-coding RNAs (typically ~19-25nt in size). They mediateta broad spectrum of biological processes through regulation of gene expression. Our experimental evidenceindicates that serum levels of miRNAs (one form of sRNA) change considerably, the vast majori stable in samplesstored for decades. Despite numerous recent developments, we are far from understanding the role of sRNAsin aging. An understanding of their role in aging mammals, and in humans in particular, is still very limited dueto the increased complexity and longer life-spans of mammals compared with invertebrate expressed circulating miRNAs(β0 years) compared with age, sex and race matched but short-term survivors (

26. **Project Title:** SENESCENCE AND GROWTH DIFFERENTIATION FACTORS AS MODIFIERS OF AGING

    Leader(s): LEBRASSEUR, NATHAN K

    MAYO CLINIC

    NIH R01AG055529 / (2018-2023)

PROJECT SUMMARY/ABSTRACTAging is the primary risk factor for the majority of chronic diseases. Studies in mice have implicated specificgrowth and differentiation factors (GDFs) and proteins secreted by senescent cells as potential modifiers ofaging. The objective of this proposal is to establish the rationale and provi health outcomes and can be altered by physicalactivity. Samples from the Lifestyle Interventions and Independence for Elders (LIFE) Study; the largest andlongest randomized trial of a physical activity intervention in older adults, will be used to test this hypothesis,and samples from the Health, Aging, and Body Composition (CCL11, ICAM1, AA and PAI2 are associated withbaseline measures of physical (i.e., gait speed, Short Physical Performance Battery (SPPB) score),cardiopulmonary (i.e., blood pressure, forced expiratory volume), and cognitive (i.e., processing speed,memory) function, inflammation, and prevalence of multimorbidity (based the number of chronic conditions (asin Aim 1), at 1 and 2 years in LIFE and at 2 and 4 years in HABC will be determined. Finally, Specific Aim 3 willaddress whether a structured physical activity intervention impacts longitudinal changes in GDF8, GDF11,CCL11, ICAM1, AA, and PAI2, compared to a health education contr may be viable targets for innovative therapiesto extend human healthspan.

27. **Project Title:** INTERMITTENT PNEUMATIC COMPRESSION FOR DISABILITY REVERSAL IN PAD: THE INTERCEDE TRIAL

    Leader(s): MCDERMOTT, MARY MCGRAE

    NORTHWESTERN UNIVERSITY AT CHICAGO

    NIH R01AG057693 / (2018-2023)

PROJECT SUMMARY Our work and that of others has established that people with lower extremity peripheral artery disease(PAD) have greater functional impairment and faster rates of functional decline than people without PAD.However, few therapies improve functioning or prevent functional decline in people with PAD. suggests that IPC improves lower extremity blood flow and walking endurance in people with PADand that benefits persist for up to 12 months after intervention completion. However, evidence is limited bysmall sample sizes, high loss to follow-up, lack of blinding, and lack of sham controls. Clinical practiceguidelines do not (2 x 2 factorial design) of 230 PAD participants randomized to one of four groups:Group A: IPC + exercise; Group B: IPC + ?no exercise? control; Group C: sham control + exercise; and GroupD: sham control + ?no exercise? control. The IPC and sham interventions will be delivered for six months. Inour primary specific aims delineate mechanisms by which IPC affects walking performance, by measuringchanges in MRI-measured calf muscle perfusion, physical activity (measured with ActiGraph), and calf musclebiopsy measures of angiogenesis, muscle regeneration, mitochondrial biogenesis, mitochondrial activity, andautophagy. Based on precli intervention will have a major impact onpreventing mobility loss and improving quality of life in the large and growing number of people with PAD.

28. **Project Title:** MECHANISMS OF OXYTOCINS ANALGESIA IN OLDER ADULTS

    Leader(s): CRUZ-ALMEIDA, YENISEL ; EBNER, NATALIE C ;

    UNIVERSITY OF FLORIDA

    NIH R01AG059809 / (2018-2023)

ABSTRACTOsteoarthritis (OA) represents a significant cause of disability worldwide in individuals aged 65 and older, arapidly growing segment of our population. The knee is the most commonly affected joint with pain being theprimary symptom, negatively impacting physical, cognitive, and emotional functioning. Sympto mechanisticmodel of OT's analgesic effects leveraging pilot data supporting efficacy and safety of self-administeredintranasal OT over 4-weeks in older individuals. Relative to placebo (P), daily administration of intranasal OTdiminished self-reported pain intensity, reduced experimental pain sensitivity, and increased self-repo effect ofintranasal OT administration on clinical and experimental pain sensitivity in older adults with symptomatic kneeOA and 2) characterize inflammatory mechanisms contributing to the inter-individual variability in analgesicresponses to OT. Older adults with symptomatic knee OA will self-administer intranasal OT or P c management in older adults with littlepotential for addiction. Embedded in a biopsychosocial framework, our proposal will help pave the way for futureinvestigations using a mechanism-based treatment optimization strategy for individuals suffering from chronicpain.

29. **Project Title:** GENOMIC ANALYSIS OF THE CALERIE TRIAL TO GENERATE NEW KNOWLEDGE FOR GEROSCIENCE

    Leader(s): BELSKY, DANIEL WALKER

    COLUMBIA UNIVERSITY HEALTH SCIENCES

    NIH R01AG061378 / (2019-2024)

SUMMARYThe graying global population makes interventions to extend healthy lifespan (healthspan) a public heathpriority. Therapies targeting basic biological processes of aging show proof-of-concept in animals: early-to-midlife intervention can delay disease onset and prolong healthspan. But translating these geroprotecti process is thought to be the root cause of increases in morbidity and disability in later life. Newresearch shows that biological aging can be measured in humans and that measures of biological agingpredict human healthspan. Geroprotective therapies that target basic biological processes of aging arehypothesized to slow the rate randomized 220 non-obese adults to 25% caloric restriction (CR, N=145)or ad libitum normal diet (AL, N=75) for a period of 2 years. We have already shown that CR slows aging-related deterioration in organ-system integrity. Now, we propose to extend this test to genomic measures ofbiological aging. We will assay whole-g healthspan-extending effects of CR in animals, e.g. themTOR pathway? (iii) Do changes to DNA methylation and gene expression mediate effects of CR on organsystem functioning? We will share the multi-omics data we generate with the CALERIE Biorepository,making the resource freely available to all interested researche advance the field of geroscience.

30. **Project Title:** FUNCTIONAL LIMITATIONS AND DISABILITY AMONG MIDDLE-AGED ADULTS

    Leader(s): BOWLING, CHRISTOPHER BARRETT

    DUKE UNIVERSITY

    NIH R01AG062502 / (2020-2023)

Project summary/Abstract The burden of functional limitations (restrictions in basic physical actions) and disability (problems with daily activities and life participation) may be more common in middle-aged US adults than previously recognized. However, studies of middle-age populations have not typically included function data collected from early adulthood through middle age to address the following aims: 1. To quantify the burden of functional limitations and disability in middle age and assess the degree to which this can be attributed to the accumulation of chronic conditions, 2. To assess domains of functional limitations and disability captu single leg balance, timed chair stands, 6-minute walk test, and grip strength) to the CARDIA Year 35 exam (projected N=3,270; 1,563 black, 1,707 white). Also, self- reported functional limitations (Patient-Reported Outcomes Measurement Information System [PROMIS] Physical Function Short Form 20a) and disability meas appropriate functional measures to an ongoing population based cohort, that represents the next wave of aging black and white adults will lead to new approaches to prevent functional decline and improve population health.

31. **Project Title:** ACTIVE ROLES OF GLIAL CELLS IN OLFACTION AND AGE-RELATED OLFACTORY DECLINE

    Leader(s): XIAO, RUI

    UNIVERSITY OF FLORIDA

    NIH R01AG063766 / (2019-2024)

Project SummaryAge-dependent olfactory decline (presbyosmia) is widely present in many species, including humans. At leastfifteen million Americans over 55 years old suffer from presbyosmia. By affecting the well-being, quality of life,and overall health, presbyosmia presents a significant challenge to public health. Patien physiology andhealth, the cellular and molecular mechanisms underlying presbyosmia are poorly understood (knowledgegap).As a major cell type in the nervous system, glial cells are typically considered as passive modulators duringneural development and synaptic transmission. Whether glial cells play active roles in sensory process across species.This proposal will bring together in vivo calcium imaging, optogenetics, molecular genetics, and behavioralanalysis to investigate and discover the molecular mechanisms through which the olfactory glial cells playactive roles in odorant detection and age-dependent olfactory decline. Since both olfaction

32. **Project Title:** BIOBEHAVIORAL BASIS OF KNEE OSTEOARTHRITIS PAIN

    Leader(s): CRUZ-ALMEIDA, YENISEL

    UNIVERSITY OF FLORIDA

    NIH R01AG067757 / (2020-2025)

Discovery and validation of strong candidate biomarkers and clinical endpoints for pain is urgently needed that can be used to facilitate the development of non-opioid pain therapeutics from discovery through Phase II clinical trials. Emerging research using a combination of biomarkers deliver individualized predictions about t biological changes using a biobehavioral perspective which is needed for predicting future health and to be able to use as clinical endpoints for interventions. The proposed study will prospectively address biobehavioral factors (i.e., cognitive, psychological, social and cultural) affecting the experience and interpretation of knee using a comprehensive biobehavioral multi- methods approach, we will be the first to prospectively determine the trajectory and interactions among pain, biological biomarkers and multiple domains of function within race/ethnic groups in OA pain. Findings will contribute towards increased understanding of pain and its biobe

33. **Project Title:** QUALIFICATION OF PROGNOSTIC AND DIAGNOSTIC BIOMARKERS OF KNEE OSTEOARTHRITIS

    Leader(s): KRAUS, VIRGINIA

    DUKE UNIVERSITY

    NIH R01AR071450 / (2017-2020)

AbstractA cure for osteoarthritis (OA) remains elusive. This is due in large part to two major obstacles, inability todetect OA sufficiently early before the onset of irreversible signs and recalcitrant symptoms, and inability toidentify individuals at high risk of progression based on traditionally used metrics (age, sex, body mass i studiesin synovial fluid, urine, and serum from knee OA radiographic progressors and non-progressors (with 3-4 yearfollow-up) and controls. The ultimate goals of this work are to qualify these new biomarker candidates in thecontexts of knee OA progression and OA diagnosis in larger well-phenotyped cohorts from the Osteo yielded by thisproposal to facilitate their use as drug development tools.

34. **Project Title:** THE EFFECT OF INTERMITTENT HEMIDIAPHRAGM STIMULATION DURING SURGERY ON MITOCHONDRIAL FUNCTION, SINGLE FIBER CONTRACTILE FORCE AND CATABOLIC PATHWAYS IN HUMANS

    Leader(s): SMITH, BARBARA K ; BEAVER, THOMAS M ;

    UNIVERSITY OF FLORIDA

    NIH R01AR072328 / (2017-2021)

Although mechanical ventilation (MV) is life-sustaining in patients with respiratory failure, it comes with a cost.MV dramatically reduces diaphragm contractility, induces ventilator-induced diaphragm dysfunction (VIDD) andsometimes leads to weaning failure. VIDD includes reduced mitochondrial respiration and increased c prevents/attenuatesVIDD in the active hemidiaphragm.Mitochondrial function is central to energy metabolism and skeletal muscle function in a chronically activemuscle, such as the diaphragm. Although abnormal mitochondrial function is thought to precipitate VIDD inanimal models, limited data are available concerning mit a within-subjects experimental design,muscle samples from a stimulated hemidiaphragm will be compared with samples from the unstimulatedhemidiaphragm. We will investigate mitochondrial dysfunction and oxidative stress during prolonged CTS/MV,and the potential of ES to attenuate or prevent VIDD (Aim 1). Next, we mechanisms contributing to human VIDD. Our long-term goal is to test variousintermittent hemidiaphragm ES protocols on a larger population to determine its ability to prevent or attenuateVIDD. Data from this R01 application will advance our understanding of mechanisms giving rise to humanVIDD, and may inspire new th

35. **Project Title:** MECHANOTRANSDUCTION IN MENISCUS HEALTH AND REPAIR

    Leader(s): MCNULTY, AMY L

    DUKE UNIVERSITY

    NIH R01AR073221 / (2019-2023)

ABSTRACT.Meniscal injuries are a significant clinical problem as each year 850,000 meniscal surgeries are performed in theUnited States and nearly twice as many worldwide. Meniscal tears in the avascular inner zone of the tissue donot heal well with suturing or conservative treatments and can ultimately lead to the develop by physical factors associatedwith joint loading. Mechanobiology, which is the influence of mechanical factors on the biologic response of cells,is important in converting physical signals into metabolic and inflammatory responses in meniscus. However,the mechanisms by which mechanical signals are transduced in meniscus cell migration and proliferation, which are important processes to enhance tissue repair. Whilewe have found that TRPV4 is expressed in the meniscus, the function of this mediator in meniscus health anddisease is currently unknown. In this proposal, we will determine how mechanotransduction occurs throughTRPV4 in menis cells.Next, we will elucidate alterations in TRPV4-mediated mechanotransduction pathways in meniscus pathology.Finally, we will enhance integrative meniscus repair and prevent the development of OA by modulation ofmechanotransduction pathways. In this proposal, we will identify the key signaling pathways downstream developmentof OA.

36. **Project Title:** REVIVE - RESVERATROL TO ENHANCE VITALITY AND VIGOR IN ELDERS

    Leader(s): ANTON, STEPHEN D

    UNIVERSITY OF FLORIDA

    NIH R01AT007564 / (2013-2019)

ted diseases in late life has proven costly and ineffective. Consequently, effective strategies are needed in midlife to prevent age-related diseases and to improve the quality of longer lives. It is now known that potentially preventable risk exposures and physiological causes of age-related disease emerge in childhood. This recognition len tudy, a longitudinal study of both problematic and positive processes of adult development and aging, in a birth cohort now entering its fifth decade. This study combines methods of demographic/economic surveys, clinical-quality health assessments, biobanking, and linkage to nationwide administrative records (health, welfare, finance us and memory, and (4) the dorsolateral prefrontal cortex and executive control. With the resulting midlife neural measures, we propose three primary aims that will generate findings about problematic and successful aging: Aim 1 tests whether prospectively ascertained early- life adversity is linked to midlife neural measures. Aim 2 tests isease and enhancing preparedness for wellbeing in late life. Beyond the proposed 5-year project, follow-up neuroimaging is envisaged. This project thus brings neuroimaging into three timely and vigorous areas of aging science: the study of early-life programming of lifelong health, the study of midlife preparation for successful aging,

ity increasingwith age. The ability of circulating sRNAs to travel among tissues enables them to transmit signals and regulatea broad spectrum of biological functions. sRNAs exist in a variety of RNase-insensitive ribonucleoprotein or lipidcomplexes, or are encapsulated inside different types of extracellular vesicles. Consequently, in co s. This projectleverages existing human sample resources from three completed NIH-funded studies (EPESE, STRRIDE andCALERIE), to discover and validate longevity-associated miRNAs in humans. Our preliminary analysis of 175circulating microRNA--in the NIA-funded Duke Established Populations for Epidemiologic Studies c

de robust clinical evidence for GDF8,GDF11, and senescence-related proteins eotaxin (CCL11), intracellular adhesion molecule 1 (ICAM1), activinA (AA), and plasmínogen activator inhibitor 2 (PAI2), as indicators of biological age and age-related conditionsin humans. The central hypothesis is that circulating concentrations of GDFs HABC) Study will be used to validate studyfindings. A novel multiplexed liquid chromatography-tandem mass spectrometry assay will be leveraged toaccurately quantify GDFs, and an advanced multiplexing platform will be used to measure senescence-relatedproteins in LIFE and HABC biospecimens. In Specific Aim 1, a multidiscipl on the ICD-9 codes for 20 chronicconditions). In Specific Aim 2, the degree to which baseline concentrations of GDFs and senescence-relatedproteins predict longitudinal changes in a) gait speed and SPPB score, b) major mobility disability (i.e., theinability to walk 400m), c) combined cardiovascular events (e.g., myocardial infarction, rol intervention, and the degree to whichchange in the concentrations of these proteins parallel change in the health outcomes described in Aim 2. Thesuccessful completion of the proposed research will fill an important translational gap in our understanding ofhow GDFs and senescence-related proteins predict and, therefore, potentially r

Intermittent pneumatic compression (IPC) is a non-invasive intervention, consisting of an air pumpinside inflatable cuffs that are wrapped around the feet, ankles, and calves and worn for two hours daily. Every20 second, the cuffs rapidly inflate, followed by rapid deflation. During deflation, arterial blood return into thearteriovenous pr mention IPC as a therapeutic option in PAD. A definitive randomized trial is needed. Walking exercise is first-line therapy for PAD. However, many PAD patients are unable or unwilling toexercise. Therefore, in people with PAD, we will determine whether IPC augments the benefits of exercise onwalking endurance and whether IPC a s, we will determine whether IPC combined with exercise improves the 6-minute walkat 6-month follow-up compared to exercise alone and whether IPC alone improves the 6-minute walk at 6-month follow-up, compared to sham control. In secondary aims, we will determine whether benefits of IPCpersist by re-measuring study outcom nical evidence that IPC increases nitric oxide abundance and promotesvasodilation in skeletal muscle distant from the lower extremities, we will determine whether IPC improvessystemic endothelial function, by measuring changes in brachial artery flow-mediated dilation. If the IPC intervention with and without exercise improves func

matic knee OAhas been traditionally attributed to peripheral mechanisms, but measures of joint damage only modestly accountfor the presence or severity of OA-related pain. The neuropeptide oxytocin (OT) has been recognized as amediator of endogenous analgesia in animal and human studies. However, little is known about theneuro rtedphysical and emotional functioning. Further, participants treated with OT, compared to P, showed decreases inbrain metabolite concentrations associated with inflammation. Thus, our overarching goal is to evaluate theeffects of intranasal OT on pain and function in aging and to determine the extent to which central and peripheralin over 4 weeksusing a double-blinded, parallel study design. With strong support from the University of Florida and the McKnightBrain Institute, our interdisciplinary project, using a comprehensive multi-methods approach, will be the first todetermine the potential benefit of OT as a novel analgesic therapy for knee OA pain in aging. OT

vetherapies to humans faces the barrier that human clinical trials of midlife geroprotective therapy wouldrequire decades of follow-up to measure healthspan extension. An alternative is a short-term acceleratedgeroprotector trial that tests if geroprotective intervention can slow the rate of biological aging. Biologicalaging is the gradual a e of biological aging. But this has not been tested. Our study will test if the best-established geroprotective intervention in animals, long-term caloric restriction, slows the rate of biologicalaging in midlife humans, who are still young enough for age-related disease to be delayed or prevented.We will conduct new assays of stored biospeci genome DNA methylation (using Illumina chips) and gene expression(using RNA sequencing) from blood samples collected at CALERIE baseline, and at 12-, and 24-monthfollow-ups. We will use this 3-time-point repeated-measures multi-omics dataset to test (i) Does CR slowsthe rate of biological aging as measured from DNA methy rs. The proposed project will generate newknowledge about effects of caloric restriction on biological aging in humans and test proof of concept for anaccelerated geroprotector trial design that can speed translation of new age-delaying therapies fromanimals to humans. Open data sharing through the CALERIE Biorepository will enable

al assessments. The Coronary Artery Risk Development in Young Adults (CARDIA) study provides a unique opportunity to study functional status in a diverse, aging cohort. The Year 35 in-person exam is scheduled for 2020 and 2021, at which time, participants will be 53 to 65 years old. We propose a CARDIA ancillary study to obta red by physical performance versus self-report, 3. To identify health-related risk factors in early adulthood for functional limitations and disability in middle-age, 4. To identify health-related, socioeconomic, and psychosocial factors that contribute to between- and within- race differences in functional limitations and disability among mi ures (basic and instrumental activities of daily living) will be added to the Year 35 exam and annual telephone calls (1 call prior to and 2 after the Year 35 exam). As studies of younger populations have not often included functional assessments, the conceptualization, measurement approaches, risk factors, and implications of functional

s with presbyosmiaoften show a decreased interest in food, can withdraw socially, and exhibit higher rates of depression.Furthermore, many age-related neurological diseases, including Parkinson's disease and Alzheimer's disease,are commonly associated with olfactory dysfunction. In fact, olfactory loss often precedes various motorics transductionand brain aging is not well understood. C. elegans is a well-established model organism for neuroscience andaging research due to its simple nervous system, short lifespan, and powerful genetic tools. Very importantly,genetic studies from multiple model organisms have shown that the evolutionarily conserved genetic prog and aging areregulated by the evolutionarily conserved genes and signaling pathways, our innovative studies on C. elegansglial cells in olfaction and age-associated olfactory decline will provide mechanistic insights into similarprocesses in other species.

future brain and body health. Our own findings suggest that behavioral chronic pain characteristics are associated with multiple biological biomarkers where a greater pain burden is associated with accelerated detrimental biological processes. However, prospective research is urgently needed to determine pain?s impact on the heterogene pain and physical function across racial/ethnic groups over time. We will prospectively assess pain along with multiple biomarkers as predictors of cognitive, psychological and physical functional progression among middle-aged and older non- Hispanic Blacks and non-Hispanic Whites with knee pain and controls over a four-year study avioral basis, with the potential to reduce race/ethnic group disparities and improve pain-related health and functional outcomes.

adex,knee pain and joint space width). The latter challenge is responsible for low powering of clinical trials andnumerous drug trial failures. Using a systematic, unbiased and iterative approach, we have created a multiplereaction monitoring (MRM) proteomic panel for serum-based prediction of knee OA structural progression anddiagn arthritisInitiative, the Johnston County Osteoarthritis Project and the Chingford cohorts. With this further qualification,these new biomarker tools will be very significant for their potential utility for clinical trial and clinical use toinform strategies for phenotyping and earlier identification and treatment of OA patients. We also intend top

oxidativestress, muscle fiber damage and decreased diaphragm force production. In animal models, intermittentdiaphragm contraction during MV support attenuates VIDD. However, there are only limited data addressingthis problem in humans. Here, we propose to directly test the hypothesis that intermittent electrical stimulation(ES) o chondrial contributions to VIDD in humans. Of evengreater importance, there are no interventions available to attenuate these defects in humans. Here, we willtest the impact of an innovative experimental treatment, intermittent electrical stimulation (ES) of thehemidiaphragm during prolonged surgeries with MV, on mitochondrial fun will investigate the effects of ES onsingle fiber contractile properties and Titin integrity (Aim 2). Finally, we will study the effect of ES on proteolyticpathways (caspase, calpain and ubiquitin-proteasome) and ribosomal RNA markers of decreased proteinsynthesis implicated in VIDD (Aim 3).This research will provide evidence concer erapeutic strategies to maintain human diaphragm function during MV support.

ment of osteoarthritis(OA). Therefore, new strategies are needed to enhance endogenous meniscus repair and tissue regeneration.The menisci play a critical biomechanical role in the knee, providing load support, joint stability, and congruity.Meniscus tissue is maintained through a balance of anabolic and catabolic activities of meniscus cells have yet to be identified. Ouroverall goal is to identify meniscus mechanotransduction pathways and modulate thesepathways to promote meniscus repair and prevent OA development.Our work has shown that transient receptor potential vanilloid 4 (TRPV4) is a critical component in cartilagemechanotransduction and meta cus and identify modulators of this pathway that will be used to enhance tissue repair and preventOA development. We hypothesize that mechanotransduction by TRPV4 plays a key role in meniscus metabolismand can be modulated to enhance meniscus repair and prevent the development of OA. In this proposal, we willdetermine the c of TRPV4 that may function as novel drug targets to 1) treat patients with immobilized joints to simulate exerciseand maintain joint health; 2) enhance meniscus tissue regeneration using tissue engineering strategies; and 3)enhance meniscus repair and prevent the development of OA. Novel therapeutic targets identified in thisproposal c

ds new scientific significance to studies that have followed cohorts from childhood. It is also
s). We propose to administer a multimodal MRI protocol to the 1004 living members of the
s whether neural measures are linked to real-world behaviors (e.g., saving behavior)
and mind-body research linking brain function to physical health.

ntrast tomessenger RNA, sRNAs are protected from extracellular RNases and are measurable and
of the Elderly(Duke EPESE) community-based cohort of elders--identified 32 differentially

and senescence-related proteinsare associated with, and predictive of, clinically important
inary team will first determine theextent to which baseline concentrations of GDF8, GDF11,
heart failure, stroke); d)adjudicated falls and injurious falls, e) cognitive function (as Aim 1), and f)
mediate aging related disabilityand disease in older women and men. Ultimately, these proteins

essure gradient generates shear stress and stimulates nitric oxide production. Preliminaryevidence
alone improves walking endurance compared to sham control. We willconduct a randomized trial
es at twelve-month follow-up, six months after the IPC intervention iscompleted. We will also
tional performance and preventsfunctional decline in PAD, this non-invasive and well tolerated

biological mechanisms underlying OT's pain-relieving properties. This proposal is based on a
flammatory mechanisms contribute to these analgesic responses. We aim to 1) determine the
is currentlyused in obstetrics and may be an inexpensive, effective method for pain

nd progressive decline in system integrity that occurs with advancing chronologicalage. This
mens from the National Institute on Aging's recently-completed CALERIE Trial, which
lation? (ii) Does CR cause changes to geneexpression in the pathways known to mediate
research beyond thescope of this project to improve understanding of caloric restriction and

in measures of function by self-report and physical performance to be paired with the existing
ddle-aged adults. We will add measures of physical performance (fast and usual gait speed,
limitations and disability are poorly understood. Filling this knowledge gap by adding

ymptoms in these deadly neurological diseases. Despite the importance of olfaction to human
;ramsand signaling pathways play pivotal roles in regulating sensory transduction and aging

;ity of these biological processes within an individual to elucidate the underlying patterns of
y period. With strong support from the University of Florida, our interdisciplinary project,

osis of knee OA. The selection of proteins was based on results of extensive discovery proteomic
ursue formal Food and Drug Administration (FDA) qualification of the optimal marker set

f the human hemidiaphragm during prolonged cardiac surgeries with MV support
tion, single fiber contractileproperties and catabolic muscle pathways in human diaphragm. Using
ning the ability to improve mitochondrial function in the stimulatedhemidiaphragm, and identify

i cells. Thesecellular activities are controlled not only by biochemical factors in the joint but also
bolism. The activation of TRPV4 can block IL-1 induced catabolic responses andalso increases
:ffects of mechanical stimulation on TRPV4-mediated metabolism in healthy meniscus
can subsequently be developed into drugs to enhance meniscus repair and prevent the

A large and growing number of older adults experience progressive declines in physical function, culminating in age-related physical disability with no clear connection to a single disease. Although the etiology of age-related physical disability is complex and multi-factorial, emerging evidence implicates the mitochondria as pl and specific Sirtuins (i.e., SIRT3) in skeletal muscle, both of which are regulators of mitochondria biogenesis. The natural compound resveratrol appears to oppose the reductions in mitochondrial function associated with aging by affecting the expression of key genes, such as PGC-1α, which support oxidative phosphorylation of resveratrol supplementation on mitochondrial function in older adults, or whether the hypothesized changes in mitochondrial function translate to improvements in physical functioning. Thus, the proposed randomized, parallel study will determine, in older men and women (> 70 years), whether 90 days of resveratrol supplen resveratrol (n=20), or 1500 mg/day of resveratrol (n=20) for a 90-day period. We will collect muscle specimens from the vastus lateralis and blood at baseline and 90 days for biochemical analyses, as well as monitor blood chemistries and adverse events at monthly clinic visits. If our hypotheses are supported, this study will be

37. Project Title: THE BENEFITS AND HARMS OF LUNG CANCER SCREENING IN FLORIDA

Leader(s): BIAN, JIANG ; GUO, YI ;

UNIVERSITY OF FLORIDA

NIH R01CA246418 / (2020-2023)

Lung cancer is the leading cause of cancer related death in both men and women in the United States. Currently, approximately 70% of lung cancer patients are diagnosed at advanced stages, and the 5-year survival rate of advanced stage lung cancer is very low, at only 16%. Investigators have been searching for effective screen years making history or former smokes who have quitted within the past 15 years. Since the release of the landmark NLST results, many medical associations published guidelines to recommend LDCT-based screening for individuals at high risk for lung cancer and the Centers for Medicare and Medicaid Services (CMS) also d and policy makers started questioning whether the complication rate and false positives in real-world settings would be even higher than the rates reported in the NLST, which was conducted in a setting with well-established facilities and proficiency in cancer care. Therefore, we propose to understand the contemporary use of l related clinical information from clinical notes such as radiology reports; 2) to determine the appropriate and inappropriate use of LDCT among high-risk and low-risk individuals in Florida and to examine the test results of LDCT, the rates of invasive diagnostic procedures, postprocedural complications, and incidental findings patients and physicians better understand the harm- benefit tradeoff of lung cancer screening and transform such knowledge into practice to prevent avoidable postprocedural complications.

38. Project Title: COCHLEAR DETOXIFICATION SYSTEM

Leader(s): SOMEYA, SHINICHI

UNIVERSITY OF FLORIDA

NIH R01DC014437 / (2015-2020)

DESCRIPTION (provided by applicant): Living organisms are continuously exposed to and must defend against naturally occurring toxins and non- nutrient foreign chemicals (1-3). Cells possess a wide range of detoxification enzymes capable of removing thousands of toxic and foreign compounds. The glutathione transferase have become attractive drug targets. Epidemiological studies found a significant association between age-related hearing loss and GSTT1 and GSTM1 null polymorphisms in a Finnish population (5) and a Hispanic population (6). McElwee et al (7) conducted a cross-species comparative analysis to compare gene exp display increased expression of Gsta4, Gstm1, Gstm5, and Gstt1 genes in the cochlea. Collectively, these results suggest that GST detoxification enzymes may play an important role in ototoxicity. Cisplatin, a platinum-containing compound, is one of the most widely used chemotherapeutic agents (8-10). Evidence indicates tha associated with increased cisplatin resistance. Our preliminary study also found that cisplatin treatment up-regulates GSTA and GSTM genes in mouse cochlear organotypic cultures. Yet, how the cochlear detoxification system fights such ototoxic drugs at the molecular level remain poorly understood. The overall goal of our re

39. Project Title: AUTOPHAGY IN LIVER INJURY

Leader(s): KIM, JAE-SUNG

WASHINGTON UNIVERSITY

NIH R01DK079879 / (2007-2020)

DESCRIPTION (provided by applicant): Mitochondrial dysfunction is the major mechanism precipitating I/R injury which commonly occurs during liver surgery, trauma, hemorrhagic shock and liver transplantation. Sirtuin 1 (SIRT1) is an NAD+-dependent deacetylase that induces longevity, stress resistance and tumor suppre Accordingly, we propose that restoration or enhancement of hepatic SIRT1 will promote mitophagy and consequently ameliorate mitochondrial failure and liver dysfunction after reperfusion. To test our hypothesis, we will use hepatocytes isolated from SIRT1 wild type (WT) and knockout (KO) mice for characterization of cell establish novel therapeutic approaches for improving I/R-mediated liver failure.

40. Project Title: Evaluation of an Adaptive Intervention for Weight Loss Maintenance

Leader(s): ROSS, KATHRYN MARIE

UNIVERSITY OF FLORIDA

NIH R01DK119244 / (2019-2024)

Obesity remains a substantial public health challenge in the United States. Behavioral weight management programs have demonstrated effectiveness for weight loss, but long-term maintenance of these weight losses after the end of treatment tends to be poor. Evidence has demonstrated that individuals who can maintain their c attendance at intervention sessions). Attendance has been closely tied to weight outcomes, but rates tend to be poor and decline over time. The once-per-month, static treatment schedules of existing programs may contribute to these suboptimal outcomes; a participant experiencing a small lapse in weight-related behaviors may n adherence to program goals, and long-term weight maintenance outcomes. We propose to evaluate an innovative method of providing phone-based extended-care adaptive to participant needs. We have built a smartphone application that can be used by participants to track weight, dietary intake, and physical activity (key self-n propose to conduct a randomized controlled trial evaluating the impact of ADAPTIVE (delivered only when indicated by our algorithm or when initiated by participants via an in-app support request) versus STATIC (the monthly, pre-scheduled format used in existing extended-care programs) treatment provision on weight regu research will fill a critical gap in the weight management literature by building a foundational evidence base of proximal predictors of weight-related behaviors for future adaptive intervention development.

41. Project Title: HEMATOPOIETIC STEM CELL DYSFUNCTION IN THE ELDERLY AFTER SEVERE INJURY

Leader(s): EFRON, PHILIP A

UNIVERSITY OF FLORIDA

NIH R01GM113945 / (2015-2020)

DESCRIPTION (provided by applicant): People of advanced age (greater than 55 years old) have significantly increased morbidity and mortality after trauma. Since the elderly population is expanding, research into this disease process is increasingly relevant, especially with the escalating economic and health care burdens on aged after severe injury and subsequent infections. Specifically, neutrophils are replaced after inflammation through a process known as 'emergency myelopoiesis.' This occurs after severe injury when bone marrow granulocyte stores are rapidly released, and increased stem cell proliferation and differentiation along myeloid pa associated with aging modifies the emergency myelopoietic response to traumatic injury, resulting in inappropriate differentiation and maturation of myeloid cells, leaving the host susceptible to subsequent infection. We further propose that this failure of emergency myelopoiesis is due to age-associated, chronic activation of N properly expand and differentiate along myeloid pathways in the elderly response to trauma, and, if the resultant dysfunctional neutrophil population seen in the elderly after trauma results from these suboptimal ST-HSCs; 2) determine if the defects in aged ST-HSC function after severe injury, as compared to their juvenile cou in aging is due, at least in part, to defects in myelopoiesis that lead to genotypically, phenotypically and functionally deranged PMNs that fail to control infection. The third specific aim will translate our 'bench side' animal work to humans and this innovative approach could identify areas for intervention in cell types that are sti

42. Project Title: THE ROLE AND MECHANISMS OF LIPID AND LIPOPROTEIN DYSREGULATION IN SEPSIS

Leader(s): GUIRGIS, FAHEEM W

UNIVERSITY OF FLORIDA

NIH R01GM133815 / (2020-2025)

Sepsis is a dysregulated response to infection that has both fatal and non-fatal morbid consequences. Unfortunately, initial survival does not provide relief from morbidity for most sepsis survivors. Initial clinical trajectories include rapid recovery, early in-hospital death, and progression to chronic critical illness (ICU stay = 14 sepsis via several mechanisms (antioxidant/anti-inflammatory function, bacterial toxin clearance, steroid synthesis), but the exact mechanisms by which HDL and LDL protects against sepsis are not known. Lipid and lipoprotein dysregulation occurs in early sepsis, leading to failure to protect against sepsis. We have shown that sepsis, and the severity of the drop is predictive of death; and 5) low baseline LDL levels are associated with increased long-term community-acquired sepsis risk. Highly biologically active lipid metabolites are also present in the circulation during sepsis that may propagate and promote inflammation resolution and contribute t illness and sepsis recidivism). To test our hypothesis, we will capitalize on an established and experienced sepsis research team and the opportunity provided by an existing bank of samples from a diverse cohort of 80 community-acquired (CA) and 85 hospital-acquired (HA) sepsis patients from two-centers. This approach has also propose two-site prospective enrollment of a small cohort of sepsis readmission patients to study this novel and important outcome. This project satisfies the NIGMS mission of researching biological mechanisms that underlay the foundation for advances in treatment of diseases such as sepsis.

43. Project Title: IMPROVE PAD PERFORMANCE WITH METFORMIN. THE PERMET TRIAL

Leader(s): MCDERMOTT, MARY MCGRAE

NORTHWESTERN UNIVERSITY AT CHICAGO

NIH R01HL131771 / (2016-2021)

PROJECT SUMMARY Improve PAD PERformance with METformin: The PERMET Trial. Our work and that of others has established that people with lower extremity peripheral artery disease(PAD) have greater functional impairment, faster functional decline, and increased rates of mobility loss compared to people without propertiesof metformin in pre-clinical models that may benefit people with PAD include: calf skeletal muscle increases inperoxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a) (a major regulator ofmitochondrial biogenesis), calf skeletal muscle increases in mitochondrial protein expression and activit skeletalmuscle perfusion. No randomized clinical trials have studied whether metformin improves lowerextremity functioning in PAD. A definitive trial is needed. We propose a placebo controlled double-blind randomized clinical trial to establish whether metformin(2,000 mgs daily) improves and/or prevents decline in walkin performance, and quality of life. Calf muscle outcomes consist ofchanges in PGC-1a abundance, mitochondrial quantity, mitochondrial enzyme activity, capillary density,reactive oxygen species (ROS)-induced tissue damage, and autophagy. If metformin improves functional performance and prevents functional decline in PAD

44. Project Title: TRANSCRIPTIONAL REGULATION OF KCNH2

Leader(s): DELISLE, BRIAN P

UNIVERSITY OF KENTUCKY

NIH R01HL141343 / (2019-2023)

SummaryCircadian rhythms help to match the optimal function of the cardiovascular system to the daily changes in theenvironment. Normal cardiovascular rhythms provide a physiological advantage to people. Unfortunately,normal circadian signaling can also unmask a time-of-day pattern in adverse events like heart attack, st that helps toentrain endogenous rhythms to the environment. SCN rhythms are synchronized to the environment via light,and its signaling helps to coordinate the molecular rhythms in cells throughout the body. What is new aboutthis application is we determine how repeated changes in light cycle will impact molecular circadia molecular clocksignaling in the mouse heart and its regulation on ion channel function.Aim 1. To identify new mechanisms with which the cardiac molecular clock regulates different ion channels.Aim 2. To determine how repeated changes in light impact molecular clock signaling in the heart and ionchannel regulation.This pr

45. Project Title: IMPAIRED MITOCHONDRIAL ENERGETICS IS A DRIVER OF HEMODIALYSIS ACCESS RELATED HAND DYSFUNCTION

Leader(s): SCALI, SALVATORE T.

UNIVERSITY OF FLORIDA

NIH R01HL148597 / (2019-2024)

PROJECT SUMMARYCurrently, in the United States, there are ~425,000 patients receiving hemodialysis (HD) and it is estimated that30-60% of this population have some element of hand dysfunction after hemoaccess surgery. The underlyingpathophysiologic mechanisms responsible for this devastating problem are poorly u AVF surgery causes significanthemodynamic changes in the extremity which presents an adaptive challenge to the skeletal muscle andneuromotor end-plate. Supported by our previous work, as well as preliminary data on RD associated skeletalmuscle mitochondrial phenotypic changes, we propose that RD driven mitochondri undergoing AVF surgery todeveloping skeletal muscle and neuromuscular junction perturbations causing clinically significant handdysfunction. RD mediated mitochondrial impairments are further exacerbated by local hemodynamic changesfollowing AVF creation through maladaptive OS metabolic responses that drives the d mitochondrial-targetedantioxidant therapies delivered prior to- and following AVF surgery in mice. Using a novel RD murine AVF model,we will determine whether global (N-acetylcysteine) or mitochondrial-targeted (AAV delivery of mitochondrialtargeted catalase) antioxidant therapy have therapeutic potential for AVF-ind outcomes modulating the spectrum ofhand function will be determined.

46. Project Title: MOLECULAR MECHANISMS REGULATING PERIPHERAL ARTERIAL DISEASE PATHOBIOLOGY IN CHRONIC KIDNEY DISEASE

Leader(s): RYAN, TERENCE E

UNIVERSITY OF FLORIDA

NIH R01HL149704 / (2020-2024)

Peripheral artery disease (PAD) is caused by atherosclerosis in the lower extremities which leads to a spectrum of life-altering symptomatology, including claudication, ischemic rest pain, and gangrene requiring limb amputation. Complicating the etiology of PAD, patients typically present with comorbid conditions or risk facto diabetes). We have uncovered a novel molecular pathway that may link CKD and PAD pathobiology. We find that many uremic metabolites, which accumulate in CKD, cause chronic activation of the aryl hydrocarbon receptor (AHR) which leads to disruption of the mitochondrial electron transport system that exacerbates isch pathobiology. This hypothesis will be tested using muscle- and vascular-specific inducible knockout of the AHR as well as adeno- associated virus-mediated expression of the a constitutively active AHR in pre-clinical models of CKD/PAD. Finally, our recent human data indicate elevated AHR signaling in PAD patients with C

47. Project Title: CIRCADIAN CLOCK REGULATION OF MYOCARDIAL ION CHANNEL EXPRESSION AND FUNCTION

Leader(s): ESSER, KARYN A ; DELISLE, BRIAN P ;

UNIVERSITY OF FLORIDA

NIH R01HL153042 / (2020-2024)

The overall objectives of this proposal are to 1) define the genomic and transcriptomic mechanisms by which the cardiomyocyte clock regulates ion channels that contribute to cardiac excitability; and 2) disrupt the cardiomyocyte clock to link changes in circadian-ordered gene expression with electrophysiological properties of link time of day with a large-scale transcriptional program to support cellular homeostasis To date, our labs have used an inducible cardiomyocyte specific mouse model to knock out the core clock gene, Bmal1 (iCSBmal1). These studies showed that disruption of the myocardial clock is sufficient to decrease ventricular K+ and approaches with our mouse model system to define the circadian clock dependent control of temporal gene expression in both atrial and ventricular tissues. To address abnormal circadian clock function, our lab has used different models of circadian disruption, such as chronic phase advance or time restricted feeding to test link myocardial clock function with outcomes that include modified ion channel expression, cardiac excitability and arrhythmia vulnerability. The aims of this proposal are designed to test the following hypotheses: 1) The molecular clocks in both atrial and ventricular cardiomyocytes are necessary to direct daily chromatin accessib

48. Project Title: EMOTIONAL ENGAGEMENT DRIV

Leader(s): DING, MINGZHOU ; KEIL, ANDRE

UNIVERSITY OF FLORIDA

NIH R01MH112558 / (2017-2022)

Project?Summary??Emotional?dysfunction?is?at?the?core?of?many?psychiatric?disorders,?in?particular?fear,?anxiety,?post-?traumatic,?and?mood?disorders. ?Describing?the?neural?mechanisms?associated?with?emotional?processing?is?therefore?a?critical?issue?in?mental?health?care. ?Previous?attempts?to?define?the?neu functional? brain? imaging,?which? is? high? in? spatial? precision. ?This?approach,?called?steady-?state?potential?frequency-?tagging,?achieves?stimulus?specificity,?temporal,?and?spatial?resolution?across?the?whole?brain. ?It?is?unique?in?that?it?allows?researchers?to?identify?distinct?brain?networks?selectively?activa large-?scale? brain?dynamics? mediating? the? emotional? response? to? an? element? that? is? embedded? in? a? complex? visual? array. ? (2)?We? determine? how? conflicting? appetitive? and? aversive? information,? visual? and? auditory,? affects? these? brain?dynamics.? (3)? Finally,? we? translate? this? novel? method? avenues? for? objectively? evaluating? pre-?? to? post-?treatment? changes? in? appetitive/aversive?neural? reactivity. ? It? also? enables? measuring? neural? circuit? function? to? enable? quantitative? measurements? of?specific?psychopathology?and?for?identifying?treatment?targets?in?a?personalized? medicine? framework

laying a key role in the initial onset and progression of functional decline in many older adults. Additionally, our pilot data strongly suggest functional declines are associated with reductions in mitochondrial respiration, as well as decreases in oxidative mitochondrial enzyme activities and enzyme content. These changes were linked to and mitochondrial biogenesis. In another recently completed pilot study, we found resveratrol, at a dose of 1000 mg/day, significantly enhanced resting muscle oxidative metabolism (measured using near infrared spectroscopy), as well as cognitive and physical function, in older adults (age > 65 years). Despite promising findings from our mentation is associated with (i) increases in muscle mitochondrial function (State 3 & 4 respiration), (ii) increases in levels of PGC-1a, AMP-activated protein kinase (AMPK), and Sirtuins (i.e. SIRT1 and SIRT3), and (iii) improvements in functional performance, as well as metabolic risk factors. To achieve these aims, 60 moderate to lo the first to show that resveratrol improves mitochondrial function in muscle, and that these changes are associated with increased levels of physical function in moderate to low functioning older adults - the population who is at greatest risk of functional decline and physical disability.

ning modalities for the early detection of lung cancer so that patients can receive curative treatments at an early stage. When the National Lung Screening Trial (NLST) demonstrated the effectiveness of using low-dose computed tomography (LDCT) scan for lung cancer screening (LCS), researchers and physicians hope to save lives fro ecided to cover the LCS for Medicare beneficiaries who are at high risk for lung cancer. While many efforts have been made to accelerate the dissemination the beneficial LCS, the concerns over the high false positive rates (96.4% of the positive results), invasive diagnostic procedures, postprocedural complications and health care costs lung cancer screening and associated health care outcomes and costs using data from a real-world setting. Our study has three goals: 1) to develop an innovative computable phenotype algorithm to identify high-risk and low-risk individuals for LCS from both structured and unstructured (i.e., clinical notes) electronic health record (EHR) in real-world settings; and 3) to develop and validate a microsimulation model of the clinical courses of LCS incorporating the real-world data in LCS to estimate the long-term benefits and the cost-effectiveness of LCS. Our proposed study has the potential to reduce lung cancer incidence and mortality by informing policymakers and p

: (GST) detoxification system converts a non-polar toxic compound into a more water-soluble and less toxic form by conjugating the toxic compound to reduced glutathione by a variety of GST enzymes. GSTs are a superfamily of enzymes that are divided into several classes on the basis of their primary structure (1-3). Because of their pression changes in long-lived worms, flies, and mice, and found that GST and other cellular detoxification gene categories were significantly up- regulated in long-lived members of the three species, suggesting the GST detoxification system plays a major role in longevity or protection against aging in multiple species. Consistent with t one-third of all cisplatin-treated patients develop hearing loss. Such hearing impairment is dose-dependent, irreversible, and associated with loss of hair cells. Wheeler et al (11) performed meta-analyses of over 3 million single-nucleotide polymorphisms (SNPs) for cisplatin-induced cytotoxicity in 608 lymphoblastoid cell lines from se esearch proposal is to provide new basic knowledge of the molecular basis for the cochlear detoxification system and its role in the elimination of foreign chemicals throughout the lifespan.

ssion. The role of SIRT1 in ischemia/reperfusion-mediated liver injury is unknown. The goal of this study is to investigate the role of SIRT1 in I/Rinjury to liver and to develop therapeutic strategies to improve liver function after I/R. Our principal hypothesis is that calpain-dependent SIRT1 loss causes a sequential chain of defective mi ular mechanisms causing SIRT1 depletion, defective mitophagy, and onset of the MPT and cell death after I/R. In addition, we will use anesthetized WT and KO SIRT1 mice to confirm and extend our in vitro findings to an in vivo model of hepatic I/R. Finally, we will extend and translate our findings from mice into human liver biopsi

hanges in eating and activity can successfully maintain their weight loss; thus, attempts to improve weight loss maintenance have often involved provision of continued support through monthly ?extended-care? intervention sessions. While these interventions have demonstrated significant improvements in weight loss maintenance, effe ot receive support for several weeks, by which point they may be experiencing a larger lapse or weight regain. This can lead to feelings of frustration, shame, or embarrassment and disengagement from intervention. In contrast, tailoring intervention delivery such that sessions are provided when individuals are at ?high risk? for weight r onitoring behaviors in traditional behavioral weight management programs) and can further query participants throughout the week regarding self-report factors (e.g., ratings of hunger and the importance of staying on track with weight management goals) that indicate high risk for weight regain. We have also developed a predictive alg ain at 24 Months in 258 adults who successfully lose = 5% of initial weight during a gold-standard 16-week behavioral weight management program. Results of this study have clear treatment implications for the timing/frequency of sessions within extended-care weight maintenance programs, and this study will result in an innovative, l

our society. Despite decades of promising preclinical and clinical investigations in trauma, our understanding of this entity and why its effects are exacerbated in the elderly remains incomplete, with few therapies demonstrating success in any patient population. Recently, several aspects of innate immunity have been determined to be of thways results. Proper differentiation of myeloid cells from stem cells is dependent on activation of nuclear factor kappaB (NF. a protein complex that partially controls DNA transcription after stressful stimuli. Anappropriate emergency myelopoietic response to inflammation is essential to host survival but appears to be inadequate in the FB-dependent inflammatory pathways, and a failure of hematopoietic stems cells (LSK populations) after trauma to create functional myeloid populations in a NFB-dependent manner. Using a novel murine polytrauma (PT) model of murine hemorrhagic shock and injury that better recapitulates the human condition, we will: (1) determi nterparts, are caused by a chronic low-grade NF B-dependent inflammatory state and a subsequent failure to appropriately activate NFB-dependent pathways after trauma; and, (3) determine if the HSC senescence associated with elderly humans after severe trauma is also due to a failure to appropriately activate NFB-dependent pathway ll exhibit plasticity.

days with organ dysfunction). Late complications include sepsis readmission and late death, both of which have rates of approximately 40% at 90 days and 6 months, respectively. Circulating lipids play an important role in sepsis and cholesterol levels of both high density lipoproteins (HDL-C) and low density lipoproteins (LDL-C) are :: 1) HDL becomes dysfunctional (pro-oxidant and pro-inflammatory) in early sepsis (Dys-HDL); 2) elevated Dys-HDL levels positively correlate with and predict organ failure severity and are associated with poor outcomes including 28-day mortality; 3) HDL from older septic patients exhibits impaired cholesterol efflux capacity (requ o cholesterol dysfunction. Our data strongly suggest that lipid and lipoprotein dysregulation occurs in sepsis and leads to altered function, oxidation, and reduced levels that may influence clinical outcomes. We hypothesize that specific functional, lipidomic, and genomic changes in lipid and lipoprotein metabolism occur in early sepsis a several advantages: 1) cost-savings from use of existing samples with isolated mRNA, 2) a recent cohort of sepsis patients (2016-2018) consistently treated with institutional evidence-based management bundles, 3) availability of serial samples over time (enrollment, 48h, 28d, and 90d), sepsis readmission samples, and mRNA for the C/

PAD. However, few therapies are available that improve functioning or preventfunctional decline in people with PAD. Metformin is an inexpensive, widely available, well tolerated biguanide medication and the mostcommonly prescribed drug for Type 2 diabetes mellitus worldwide. Recent pre-clinical and preliminary humanevidence y,increases in capillary density in ischemic tissue, reductions in oxidative stress, increased autophagy (repair ofcellular damage), and improved endothelial function. These therapeutic properties target pathophysiologicconditions present in PAD. Therefore, we hypothesize that metformin will improve lower extremity functioningin peopl g performance in people with PAD. Participantswill be 212 people with PAD who do not have diabetes mellitus, since metformin is a first-line therapy for Type2 diabetes. Our primary outcome is change in six-minute walk at 6-month follow-up. Secondary outcomes are6-month changes in treadmill walking performance, brachial artery), this widelyavailable, inexpensive, and well tolerated medication will have a major impact on preventing mobility loss andimproving quality of life in the large and growing number of people with PAD.

roke,and sudden death in patients with underlying cardiovascular disease.Emerging data now show that abnormal or unhealthy daily rhythms can create a negative impact on normalhealth too. For example shiftwork, which repeatedly causes shifts in endogenous circadian rhythms, is anindependent risk factor for cardiovascular disease.I n signaling inthe heart.Most cells have a molecular clock signaling mechanism that cycles with a periodicity of ~24 hours. We foundgenetic disruptions in the molecular clock mechanism of heart cells (cardiomyocytes) primarily causesabnormal changes in cardiac electrophysiology by disrupting the regulation of ion channel function.T oject creates new knowledge at the interface between chronobiology and cardiac electrophysiology.

nderstood. The renaldysfunction (RD) milieu causes a variety of physiologic derangements in HD patients including increasedoxidative stress (OS) and chronic inflammation that have been implicated as major contributors to acceleratedatherosclerosis and elevated mortality. Profound changes in OS contribute to skeletal muscle and ne al dysfunction alters skeletalmuscle and neuromuscular junction responses to AVF induced ischemia leading to clinically apparent handdysfunction. Further, these pathways can be modified either prior to AVF creation or at first evidence of handdysfunction to reverse/prevent the functional impairment. Our hypothesis is that the RD mil iversity of clinicallyapparent hand dysfunction. Aim 1 will establish how RD impacts mitochondrial and cellular energetics that areexacerbated by AVF-induced limb ischemia. Using a series of in vitro experiments, we will uncover thebiochemical mechanisms by which RD impacts mitochondrial energetics leading to impaired oxidativ uced muscle dysfunction. Aim 3will evaluate the association between mitochondrial health and AVF-induced hand dysfunction in humanpatients. Mitochondrial health will be examined in-situ using permeabilized myofibers prepared from RD patientsbefore and after AVF surgery: mitochondrial phenotypic changes will be evaluated an

ors that accelerate disease evolution and substantially worsen pathology contributing to increased mortality risk. Among these, chronic kidney disease (CKD) accelerates the development of atherosclerosis, decreases functional capacity, and increases risk of amputation or death, however the underlying biologic mechanism(s) are poorly u emic muscle injury and impairs angiogenesis. Preliminary experiments demonstrate that genetic knockdown of the AHR is protective against uremic toxicity, whereas expression of a constitutively active AHR causes mitochondrial dysfunction. Thus, we propose to test the novel hypothesis that the chronic activation of the AHR pathwa CKD. We propose to extend these findings to establish a clinical link between muscle health/function, mitochondrial energetics, and AHR signaling in human PAD patients. Success in these studies will provide mechanistic insight into the impact of CKD on PAD pathology, and would provide a novel target for therapeutic developmen

atrial and ventricular cardiomyocytes. The outcomes will address significant gaps in our understanding for how the myocardial circadian clock regulates the expression of key cardiac ion channels and how abnormal cardiac clock function contributes to arrhythmia vulnerability. The mechanism regulating circadian timing, the molecular l Na+ channel gene expression, disrupt current levels, disrupt cardiac excitability, and increase arrhythmia susceptibility. These studies establish a critical role for the cardiomyocyte clock, independent of the central clock, in regulating the expression of different families of ion channel genes that impact the ionic balance needed for norm s between circadian disruption and arrhythmia vulnerability in mouse models. We have found that disrupting either light or feeding time cues is sufficient to induce pathological changes in cardiac rhythms in normal mice and to accelerate sudden cardiac death in a genetic mouse model of arrhythmia susceptibility. These studies support ility and transcriptional output including expression of key ion channel and ion channel regulatory genes. 2) Chronic disruption of the cardiomyocyte clock using altered time of feeding is sufficient to cause dysregulation of the cardiac clock resulting in an imbalance in cardiac ion channel expression and currents leading to altered excita

VEN BY COMPLEX VISUAL STIMULI: NEURAL DYNAMICS REVEALED BY MULTIMODAL IMAGING

AS ;

rophysiology?of?human?emotions?in?the?cognitive? neuroscience? laboratory? have? been? hampered? by? the? unavailability? of? conceptual? and?methodological? frameworks? for? studying? complex? emotional? responses? in? context? and? with? conflicting?information?present.?The?proposed?research?establishes?a?novel?tec ted?by?different?elements?of?a?complex?visual?scene?even?when?the?elements?are?spatially?overlapping? and? accompanied? by? stimulation? in? other? sensory? modalities.? We? combine? this? innovative?approach?with?a?novel?conceptual?framework?that?considers?changes?in?visual?perception?an?active?part?of?an?observe ? to? socially? anxious? observers,? testing? mechanistic?hypotheses? regarding? the? interactive? effects? of? trait? anxiety? and? chronic? stress? on? short-?term? reactivity? to?emotional? challenge.? The? long-?term? clinical? implications? of? the? proposed? research? are? manifold:? For?diagnostic?assessment?and?for?monitoring .?

large decline in peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a)
ne recent clinical trial involving obese, middle-age men, no study to date has examined the effects
w functioning participants will be randomized to receive a placebo (n=20), 1000 mg/day of

m lung cancer by screening high-risk population who aged 55 to 77 years and have a 30 pack
may hinder the utilization of lung cancer screening. This concern was magnified as researchers
data and to develop advanced natural language processing (NLP) methods to extract LCS
ractitioners on the appropriateness of contemporary use of LCS. This knowledge will help both

ytoprotective role and involvement in the development of resistance to anti-cancer agents, GSTs
hese reports, our preliminary studies found that long-living calorie-restricted C57BL/6 mice
ven HapMap panels. The study found that increased GSTM1 and GSTT1 expression was

itophagy, mitochondrial permeability transition (MPT) onset and hepatocyte death after I/R.
es. These studies provide critical mechanistic insights into lethal I/R injury to the lver, and will

ts have been modest. A key challenge is continued participant engagement (often assessed as
egain offers potential to disrupt this cycle and significantly improve program engagement,
orithm that uses this data to identify when individuals are at ?high risk? of weight regain. We
ow-cost, and easily scalable intervention for weight loss maintenance. Further, the proposed

vital importance to the young adult immune response, and this response is suboptimal in the
elderly as compared to younger patients. Specifically, we hypothesize that the myelodysplasia
ne if certain hematopoietic stem cells (HSCs), specifically short term-HSCs (ST-HSCs), fail to
s in bone marrow HSCs. This work proposes that increased susceptibility to infection after trauma

dynamically regulated in sepsis. HDL and LDL are both thought to play protective roles in
uired for toxin clearance and steroidogenesis); 4) HDL and LDL levels drop precipitously during
nd relate to relevant clinical trajectories (rapid recovery, early death, and chronic critical
l cohort, 4) age/gender matched control samples, 5) available clinical and outcomes data. We

suggest that metformin has previously unrecognized therapeutic properties. Therapeutic
e with PAD, by facilitating favorable changes in calf skeletal muscle and by increasing calf
flow-mediated dilation, calf skeletal musclebiopsy measures, patient-reported walking

n mammals the suprachiasmatic nucleus (SCN) in the brain is the primary circadian pacemaker
he goal of this application is to determine how repeated shifts in the light cycle impact

romuscularjunction dysfunction associated with muscle atrophy and frailty in this population.
ieu disruptsmitochondrial and cellular energetics resulting in elevated OS predisposing patients
ephosphorylation and increased OS. Aim 2 will determine the efficacy of global or
d their association withchanges in serial hemodynamic, neurophysiological and biomechanical

nderstood and vastly understudied compared with other comorbidities (i.e. smoking and
y results in ischemic muscle injury and impaired angiogenesis, thereby linking CKD and PAD
t aimed to treat a patient population that currently has few available options.

clock, exists in virtually all cell types in the body. A critical function of the molecular clock is to
al excitability. One goal of this project is to utilize large scale genomic and transcriptomic
our premise that disruption of day- night rhythms through environmental factors leads to altered
bility and increased arrhythmia vulnerability.

hnique?for?combining?electrophysiological?recordings,? high? in? temporal? precision,? with?
r?s? emotional? response,? to? address? the? following? Aims:? (1)? We? characterize? the?
?treatment?efficacy,?a?quantitative?brain-?based?marker?of?emotional?engagement? opens?

49. Project Title: BIOBEHAVIORAL MECHANISMS UNDERLYING SYMPTOMS AND HEALING OUTCOMES IN OLDER INDIVIDUALS WITH CVLU

Leader(s):   STECHMILLER, JOYCE K. ; LYON, DEBRA E ;

UNIVERSITY OF FLORIDA

NIH R01NR016986 / (2018-2023)

ABSTRACT Our long-term goal is to elucidate the complex biobehavioral mechanisms responsible for symptoms and healing outcomes for older adults? with venous leg ulcers (VLUs) for the development of targeted therapies that address both the patient-oriented outcomes and healing outcomes in this growing group of affected both wound-related symptoms and symptoms of pain, depression, anxiety, fatigue and cognitive dysfunction, collectively labeled as? psychoneurologic symptoms (PNS).? Guided by the National Institutes of Health Symptom Science Model (NIH-SSM) framework, the central hypothesis of this application is that there are interrelated wound-related; and,(2) Test associations and models over time for: (a) Patient-host factors and systemic inflammation with wound microenvironment; (b) Patient-host factors and wound microenvironment with systemic inflammation; (c) Patient-host factors, systemic inflammation, and wound microenvironment with wound he... across eight weeks time. We willfully characterize patient-host characteristics (age, comorbidities, sex, race/ethnicity, BMI, nutritional status, lifestyle habits, and wound treatment [pressure therapy, debridement, antibiotics]); systemic inflammatory activation (C-reactive protein and cytokines); wound microenvironment factors from a holistic perspective and to provide a basis for preventing or reversing the adverse health outcomes of CVLUs, a condition that differentially affects older and minority individuals.

50. Project Title: OPTIMIZING AAV VECTORS FOR CENTRAL NERVOUS SYSTEM TRANSDUCTION

Leader(s):   HELDERMON, COY D

UNIVERSITY OF FLORIDA

NIH R01NS102624 / (2017-2022)

Project Summary Mucopolysaccharidosis (MPS) IIIB is a neurodegenerative lysosomal storage disease (LSD) caused by deficient degradation of heparan sulfate. Clinically this manifests as cognitive decline, developmental regression, impaired mobility and ultimately premature death. There are currently no effective therapies. D been published for AAV9. However, for translation to human trials, it is essential to study a highly effective AAV capsid serotype which will deliver to cells in the requisite brain regions. More generally, for any treatment of human neurologic disease in which the central nervous system (CNS) is of substantially larger volume genetic bar code that identifies each vector and a second barcode that is incorporated during PCR amplification of each brain region isolated. The bar code system allows determination of distribution and the expression levels of each serotype in anatomical areas of interest. We will use this novel two-step barcoded AAV vector s provide the best delivery by region, are altered by presence of the disease, and are similar between primate and mouse models. The results will inform clinical trial vector selection across the spectrum of central neurologic disorders, including MPS III. Subsequently, our MPS IIIB gene construct will be packaged into the optimal two-step bar-coded AAV vector system to allow simultaneous delivery and assessment of 40 serotypes with capsid variants in each animal via injections into the brain or surrounding fluid. Brain distribution for each serotype will be assessed by quantitative next generation RNA sequencing of the various brain regions. The top enzyme assays to determine preclinical benefit in the mouse model. Overall, these studies will determine the effects of species, delivery site and disease state on brain delivery from a multitude of AAV serotypes. Through this study, we will identify the most promising vector(s) for clinical trial development in MPS IIIB and other

51. Project Title: ADHERENCE TO VENOUS THROMBOEMBOLISM PROPHYLAXIS GUIDELINES IN HOSPITALIZED ELDERS

Leader(s):   PAVON, JULIESSA M

DUKE UNIVERSITY

NIH R03AG048047 / (2014-2016)

DESCRIPTION (provided by applicant): There are important public health concerns related to inappropriate use of venous thromboembolism (VTE) prophylaxis among medically ill hospitalized elderly patients with low risk of VTE occurrence. Specifically, use of anticoagulants (heparin products) for VTE prophylaxis when ... sufficient risk to warrant prophylaxis, and use in this population is inappropriate. The first aim of this application proposes to determine the magnitude and scope of inappropriate use of anticoagulant VTE prophylaxis in low risk older adults. This aim will be achieved by using data abstraction from the Duke University Health S... Our second aim proposes to determine whether level of mobility during hospitalization is being used to influence use and duration of VTE prophylaxis among medically ill hospitalized elders. To achieve this aim, we will collect prospective observational data to objectively measure inpatient mobility using patient mounted acce... appropriate use and safety of anticoagulants in hospitalized older adults. Information from this study could be used in future proposals to study interventions to ultimately improve hospital practice in the care of older adults. Our investigative team at Duke is unique since we have expertise in all key fields of study: geriatrics, hos...

52. Project Title: METABOLOMICS OF LOW-TRAUMA FRACTURE AMONG OLDER WOMEN WITH DIABETES

Leader(s):   LEE, RICHARD H.

DUKE UNIVERSITY

NIH R03AG048119 / (2014-2017)

DESCRIPTION (provided by applicant): Among its associated medical complications, diabetes is associated with low-trauma bone fracture: Compared to older women without diabetes, older women with diabetes have 2-times the fracture risk. Paradoxically, this increased risk occurs despite diabetic women having a higher av... fracture will be significantly different. As prior studie have shown, there are significant differences in metabolic profiles, related to fatty acid and amino acid metabolism, associated with diabetes. Additionally, in an animal-based model of osteoporosis, significant differences were observed in the levels of fatty acids and branch... be addressed: 1) Assess the levels of amino acids, organic acids, and acylcarnitines in older women with diabetes, both with and without a history of low-trauma fracture; 2) Compare the metabolic profiles of older, diabetic women without a history of low-trauma fracture to those with a history of fracture. Under the first aim, aff... identifying candidate, fracture-associated metabolic profiles, by utilizing metabolomics. Given the increasing prevalence of diabetes and substantial fracture-related morbidity among older adults, the proposal is significant because it is critically important to understand the key factors in thi population that contribute to low-traum...

53. Project Title: EFFECTS OF AGING AND THE URINARY MICROBIOME ON RECURRENT URINARY TRACT INFECTIONS

Leader(s):   SIDDIQUI, NAZEMA Y

DUKE UNIVERSITY

NIH R03AG060082 / (2018-2020)

PROJECT SUMMARY/ABSTRACT Urinary tract infections (UTIs) are one of the most commonly diagnosed infections in older adults. UTIs cost $1.6 billion annually, impair health-related quality of life, and can have serious sequellae such as hospitalization, sepsis, or death. At all ages, UTIs are more prevalent in women than ... period. Recurrent UTI is not only more common in women, but especially more common in the post-menopausal life stage. In some women with recurrent UTIs, genetic factors facilitate bacterial adherence and repeated infection. However, recurrent UTI prevalence rises significantly in post-menopausal women, suggesting addit... and to determine whether particular microbial community types are associated with recurrent UTI. We aim to compare urinary lactobacilli in populations of women without recurrent UTIs to assess how lactobacilli change with aging and with the presence of vaginal estrogen therapy. Next, we aim to assess whether urinary lactob...

54. Project Title: HEAT SHOCK PROTEINS AND DISUSE MUSCLE ATROPHY

Leader(s):   JUDGE, ANDREW ROBERT

UNIVERSITY OF FLORIDA

NIH R03AR056418 / (2009-2013)

DESCRIPTION (provided by applicant): Project summary/Abstract Skeletal muscle disuse atrophy is a widespread physiological phenomenon associated with immobilization, bed rest, denervation, and space flight, or any general reduction in weight bearing activity. However, our understanding of the signaling molecules that r... rapidly, induced by a variety of cellular stresses. This induction has been shown to provide a variety of cytoprotective functions. During muscle disuse a member of the heat shock family, Hsp70, is consistently down-regulated and overexpression of Hsp70 during disuse abolishes the increase in NF-:B and Foxo3a transactivation Aims 1 and 2 if an increase in Hsp70 expression is sufficient to inhibit NF-:B-induced or Foxo3a-induced muscle fiber atrophy, and in Aim 3 if knock down of Hsp70 is sufficient to cause muscle fiber atrophy. To address these specific aims we will inject WT IKK2 plus Hsp70 expression plasmids (Aim 1), WT Foxo3a plus Hs... The findings from these experiments will lead to a greater understanding of Hsp70 in the regulation of NF-:B and Foxo3a signaling during skeletal muscle atrophy. PUBLIC HEALTH RELEVANCE: Project Narrative Skeletal muscle wasting due to disuse is associated with immobilization, bed rest, denervation, and space fligh... wasting.

55. Project Title: PROSOCIAL BEHAVIOR AND EXERCISE AMONG OLDER ADULTS

Leader(s):   FOY, CAPRI G

WAKE FOREST UNIVERSITY HEALTH SCIENCES

NIH R21AG027413 / (2008-2011)

DESCRIPTION (provided by applicant): Regular physical activity has been shown to enhance physical function and health-related quality of life and reduce morbidity and mortality among older adults. Unfortunately, compliance rates to physical activity programs are distressingly low, even among asymptomatic populations. M... These actions are a form of prosocial behavior, defined as voluntary, intentional behavior that results in benefits for another. The opportunity to help others seems to be a motive to inspire these individuals to at least engage in acute moderate physical activity. In previous pilot work (Section 4.1.a), we found that participants ran... behavior intervention to increase physical activity among 80 underactive older adults. To our knowledge, the use of prosocial behavior as a motivational tool for physical activity has not been investigated, and represents a novel approach. The PBPA program will allow participants to earn boxes of food for donation to the Secon... trial.

56. Project Title: A PILOT STUDY TO ADVANCE TRANSLATION OF MOLECULAR SIGNATURES OF BIOLOGICAL AGING

Leader(s):   BELSKY, DANIEL WALKER

COLUMBIA UNIVERSITY HEALTH SCIENCES

NIH R21AG054846 / (2017-2020)

PROJECT SUMMARY The broad aim of this proposal is to determine if any of several proposed methods to quantify biological aging in humans are promising for use in trials of interventions to increase healthy lifespan. The biological process of aging is thought to drive risk for many disabling health conditions and mortality. T... relative to theirpeers. For example a 30-year-old person with the body and mind of an average 50-year-old would have abiological age of 50. Interventions shown to reduce biological age or slow its increase would thus be strong candidates for increasing healthy lifespan. But in order to identify such interventions, measures of bi... modified, would extend healthy lifespan. The research proposed in this application aims to fill that knowledge gap by implementing and testing five of the most promising algorithms in an already-created database, the Dunedin Study. The Dunedin Study follows a population-representative birth cohort now in it's fifth decade of li... questions: 1) Are the different algorithms related to one another, i.e. do they measure the same thing? 2) Can they measure changes occurring in young adults as their trajectories of aging begin to diverge ? the time interventions would likely have their greatest benefit? and 3) Do they measure real-life experiences of health declin... what works and what doesn't.

57. Project Title: MOBILE INTERVENTION TO REDUCE PAIN AND IMPROVE HEALTH (MORPH) IN OBESE OLDER ADULTS

Leader(s):   BROOKS, AMBER K ; FANNING, JASON ;

WAKE FOREST UNIVERSITY HEALTH SCIENCES

NIH R21AG058247 / (2017-2020)

PROJECT SUMMARY Chronic pain has emerged as an urgent age-related health issue that significantly compromises physical functioning and quality of life, with the adverse effects amplified by both obesity and sedentary behavior. The annual cost of pain in the United States is nearly 30% higher than the combined costs of c... feasibility and acceptability of a novel, patient-centered intervention to reduce chronic pain and improve physical functioning in older adults, leveraging the combination of telecoaching and individually-adaptive mHealth tools to decrease both body mass and sedentary behavior. The proposal consists of two phases. The first phas... function) associated with the proposed intervention, and to estimate the sample size needed for a full scale randomized controlled trial design that compare the effects of the intervention versus usual care on pain ratings and physical function in overweight/obese older adults with chronic pain.

58. Project Title: WEARABLE TECHNOLOGY INFRASTRUCTURE TO ENHANCE CAPACITY FOR REAL-TIME, ONLINE ASSESSMENT AND MOBILITY (ROAMM) OF INTERVENING HEALTH EVENTS IN OLDER ADULTS

Leader(s):   MANINI, TODD ; RANKA, SANJAY ;

UNIVERSITY OF FLORIDA

NIH R21AG059207 / (2019-2021)

ABSTRACT Older Americans experience approximately 29 million falls and 13 million hospitalizations per year. The intervening health events (IHE - episodic falls, injuries, illnesses, and hospitalizations) are strong precipitants of disability in older adults. Because of their episodic nature, IHEs are extremely difficult to study. ... continuous connectivity, bidirectional interactivity and remote programming. ROAMM will create a detailed narrative about mobility (activity patterns, walking speed, life space), patient reported outcomes/symptoms (pain, poor mood, fatigue, disability), cognition (working memory, processing speed, and executive functioning) ... framework consisting of the watch application and accompanying server. We will also assess test-retest reliability, convergent validity and participant usability/acceptability. Each year, an Independent Advisory Panel and External Advisory Committee will evaluate milestone-driving activities and our Go/No-Go checkpoints for t... collected by ROAMM are independent predictors of incident IHE's; 2) IHE's will negatively impact the course of ROAMM measures; and3) Additional value will be gained for explaining the change variability and recovery trajectories. An exploratory aim will evaluate safety while using ROAMM features and identify predictor... become the go-to place for remote data capture. These activities will create a sustainable infrastructure to ensure research on older adults is keeping pace with the state-of-the-art ?smart and connected? health with wearable technology.

59. Project Title: SYSTEMATIC ANALYSIS OF CLINICAL STUDY GENERALIZABILITY ASSESSMENT METHODS WITH INFORMATICS

Leader(s):   HE, ZHE ; BIAN, JIANG ;

FLORIDA STATE UNIVERSITY

NIH R21AG061431 / (2019-2021)

Clinical studies are often conducted under idealized and rigorously controlled conditions to improve their internal validity and success rates, but compromise their external validity (i.e., generalizability to the target populations). These idealized conditions are sometimes exaggerated and reflected as overly restrictive eligibility c... assess the generalizability of a clinical study, so that stakeholders including pharmaceutical companies, policymakers, providers, and patients would be able to understand and anticipate the possible effects of the interventions in the real world. In the past two decades, a large number of studies have assessed generalizability, but ... two-fold: (1) the lack of evidence to demonstrate their validity, which also leads to the lack of consensus on the best practice for generalizability assessments; and (2) the lack of readily available, well-vetted statistical and informatics tools. Motivated to fill this gap, we propose to first systematically review the extant methods f... documentations and tutorials. The success of this R21 project will (1) fill a knowledge gap on the validity and utility of the different generalizability assessment methods; (2) provide an easy-to-use toolbox ctGATE for assessing study generalizability much-needed by the clinical research community; (3) help the clinical researc...

60. Project Title: ADVANCING INTERDISCIPLINARY SCIENCE OF AGING THROUGH IDENTIFICATION OF IATROGENIC COMPLICATIONS: THE UF EHR CLINICAL DATA INFRASTRUCTURE FOR ENHANCED PATIENT SAFETY AMONG THE ELDERLY (UF

Leader(s):   INGIBJARGARDOTTIR, RAGNHILDUR ; LUCERO, ROBERT J ;

UNIVERSITY OF FLORIDA

NIH R21AG062884 / (2019-2021)

Iatrogenic conditions are a continuing public health concern, causing death among an estimated two hundred and fifty thousand older adults annually in United States (US) hospitals. Hospital-acquired falls and hospital- induced delirium are among the most common and costly iatrogenic conditions, and their occurrences are link... methods. The development of a research data infrastructure that supports the use of text and structured data is critical for a learning health system aimed at improving care and patient outcomes. In this project, we propose to expand the research infrastructure for electronic data-driven knowledge generation through the developm... registered nurses' (RNs) progress notes for prediction of hospital-acquired falls. We will employ a combination of supervised and unsupervised text-mining methods to identify text attributes associated with patient falls. We will then leverage a predictive model of patient fall risk factors developed in previous work to generate a... into the existing UF Health Clinical Data Warehouse (CDW) infrastructure and test to assess functionality, durability and scalability. In addition, we propose to develop the human resource infrastructure to support data-driven interdisciplinary aging research. This will be achieved by training graduate students in interdisciplinar... every day.

61. Project Title: NICOTINAMIDE RIBOSIDE AS AN ENHANCER OF EXERCISE THERAPY IN HYPERTENSIVE OLDER ADULTS: THE NEET TRIAL

d individuals.VLUs, which account for 70?90% of ulcers found in the lower leg, affect 2 million persons annually, includingnearly 4% of people over age 65 years. To date, the basic biology underlying the development and persistenceof VLUs and the influence of aging and multiple disease conditions on wound healing are generally no
lated molecularmechanisms by which the immune activation that contributes to the development and persistence of CVLUalso leads to the development, persistence and severity of PNS. The specific aims of the proposed study areto: (1) Characterize the strength of the associations at baseline among patient-host factors, systemicinflamm
sling; (d) Patient-hostfactors, systemic inflammation, and wound microenvironment with symptoms (PNS and wound-related) and (e)Patient-host factors, systemic inflammation, wound microenvironment and wound healing with symptoms (PNSand wound-related). To achieve the specific aims, we will longitudinally examine 200 older
(local inflammation [Matrixmetalloproteinase (MMP) enzymes C-reactive protein, cytokines], biofilm, and micro RNAs); symptoms (PNS[cognitive dysfunction, pain, fatigue, and depressive/anxiety symptoms] and wound-related); and woundcharacteristics and healing trajectory at the five timepoints. This knowledge is critical to provi

ue to the neurodegenerativenature of this disease, optimal CNS transduction is necessary for human trials. Several groups havedemonstrated improvement of the mouse model using different adeno-associated viral (AAV) vectors. We haverecently demonstrated that AAV8 has better brain gene delivery in MPS IIIB than wild type mice.
and is phylogenetically distant compared toour current mouse models, we will need to identify an optimal vector and delivery method for CNS approaches.To this end, we have developed a novel two-step bar code AAV vector system that allows assessment of multipleAAV vector serotypes within the same animal, greatly reducing the n
ystem electronic records to determine (1) the prevalence of low risk elders using criteria proposed by ACCP guidelines, and (2) anticoagulant VTE prophylaxis use in this group. Guideline directed use of pharmacologic VTE prophylaxis on mobility evaluation. Mobility is a key component of risk stratification. Poor mobilit
lerometers during patient hospital stays. Our goal is to improve the appropriateness of use of VTE prophylaxis among those in which the risks of harm may outweigh the benefit. Results from our study will provide important insights about use of risk assessment, and the relationship between patient mobility and VTE prophylaxis. These
vector to assess treatment effect in MPS IIIB mice. We hypothesize that CNStransduction and distribution will differ by serotype and species and that some serotypes will transduce differentlybetween wild type and Sanfilippo Syndrome mice. Our specific aims are therefore:1. We will determine the brain delivery of AAV serotypes in no
three vectors for brain delivery by this method will be used individually to identify the cell types treated and pattern of gene expression in mice and NHP.2. Assess the effect of the AAV serotype with the best distribution in the thought processing and motor coordination regions of the brain carrying the MPS IIIB gene to treat the MPS II
r neurodegenerative disorders. If this project is successful, we will be in aposition to quickly move towards such clinical trials.

ot medically indicated may be harmful, and is a major patient safety issue that also has a significant cost effect on health systems. To this end, the American College of Chest Physician (ACCP) 9th Edition guidelines explicitly recommend a risk-stratification approach, rather than universal use of anticoagulants for VTE prophylaxis. Eve

erage bone mineral density. The long-term goal is to understand how diabetes among older adults contributes to osteoporosis and low-trauma bone fractures. The objective of this application is to identify, among older, diabetic women, candidate fracture-related metabolic profiles. The central hypothesis is that compared to older, diabeti
ed chain amino acids, using targeted metabolomics. The rationale for the proposed study is that the contribution to incident fracture risk among older women with diabetes can be determined in prospective studies, once candidate metabolic profiles are known in this population. In this proposed, cross-sectional study of diabetic women, a
ter controlling for both measures of bone metabolism and functional status, the association between a history of low-trauma fracture and the levels of branched-chain amino acids and acylcarnitines, will be measured using targeted metabolomics. Under the second aim, the association between a history of low-trauma fracture and other me
na fractures. The results from the proposed study will inform the design of future studies to develop clinically applicable prospective screening tools toidentify at-risk individuals.

men, with up to 50% of all women experiencing a UTI during their lifetime. Theincidence of UTI rises in older women with over 10% of women older than 65 and almost 30% ofwomen older than 85 reporting a UTI within the prior 12 months. Among women with UTIs, there exists a subgroup with recurrent UTIs, defined as 3 or mor
ional non-genetic mechanisms associated with aging. The urinary microbiome is one potential non-genetic factor that could influence recurrentUTIs with aging. We now have significant evidence that a urinary microbiome exists, and thatdysbiosis may be associated with health versus disease. Our long-term goal is to improve ourunders
acilli or other microbes are associatedwith recurrent UTI in postmenopausal women who are using vaginal estrogen. Finally, we aim todetermine whether there are distinct microbial community types that are associated withrecurrent UTI in older women.

regulate muscle mass during disuse are ill defined. Therefore the long-range goal of our research program is to understand the regulation of signaling pathways that cause muscle atrophy during disuse. Eventually improved understanding will lead to the identification of targets for specific interventions. Heat shock proteins (Hsps) are a fa
n, and completely prevents skeletal muscle atrophy. This is important since NF-:B and Foxo3a are required for disuse muscle atrophy. However, it is currently unknown whether Hsp70 overexpression is sufficient to specifically inhibit NF-:B-induced or Foxo3a-induced muscle atrophy. It is also unknown whether knock down of Hsp70 i
p70 expression plasmids (Aim 2), or a plasmid producing shRNAs specific for Hsp70 (Aim 3) into the skeletal muscle of rats and measure NF-:B or Foxo3a activity, the mRNA expression of specific atrophy genes and muscle fiber cross sectional area. If an increase in Hsp70 expression inhibits NF-:B activity and/or Foxo3a activity we
t, or any general reduction in weight bearing activity. In the proposed work we will genetically overexpress or knock down a protein that is believed to regulate muscle size and is known to be down-regulated during muscle wasting caused by disuse. This will allow us to directly determine the involvement of this protein in the regulatio

Many traditional exercise interventions do not provide the self-regulatory skills necessary for long-term behavioral change. These issues become more prominent as the population of older Americans continues to increase. Although only a small percentage of older adults engage in habitual physical activity, there are episodic charity even
domized into a prosocial behavior physical activity group demonstrated increased physical activity at 3 months compared to those in a standard exercise group. Our current research question contemplates whether prosocial behavior may be implemented as a viable behavioral incentive for long-term physical activity. Therefore, the prima
d Harvest Food Bank of Northwest North Carolina based upon their weekly physical activity. Other specific aims include determining the ability to successfully recruit participants into the study, the ability of participants to adhere to the PBPA program, and the ability to retain participants throughout the study. If successful, preliminary

here is evidence thattrajectories of aging begin to diverge as early in life as young adulthood. If this process can be measured, itwill speed development of interventions to prevent disease and disability and prolong healthy life. Onemeasurement approach is to calculate a ?biological age.? In contrast to a person's chronological age, which
ologicalage are needed. Several algorithms have been proposed to calculate a person's biological age from panelsof clinical biomarkers and whole-genome data on blood DNA methylation and RNA expression. Thesealgorithms represent highly-scaleable methods ideal for implementation in intervention trials. But a criticalknowledge ga
fe. Thedatabase includes genome-wide DNA-methylation, RNA-expression, SNP, and clinical biomarker data on 954individuals along with extensive physical and cognitive function testing. Research aims will test if the differentalgorithms measure a common process of biological aging that drives disease and disability. Studying all of t
: imaging ? deficits in physical and cognitive functions and subjective perceptions of aging? Results will informwhich, if any, of the proposed biological aging algorithms show promise for implementation in interventiontrials. This could lead immediately to their implementation in archived biospecimens from completed trials.Results wil

ancer and diabetes. In 2016, the NIHcalled for a National Pain Strategy to: 1) expand non-pharmacological treatment options in older adults, who areparticularly susceptible to the side effects of opioid and other pain medications; 2) develop accessible treatments that aretailored to individuals; and 3) increase the development of self-man
e will use an iterative user-centered design process to develop the mHealth application, to adaptthe weight loss and sedentary behavior components of the intervention to a telecoaching model, and to evaluate theusability and feasibility of the intervention for obese, older adults with chronic pain. In the second phase we will conducta pilo

. Continuous,long-term monitoring with remote capabilities using wearable technology is an ideal solution for capturinginformation surrounding an IHE and in particular, preceding it. This R21/R33 project aims to develop asustainable research infrastructure built on the foundation of a smart watch application and server calledROAMM
and reports ofhealth events (falls and hospitalizations). The infrastructure is composed of a diverse group of investigatorswith expertise in mobile technology/data science and applied/medical sciences who will serve in the followingcores: Wearable Technology, Phenotyping, Clinical Outcomes, Data Science Management & Quality, an
ransitioning to the R33phase. Work proposed in the R33 phase will showcase the ROAMM infrastructure by conducting aprospective, longitudinal study (range 1.25-2.5 yrs) in 200 community-dwelling persons aged 70+ yrs. Thisphase will test a field deployable version of ROAMM in real world settings to address the following hypoth
s of ROAMM adherence using bothkey-informant interviews and examine demographic and health histories to create boundaries for usingROAMM and other systems like it for long-term, continuous monitoring in research and practice. We willsustain ROAMM by targeting grant opportunities for the wearable technology surge for reme

riteria. Certain population subgroups are often excluded with unjustified criteria and are subsequently underrepresented. Older adults have been especially underrepresented in cancer studies. The underrepresentation of these population subgroups reduces the treatment effects and increases the likelihood of adverse outcomes in diverse po
mostly were after the fact, ad hoc, not systematic, and focused on specific diseases and sets of trials without a formalized approach. So far, there is a significant knowledge gap between the available methods for generalizability assessment and their adoption in research practice. Most generalizability assessments have been conducted as
r generalizability assessments, and then use a data-driven strategy to reproduce, evaluate, and compare these methods with our unique data resource, the OneFlorida Data, one of the 13 PCORI-funded Clinical Data Research Networks that contains linked EHRs, claims, and cancer registry data for ~15 million Floridians. We will develop
hers choose the most appropriate generalizability assessment methods with readily available implementations; and (4) build a body of evidence to support the development of an eligibility criteria design tool for optimizing study generalizability at the study design phase.

-ECLIPSE)

ked to each other. Advances in computing technology and availability of electronic data presents opportunities to more accurately identify identifying patients at risk of suffering a hospital-acquired fall or hospital-induced delirium. Clinical data is now being captured electronically for about 80% of the US population. Approximately 75-
ent of the University of Florida (UF) EHR Data Infrastructure for Patient Safety among the Elderly (UF-ECLIPSE). The long-term goal of our research program is to enhance the safety of hospitalized older adults by reducing iatrogenic conditions through an effective learning health system. We plan to carry out the following aims: Spe
composite model of text and structured data to predict the odds of a patient falling. Specific Aim 2 (R33 Phase): Determine and evaluate the structural and human resources of an expanded research-data infrastructure to support sustained interdisciplinary aging studies. We will develop and pilot test text-mining pipelines to generate a pr
y data science for aging research. The UF-ECLIPSE research team will be among the first to implement and test an integrated data repository that utilizes nurse-generated structured and text data to support a learning health system. This study will create important new research data infrastructure, and will be a model for health care organ

t wellunderstood. Individuals living with chronic VLU (CVLU) have a high symptom burden of
ation, and wound microenvironment with wound area and symptoms (PNS and
adults (age >60)who are receiving state of the art, standardized wound treatment biweekly
de a foundationfor developing targeted interventions to address this critical health problem

A similar findingof altered brain delivery in Sly Syndrome compared to wild type mice has
number of animals needed for statisticalcomparisons of brain delivery. This system has a
a better vector distribution. We will identify which wild-type AAV serotypes or capsid mutants
on-human primates (NHP) and in wild type and MPS IIIB affected mice. We will use a novel
IB mouse. We will use day/night activity, hearing, coordination, lifespan, lysosomal storage and

n though many medical inpatients are at high risk for VTE, there are others whom do not have
y evaluation by providers may be a significant barrier to appropriate use of VTE prophylaxis.
results are critical to understanding how to take the next steps toward improving the

: women without a fracture history, the metabolic profiles of those women with a low-trauma
ge   65 years, recruited from general endocrine and primary care clinics, the following aims will
etabolite classes will be measured using non-targeted metabolomics. The approach is innovative in

eculture proven infections within 12 months, or >2 culture proven infections in a 6 month
tanding of the microbes that occupy the urinary niche, how these microbes change withaging,

mily of proteins that are constitutively expressed in cells, but whose expression is further, and
s sufficient to cause skeletal muscle atrophy. The objective of the current proposal is to determine in
will determine the mechanisms of this by determining the proteins in each pathway that Hsp70 binds.
of skeletal muscle mass, and could identify the protein as a novel therapeutic target for muscle

ts involving moderate physical activity that attract large numbers of participants of all age ranges.
ry aim of this investigation is to determine the feasibility of conducting a 9-month prosocial
data from this study will be used to seek R01 funding to conduct a fully powered, longitudinal

scounts time since birth, a person's biological age reflects the condition of their body and mind
p is whether the algorithms actually measure the process of biological aging that, if
he algorithms together in a young, still-healthy cohort followed over time will answer three
l also inform future approaches to developing measures of biological aging by identifying

agement programs for chronic pain. The purpose ofthis R-21 is to develop and test the
t randomized controlled trial to provide initial evidence for effect sizes (pain and physical

(Real-time Online Assessment and Mobility Monitor). It will offer long-term and
dRecruitment, Retention & Compliance. In the R21 phase, we will create the ROAMM
eses:1) Pre-event patterns of low mobility, disability, fatigue, pain and depressive mood
te patientinteraction, adopting licensing fees, and aligning our services with larger entities to

pulations when the interventions were moved into clinical practice. It is imperative to rigorously
an ad hoc auditing effort by a third party after the fact. We believe the key barriers are
an open-source generalizability assessment software toolbox and its accompanying

80% of clinical data is text data which cannot be analyzed using traditional statistical
cific Aim 1 (R21 Phase): Identify and test the feasibility of text-mining pipelines to process
ediction model of hospital-induced delirium. We will then integrate the developed pipelines
izations to increase safe effective care for the millions of older adult Americans hospitalized

Leader(s):

MANKOWSKI, ROBERT

UNIVERSITY OF FLORIDA

NIH R21AG064282 / (2019-2021)

ABSTRACTMore than 80% of older adults have hypertension, with higher prevalence of high systolic blood pressure (SBP)putting them at high risk for cardiovascular (CV) disease and death. Because drug therapy that lowers SBP isassociated with side effects such as hypotension, syncope, and kidney dysfunction, there is a g adeninedinucleotide (NAD+), a cofactor for the deacetylase sirtuin1 (SIRT1), may contribute to age-related vasculardysfunction via oxidative stress and reduced nitric oxide (NO). Exercise-induced overexpression of NAD+-dependent SIRT1 improves the bioavailability of NO. Preclinical evidence suggests that poor vascular-f SBP-lowering effect in hypertensive older adults. Initial human clinical trials demonstrated that nicotinamide ribosidesupplementation (1,000 mg/day) was safe and showed a higher potential to reduce SBP and arterial stiffnessin participants with elevated SBP. As we have preclinical evidence that combining NAD+ replenishm center-basedwalking exercise, or (2) the same exercise program combined with placebo, or (3) 1,000 mg/day ofnicotinamide riboside alone. All participants will undergo daytime continuous SBP and arterial-stiffnessmeasurements by pulse-wave velocity at baseline and at 6 weeks. Elevated SBP will then be determined asdaytim Phase III clinical trial in hypertensive older adults. The ultimate goal of this line of research is to findadjuvant strategies to improve the exercise's SBP-lowering effects in older adults.

62. **Project Title:**   EVALUATING EFFECTS OF AGE-RELATED MICROBIOTA MODULATIONS IN HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS

Leader(s):   SUNG, ANTHONY ; CHAO, NELSON J. ;

DUKE UNIVERSITY

NIH R21AG066388 / (2019-2021)

Allogeneic hematopoietic stem cell transplant (HCT) has the potential to cure patients with hematologicmalignancies. However, HCT is associated with significant treatment related mortality (TRM) ranging from 20-30%. (1). TRM is particularly high in patients with advanced age (hazard ratio 1.84, age >60 years vs.

63. **Project Title:**   DYSREGULATION OF SARCOMERE STABILIZING PROTEINS CAUSE MUSCLE ATROPHY AND WEAKNESS DURING CANCER CACHEXIA

Leader(s):   JUDGE, ANDREW ROBERT

UNIVERSITY OF FLORIDA

NIH R21CA194118 / (2015-2018)

DESCRIPTION (provided by applicant): Cachexia is characterized by progressive skeletal muscle and body weight loss and affects up to 80% of cancer patients. This loss of muscle mass contributes to significant muscle weakness and diminished physical function and is associated with reduced tolerance to chemotherapy and i stimulus, and there is speculation that these disruptions may initiate catabolic processes which lead to the muscle atrophy and weakness. From our lab has identified that Kyphoscoliosis peptidase (Ky), which is essential to the structural integrity of the sarcomeric Z-disk, and Myocilin (Myoc), v downregulation of Ky and Myoc are causative to the loss of muscle structure leading to muscle wasting and weakness during the progression of cancer cachexia. Unpublished bioinformatics analyses of the -1kb to +1kb proximal promoters of genes significantly downregulated in skeletal muscle of C26 tumor-bearing mice reve activity in skeletal muscle of tumor-bearing hosts is causative in the downregulation of Ky and Myoc, and initiates disruptions in muscle fiber integrity and muscle wasting. Thus, our two specific aims are: Specific Aim 1: To test the hypothesis that the downregulation of Kyphoscoliosis peptidase (Ky) and Myocilin (Myoc) pla muscle wasting and weakness, opening up new avenues for therapeutic interventions.

64. **Project Title:**   DEVELOPING RESEARCH AT THE INTERFACE OF HIV AND AGING

Leader(s):   HIGH, KEVIN P.

WAKE FOREST UNIVERSITY HEALTH SCIENCES

NIH R24AG044325 / (2013-2018)

DESCRIPTION (provided by applicant): Effective antiretroviral therapy (ART) has resulted in many people with chronic HIV surviving into middle and old age. However, even those with controlled HIV viral replication, are more likely than uninfected subjects to experience premature chronic illness, multi-morbidity and func methodology, data acquisition and sharing, and research workforce education/training have hampered this goal. Multi-morbidity, functional decline and disability are typically research domains of geriatrics and gerontology. The Claude D. Pepper Older Americans Independence Centers (OAICs; aka 'Pepper Centers') were estab shared research platform, enhancing and accelerating investigation at the interface of HIV and aging by: 1) Harmonizing processes for data collection across OAICs and CFARs and providing a coordinated platform for data collection; 2) Validating key instruments/measures of function and geriatric phenotypes in HIV- infected healthcare needs in a rapidly growing population aging with HIV.

65. **Project Title:**   EPIGENETIC MECHANISMS PROMOTING LONGEVITY

Leader(s):   KRAUS, VIRGINIA

DUKE UNIVERSITY

NIH R56AG054840 / (2017-2018)

AbstractCirculating sRNAs are short non-coding RNAs (typically ~19-25nt in size). They mediate a broad spectrum ofbiological processes through regulation of gene expression. Experimental evidence indicates that the serumlevels of sRNAs change considerably--the vast majority increasing?with age. The ability of circulatin numerousrecent developments, we are far from understanding the role of sRNAs in aging. An understanding of their rolein aging mammals, and humans in particular, is still very limited due to the increased complexity and longerlife-spans of mammals compared with invertebrates. This project leverages existing human sample

66. **Project Title:**   EXTRACELLULAR VESICLES AND THEIR ROLE IN HALLMARKS OF AGING

Leader(s):   KRAUS, VIRGINIA

DUKE UNIVERSITY

NIH R56AG060895 / (2018-2019)

AbstractExtracellular vesicles (EVs) are membranous particles released from nearly all cell types into all bodily fluidsevaluated to date ? including serum and plasma. Depending on tissue of origin, health state and organismage, they carry a variety of complex cargo consisting of nucleic acids (5,000 microRNA documented to d establish EVswith their microRNA and protein constituents as biomarkers of healthspan and lifespan and to informbiological mechanisms promoting healthspan and lifespan. We focus particularly on three of the hallmarksof aging, epigenetic alterations, cellular senescence and altered inter-cellular communication. Increasingev models. In collaboration with Meso Scale Diagnostics, LLC (MSD), a premier developer of highlyreliable and highly sensitive biomarker assays, we will develop new biomarkers of EVs informing agingmechanisms and test their function in vitro. These biomarkers will be qualified in the context of aging in ourexisting extensiv detection) assays by MSD for soluble cytokines and circulating microRNAs we have identified asassociated with healthspan and lifespan in elders. Taken together, we believe our broad expertise inbiomarkers and aging, our interdisciplinary team and our partnership with a company with the capability tocommercialize assays p

67. **Project Title:**   MOLECULAR BIOLOGY IN BURNS AND TRAUMA

Leader(s):   MOLDAWER, LYLE L

UNIVERSITY OF FLORIDA

NIH T32GM008721 / (1999-2024)

This Ruth Kirschstein NRSA training Program proposes to take primarily surgeons and other critical caremedicine physicians during the second or third year of their general residency programs, and expose them totwo, three and even four years of mentored research in inflammation biology with highly productive basic science research experience. Select trainees will have the opportunity to complete a Ph.D. program in the GraduateSchool in three to four years. Other trainees can participate in graduate certificate programs which are formalcollections of courses that together form a coherent program of study offered through an academic unit. Thistrai vascular injury,delayed wound healing and the burn wound. The faculty will be drawn from funded basic and clinical scientistsin the Surgery, Medicine, Pathology, Aging and Geriatric Research and Molecular Genetics and MicrobiologyDepartments, who will serve as research mentors to the trainees. Clinical mentors from the Jacksonville). Successfulapplicants with the Executive Committee will identify a research and clinical mentor who will help formulate aformal training program and periodic review of the trainee?s progress. Furthermore, trainees are expected toparticipate in basic science seminars in the Institute on Aging, Emerging Pathogens successfully compete fortransitional funding in inflammation research and become leaders in academic surgery.

68. **Project Title:**   THE ENRGISE STUDY

Leader(s):   PAHOR, MARCO ; AMBROSIUS, WALTER T ;

UNIVERSITY OF FLORIDA

NIH U01AG050499 / (2015-2019)

DESCRIPTION (provided by applicant): Growing evidence from our group and others shows that low-grade chronic inflammation, characterized by elevations in plasma C-reactive protein, tumor necrosis factor alpha, and particularly Interleukin-6 (IL-6), is an independent risk factor o disability, impaired mobility, and lower w interventions for preventing major mobility disability by improving or preserving walking ability. We have maximized the public health impact of our proposed interventions by selecting interventions that are safe, tolerable, acceptable, and affordable for vulnerable older persons. Based on an extensive literature review, we prop impairment, as measured by slow gait speed and self-reported mobility difficulty, and who have elevated levels of IL-6, the marker most consistently associated with mobility limitations. Preliminary data regarding feasibility need to be gathered before such a tria can be effectively designed and implemented. We propose to con needed for the ENRGISE pilot and main trials, including the biorepository, and we will develop the materials needed for implementing the trials, including the protocol, manual of operations, data and safety monitoring plan, forms, quality control and quality assurance plan, and recruitment and retention materials.

69. **Project Title:**   THE ENRGISE STUDY

Leader(s):   PAHOR, MARCO ; AMBROSIUS, WALTER T ;

UNIVERSITY OF FLORIDA

NIH U01AG050499 / (2015-2019)

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70. **Project Title:**   THE ENRGISE STUDY

Leader(s):   PAHOR, MARCO ; AMBROSIUS, WALTER T ;

UNIVERSITY OF FLORIDA

NIH U01AG050499 / (2015-2019)

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71. **Project Title:**   UF PASS: REGULATION OF EXERCISE TRANSDUCERS

Leader(s):   ESSER, KARYN A

UNIVERSITY OF FLORIDA

NIH U01AG055137 / (2016-2022)

Abstract Exercise is a powerful and pleiotropic physiological stimulus that helps prevent many chronicdiseases and is used as a therapeutic for disease. While the beneficial effects of exercise are extensivelyacknowledged there is still very little understood about the molecular transducers of the systems-wide effects.The goal of support screening of novel transducers to quickly move the field forward.In Phase 1, UF PASS proposes to collect biospecimens for the Chemical Analysis sites following endurance(run-training) or resistance exercise protocols on male and female Fischer 344xBrown Norway rats (F344-BN)at three different ages. To better cap transducersthat function throughout the system to improve the well-established stress tolerance. The goal of these studieswill be to employ high throughput screening technologies to test up to 1500 myokines. We will then usesecondary screening techniques to test 100 candidates from which we will select up to 3 candidates for at 3-4, 16-18, and 27-29 mo.Specific Aim 3: Phase 2 Studies. The goal in Aim 3 is to test myokines as the exercise transducers forimproved stress tolerance.

72. **Project Title:**   MULTIMODAL IMAGING OF BRAIN ACTIVITY TO INVESTIGATE WALKING AND MOBILITY DECLINE IN OLDER ADULTS

Leader(s):   MANINI, TODD ; CLARK, DAVID J. ; SEIDLER, RACHAEL D ;

UNIVERSITY OF FLORIDA

NIH U01AG061389 / (2018-2023)

Project Description: Mobility impairments in older adults decrease quality of life and are associated with highsocietal and economic burden. NIH RFA-AG-18-019 solicits applications ??to investigate the central neuralcontrol of mobility in older adults?using innovative and cutting-edge methods.? Current approaches to studyth Wewill achieve this by using innovative mobile brain imaging with high-density electroencephalography (EEG).This approach relies upon innovative hardware and software to deliver three-dimensional localization of activecortical and subcortical brain regions with high spatial and temporal resolution during walking. The resu walking explainsmobility decline. In both cross sectional and longitudinal designs, we will determine whether poorer walkingperformance and steeper trajectories of decline are associated with the Compensation Related Utilization ofNeural Circuits Hypothesis (CRUNCH). CRUNCH is a well-supported model of brain activity tasks of increasingcomplexity. When the ceiling is reached, performance suffers. The RFA also calls for proposals to?Operationalize and harmonize imaging protocols and techniques for quantifying dynamic gait and motorfunctions?. In accordance with this call, our second aim is to characterize and harmonize high-density EE amajority of the objectives in NIH RFA-AG-18-019 and will identify the neural correlates of walking in olderadults, leading to unprecedented insight into mobility declines and dysfunction.

73. **Project Title:**   MOLECULAR TRANSDUCERS OF PHYSICAL ACTIVITY AND HEALTH: NC CONSORTIUM CLINICAL SITE

Leader(s):   KRAUS, WILLIAM E ; HOUMARD, JOSEPH A ; NICKLAS, BARBARA J ;

DUKE UNIVERSITY

NIH U01AR071128 / (2016-2022)

ABSTRACT Exercise is a powerful physiological stimulus contributing to disease prevention and intervention. Theprotective and preventive effects of exercise are well-documented for metabolic, neurodegenerative, andcardiovascular diseases, and certain cancers. While scientists acknowledge the extensive benefits ofexercise and health investigators well into the future. Two products of the MoTrPAC collective efforts will be apublically available data resource that will enhance and accelerate subsequent mechanistic research ondiseases and conditions affected by physical activity; and a biorepository of clinical and animal model samplesto be used i Consortium (NCCSC). The NCCSC consists of the experienced research teams Duke University Schoolof Medicine; East Carolina University (ECU); and Wake Forest School of Medicine (WFSM). As described inthe study plan, the NCCSC weighed a number of alternatives for training regimens, timing, and type of tissuesam responses of molecular transducers to a chronic exercise training program of either aerobic or resistance training. ? Aim 3: To determine the responses of molecular transducers to a detraining period following either aerobic or resistance training.

reat need foreffective lifestyle SBP-lowering interventions for the older population that can replace drug therapy. Whileaerobic exercise is a recommended lifestyle intervention for controlling SBP and preventing CV diseasenaturally, in older adults it has been shown to be less effective in vascular-tissue remodeling because ofarterial sti
function improvement in response to exercise in older mice is caused by insufficient NAD+ levels to stimulate SIRT1activity. Importantly, replenishment of NAD+ levels induced vascular remodeling, improved vascularfunction, and reduced SBP in mice. An objective of this study, therefore, is to test a combination of aerobicexercise and
ment with exercise is an ideal strategy for improving vascular function, our central hypothesis is that the intervention ofaerobic-exercise training combined with nicotinamide riboside supplementation will reduce SBP inhypertensive older adults more effectively than will exercise alone. We will enroll 45 participants 65 years andolder into
e average above 130 mmHg, measured by the 24-hour blood-pressure device. To our knowledge, thisstudy will be the first attempt to enhance exercise therapy with nicotinamide riboside in hypertensive olderadults. We believe that nicotinamide riboside is ?the missing piece of the puzzle? in improving vascularremodeling and SBP ma

ncreased complications from surgical/radiotherapeutic treatments. Consequently, cachexia decreases both quality of life and survival time in cancer patients and cachexia itself is responsible for up to 30% of all cancer-related deaths. Interestingly muscles from preclinical models of cancer cachexia as well as cachectic human cancer pati
which is important to the sarcolemmal dystrophin associated protein complex (DAPC), are highly downregulated at the mRNA and protein level at time points which precede and parallel muscle atrophy and weakness during tumor progression. Moreover, preliminary data show that overexpression of Ky in the muscles of tumor bearing m
aled a conserved consensus binding motif for myocyte enhancing factor-2 (MEF2) among the top most commonly shared motifs. Moreover, both the Ky and Myoc gene promoters contain conserved MEF2 binding motifs. This observation, coupled with the findings that MEF2 protein c (MEF2c) is decreased at the mRNA and protein lev
y causative roles in the cancer-induced loss of muscle fiber integrity and the initiation of muscle wasting. Specific Aim 2: To test the hypothesis that loss of MEF2c transcriptional activity is causative in the cancer- induced downregulation of Ky and Myoc and initiates muscle wasting. The results of these studies will provide new insight

tional decline. For example, 58% of HIV- infected subjects age >= 50 years have one or more of the following: renal failure, diabetes mellitus, bone fracture, hypertension or overt cardiovascular disease vs. only 35% of HIV-uninfected controls. Further, geriatric syndromes such as frailty and falls are becoming more prevalent in HIV-in
lished to advance research into the causes, mechanisms, prevention and treatment of functional decline with age, but lack expertise in HIV. In contrast, the Centers for AIDS Research (CFARs) have unparalleled expertise in HIV- related basic, clinical and social/behavioral research, but lack resources or expertise in aging biology, clinic
l subjects age > 50 years; 3) Supporting pilot projects at the interface of HIV and aging; 4) Identifying and mentoring junior faculty with a research focus in HIV and aging; and 5) Disseminating information and data sharing opportunities to the larger scientific community. Accomplishing these aims will efficiently amplify NIAID invest

g miRNAsto travel among tissues enables them to transmit signals and regulate a broad spectrum of biological functions.sRNAs exist in a variety of RNase-insensitive ribonucleoprotein or lipid complexes, or are encapsulated insidedifferent types of extracellular vesicles. Consequently, in contrast to messenger RNA, sRNAs are protecte
resourcesfrom three completed NIH-funded studies (EPESE, STRRIDE and CALERIE) to discover and validatelongevity-associated sRNAs in humans. Our preliminary analysis of 175 circulating microRNA--in the NIA-funded Duke Established Populations for Epidemiologic Studies of the Elderly (Duke EPESE) community-based co

late),proteins (93,000 documented to date including cytokines) and metabolites. Due to their coordinate regulationof tissue homeostasis and biological processes through intercellular trafficking of microRNA and protein cargo,EVs are particularly attractive for this project because they can potentially serve as DIRECT biomarkers ofagin
idence suggests that EVs secreted from senescent cells have unique characteristics and contribute tomodulating the phenotype of recipient cells; thus, they have been newly deemed novel senescence associatedmolecular pattern (SASPs). We hypothesize expression of different amounts and different compositions of EVsare associated wi
e human sample sets: individuals (n=3056) from multiple longitudinal cohort studies (EPESEaged >71 years; PALS aged 20-100 years) and NIH-funded controlled trials of geroprotective interventions(STRRIDE exercise aged 18-70 years; and CALERIE caloric restriction aged 22-45 years). Complementingthis new biomarker develop
rovide a unique project responsive to RFA-AG-18-018 for ?Development of validreliable markers of aging-related biologic mechanisms for human studies?.

mentors focused on inflammation-related topics. Four training positions are requested. The overall researchprogram will focus on mastery of molecular biology, functional genomics and gene regulation, as it appliesbroadly to inflammation research. Although the bulk of the training program will be in the laboratory of anexperienced res
ning program takes advantage of the unique strengths of the College of Medicine in the expanding field offunctional genomics and molecular biology, as well as the existing collaborations between basic scientists andclinicians committed to the training of future clinical academicians. The interface between molecular biology andinflamm
Surgery, Medicineand Pathology Departments will interact with the trainees and the research faculty to assure that the traineesare being exposed to clinically-important issues in inflammation research. Overall direction of the program willrest with the Program Director and an Executive Committee. Candidates for the fellowship are recr
Institute and GeneticsInstitute, and in their own basic science departments, as well as laboratory research meetings. They will also beexpected to attend clinical seminars, including Surgery and Critical Care Medicine Grand Rounds and theDepartment of Surgery Academic Research Conference. Based on our past experiences, it is antici

walking speed. Low-grade chronic inflammation is a modifiable risk factor. However, it is unknown whether interventions that reduce the levels of inflammatory markers per se improve mobility, or avert decline in mobility in older persons. To address this gap in evidence we propose the randomized clinical trial ENRGISE (ENabling Re
pose to test the efficacy vs. placebo of the angiotensin receptor blocker losartan and omega-3 polyunsaturated fatty acids in the form of fish oil, alone and in combination. Both angiotensin receptor blockers and omega-3 polyunsaturated fatty acids have shown to reduce IL-6 in clinical trials and preliminary data suggest that they may imp
duct a feasibility phase that includes performing meta-analyses of existing trials and cohorts, and conducting a pilot trial to assess the effects of the interventions on several inflammatory markers and walking speed. This will allow us to refine the design, recruitment yields, target population, adherence, retention, tolerability, sample-size,

this University of Florida Molecular Transducers of Physical Activity Preclinical Animal StudySites application (UF PASS) is to conduct experiments in animals that will provide tissues/blood (i.e.biospecimens) to the Chemical Analysis Sites for identification of molecular transducers induced by definedmodels of physical activity from
ture the dynamics of the exercise/adaptation responses we propose to:1) Collect biospecimens at 5 selected timepoints following an acute bout of exercise on na?ve and trained rats;2) Collect biospecimens following short duration training (after 5 bouts) and 3) Collect biospecimens followinglong-term (8 weeks) training.For Phase 2, ou
in vivotesting. The results of the experiments in Aim 3 will provide molecular evidence identifying a set of transducers,released from muscle, that are necessary for exercise induced systemic health. The goals of the UF PASS willbe pursued by the following Specific Aims:Specific Aim 1: Center Coordination Phase.Specific Aim 2: Pha

e neural control of walking are limited by either the inability to measure people during walking (functionalmagnetic resonance imaging, fMRI) or the inability to measure activity below the cortex (functional near-infrared spectroscopy, fNIRS). We assert that a full and accurate understanding of the neural control of walkingin older adult
It unprecedented insight into the central neural control of walking. Here, our overarching objective is to determine thecentral neural control of mobility in older adults by collecting EEG during walking and correlating these findingswith a comprehensive set of diverse mobility outcomes (clinic-based walking, complex walking and community
patterns that areseen when older individuals perform tasks of increasing complexity. CRUNCH describes the over-recruitmentof frontoparietal brain networks that older adults exhibit in comparison to young adults, even at low levels oftask complexity. CRUNCH also describes the limited reserve resources available in the older brain. T
Gduring walking with fNIRS (during actual and imaged walking) and fMRI (during imagined walking). This willallow us to identify the most robust CRUNCH-related hallmarks of brain activity across neuroimagingmodalities, which will strengthen our conclusions and allow for widespread application of our findings. Ourthird aim is to

, there is still insufficient understanding about the underlying mechanisms by which exercise preventsdisease and improves health across diverse organ systems. The NIH Common Fund has developed aforward-looking funding mechanism ? six tethered RFA's tied to creating a research consortium, the MolecularTransducers of Physical
n studying exercise biology. Based on prior collaborative efforts, our group believes that we aredeally positioned to propose a protocol that will respond directly to the RFA, while at the same time executethe large volume of tests to complete the ~450 people required at each site within the MoTrPAC consortium.To accomplish all of our
pling, sample sizes for the four obligated study groups, and other factors, while staying within budgetconstraints. The following Aims will maximize the value of the data and sample repositories; this will beaccomplished with the enrollment of 540 individuals and finishing 450. ? Aim 1: To determine the response of molecular transduce

ffness, resulting in less efficient SBP control. Reduced bioavailability of nicotinamide
l nicotinamide riboside, a compound that replenishes NAD+ levels, to optimize exercise's
either: (1) 1,000 mg/day of nicotinamide riboside plus 3 days/week of supervised,
nagement in older adults. Preliminary evidence from this pilot study may support a full-scale

ents show disruptions in sarcomere and myofiber membrane integrity despite the lack of an injury
nice inhibits muscle fiber atrophy. These observations support our first hypothesis that the
vel in tumor bearing mice, supports our second hypothesis that loss of MEF2c transcriptional
into transcriptional mechanisms involving protein downregulation which initiate cancer-induced

fected adults. While the need for research in HIV and aging is widely recognized, challenges in
al phenotypes, or functional measures. This proposal leverages CFAR/OAIC expertise to create a
ment in the CFARs, NIA investment in the OAICs, and, more importantly, address critical

dfrom extracellular RNases and are measurable and stable in samples stored for decades. Despite
hort of elders--identified 32 differentially expressed circulating miRNAs (p

g, namely indicators AND mediators of the aging process. The goal of this project is to
th different lifespan and healthspan of humans, and with different senescence states inmurine
nent work, we will validate and qualify: the new S-PLEX high sensitivity (femtomolelevel

earch mentor, trainees will be expected to participate in didactic experiences that complementtheir
ation research will be targeted to trauma, sepsis syndromes, ischemia/reperfusion injury,
ruitednationally and from the University of Florida College of Medicine (Gainesville,
ated thatsuccessful graduates of this training program will possess sufficient research skills to

duction of low-Grade Inflammation in SEniors) to test the ability of anti-inflammatory
rove physical function. We plan to recruit older persons who are at risk for, or with, mobility
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tissues that cannot be obtained from humans as well as to conductmechanistic studies that can
r hypothesis is that factors released from muscle (i.e. myokines) are the molecular
se 1 Studies. To perform endurance and resistance exercise using male and femaleF344BN rats

s requires real time measurement of active regions throughout the brain during actual walking.
mobility measures). Our first aim is to evaluate the extent to which brain activity during actual
hesefactors cause older adults to quickly reach a ceiling in brain resources when performing
study the mechanisms related to CRUNCH during walking. Thus, our project will address

Activity Consortium (MoTrPAC) ? to create resources and critical information forexercise
Clinical Center goals, we have developed a consortium ? the North Carolina ClinicalSite
rs to a single acute bout of either aerobic or resistance training. ? Aim 2: To determine the

74. **Project Title:** MOTRPAC CONSORTIUM COORDINATING CENTER

Leader(s): PAHOR, MARCO ; MILLER, MICHAEL E. ; REJESKI, WALTER JOHN ; TRACY, RUSSELL P ;

UNIVERSITY OF FLORIDA

NIH U24AR071113 / (2016-2022)

SummaryPhysical inactivity is a major public health challenge underlying a broad range of health problems at all ages.While physical activity (PA) has shown to produce relevant health benefits, the underlying molecularmechanisms are poorly known. The coordinated effort of clinical and animal studies supported bybioinform pivotal role in ensuring the cohesion of the MoTrPAC by enhancing communication and integration across allstudy components, including the Clinical Sites, the Preclinical Animal Study Sites, the Bioinformatics Center,the Chemical Analysis Sites, and the various study committees. The CCC will develop strategies and strateg goals andmaximize the progress and productivity of the MoTrPAC, the CCC will promote team science, team leadership,and innovative leadership approaches across all study components. Strategic planning that follows theprinciples of the dynamic theory of strategy will be fostered to evaluate alternative approaches, maintain the DataManagement, Analysis, and Quality Control Center (PI Dr. Miller), the Biospecimens Repository (PI Dr. Tracy),and the Exercise Intervention Core (PI Dr. Rejeski). The CCC will employ innovative project management toolsand web-based tracking of exercise adherence and diet, and will capitalize on the outstanding t multidisciplinary teams.The CCC will ensure and promote the continued success of the MoTrPAC in advancing knowledge about themolecular changes that occur in response to PA, and relating these changes to the health benefits of PA.

75. **Project Title:** 1/2 + PROMOTE WEIGHT LOSS IN OBESE PAD PATIENTS TO PREVENT MOBILITY LOSS: THE PROVE TRIAL

Leader(s): MCDERMOTT, MARY MCGRAE

NORTHWESTERN UNIVERSITY AT CHICAGO

NIH UG3HL141729 / (2019-2020)

PROJECT SUMMARY for the PROVE Trial More than 65% of people with lower extremity peripheral artery disease (PAD) are overweight or obese.People with PAD who are overweight or obese have greater functional impairment and faster functional declinethan normal weight people with PAD. Walking exercise is first li will improve walking ability more than EX alone. However, effects of intentional weight loss in overweight/obese people with PAD are unknown and maynot be beneficial if weight loss exacerbates PAD-related sarcopenia. Behavior change that achieves sustainedWL is challenging in older obese people with chronic disease. T achieved mean weight loss of 5.6 pounds andimproved the 6-minute walk by 64.1 meters in eight PAD participants with BMI> 28 kg/m2. Preclinical evidence shows that obesity is associated with impaired limb perfusion. Human evidenceshows that obesity is associated with reduced skeletal muscle mitochondrial biogenesis a University, andthe U. of Minnesota. Our primary outcome is change in six-minute walk distance at 12-month follow-up.Secondary outcomes are change in 6-minute walk distance at 6-month follow-up and change in exerciseadherence, physical activity, patient-reported walking ability (measured by the Walking ImpairmentQue arecorrect, the PROVE Trial will have a major public health impact by preventing functional decline and mobilityloss in the large and growing number of people with PAD who are overweight or obese.

76. **Project Title:** PHYSICAL RESILIENCIES: INDICATORS AND MECHANISMS IN THE ELDERLY COLLABORATIVE

Leader(s): COLON-EMERIC, CATHLEEN S ; WHITSON, HEATHER E. ;

DUKE UNIVERSITY

NIH UH2AG056925 / (2017-2019)

ABSTRACTThe overarching objectives of the PRIME Collaborative (Physical Resilience: Indicators and Mechanisms inthe Elderly) are to characterize specific resilience phenotypes, elucidate biological mechanisms, and validateclinically valuable predictive tools and measures of physical resilience. The application focuses o underlie amore generalized capacity for recovery that applies across multiple stressor/response scenarios. An inter-professional team of aging researchers from has been assembled to accomplish these objectives; the teamrepresents expertise from six NIA-funded Older American Independence Centers (OAICs) and leverages ot orthopedicsurgery, immune recovery after infection, and cognitive recovery after surgery/anesthesia. We will conduct pilotstudies to identify novel clinical tests and biomarkers associated with each of these resiliencies. Feasibility andresponse data from pilot studies will inform the design of a larger cohort study in Phase 2. In t outputmeasures, biomarkers and different types of resilience (musculoskeletal, cognitive, immune). Second,biological mechanisms underpinning resilience will be identified using newly developed mouse resiliencemodels, and in vitro human and mouse myotubule systems. These model systems are suitable for interventionstuc

77. **Project Title:** PHYSICAL RESILIENCIES: INDICATORS AND MECHANISMS IN THE ELDERLY COLLABORATIVE

Leader(s): COLON-EMERIC, CATHLEEN S

DUKE UNIVERSITY

NIH UH3AG056925 / (2017-2022)

ABSTRACTThe overarching objectives of the PRIME Collaborative (Physical Resilience: Indicators and Mechanisms inthe Elderly) are to characterize specific resilience phenotypes, elucidate biological mechanisms, and validateclinically valuable predictive tools and measures of physical resilience. The application focuses o underlie amore generalized capacity for recovery that applies across multiple stressor/response scenarios. An inter-professional team of aging researchers from has been assembled to accomplish these objectives; the teamrepresents expertise from six NIA-funded Older American Independence Centers (OAICs) and leverages ot orthopedicsurgery, immune recovery after infection, and cognitive recovery after surgery/anesthesia. We will conduct pilotstudies to identify novel clinical tests and biomarkers associated with each of these resiliencies. Feasibility andresponse data from pilot studies will inform the design of a larger cohort study in Phase 2. In t outputmeasures, biomarkers and different types of resilience (musculoskeletal, cognitive, immune). Second,biological mechanisms underpinning resilience will be identified using newly developed mouse resiliencemodels, and in vitro human and mouse myotubule systems. These model systems are suitable for interventionstuc

atics and chemical analyses will achieve the Molecular Transducers of Physical Activity Consortium(MoTrPAC) goals of assessing the molecular changes that occur in response to PA. The ConsortiumCoordinating Center (CCC) for the MoTrPAC will provide support for the organization, administration, planning,standardization, docum
icplanning processes by integrating activities of the MoTrPAC investigators with the input provided by the DataSafety Monitoring Board, the External Scientific Advisors, outside experts, and the NIH. The CCC will facilitateinteractions and communications with junior and senior investigators outside the consortium to maximize theuse
thecutting-edge scientific focus, leverage state-of-the-art coordination technologies, anticipate challenges, andmaximize future opportunities to ensure the success of the consortium. The CCC will comprise four integratedcomponents led by four highly qualified PIs who have a long-lasting track record of successfully working insynergy.
rack record andexpertise of its investigators in: (a) working together; (b) successfully coordinating, managing, and leadinglarge long-term multicenter clinical trials involving PA and other interventions; (c) implementing rigor andtransparency in research, (d) acquiring, managing, storing and analyzing biological samples; (e) conducting

ne therapy to improve functional performancein PAD. However, our observational longitudinal data show that overweight and obese PAD participants whocombined weight loss with walking exercise had less functional decline than those who walked for exercise butdid not lose weight. Therefore, we hypothesize that among people with
Therefore, among people with PAD and BMI>28kg/m2, we will test the hypothesis that WL+EX achieves greater improvement in functional performance thanEX alone. Our innovative weight loss intervention uses a group mediated cognitive behavioral framework,connective mobile technology, remote monitoring by a coach, and a calo
ad activity. Theseobesity related changes exacerbate the pathophysiology of PAD. Therefore, we hypothesize that weight losswill improve walking ability in part by improving calf perfusion, and increasing calf mitochondrial activity. We will randomize 212 participants with PAD and BMI > 28 kg/m2 to one of two groups for 12 month
stionnaire), and quality of life (measured by the SF12 Physical Component Score) at 12-month follow-up.Tertiary outcomes include MRI measured calf perfusion, MRI-measured calf muscle quantity and fatabundance, and diet quality. We will perform calf muscle biopsies in 50 participants to measure mitochondrialbiogenesis and activ

n resilience inthree systems that are central to older adults' overall health: musculoskeletal, cognitive, and immune. Thecentral hypothesis of this application is that resilience to physical stressors is influenced by biologicalmechanisms at the molecular level. We will examine whether mechanisms associated with one or more of theseven ?
nerexisting resources. The PRIME Collaborative team will use a two-phased approach. In Phase 1, workgroupswill define specific resilience phenotypes in existing datasets using latent class trajectory analysis of sequentialoutcome measures following a stressor. The three resilience phenotypes, selected for their over-archingrelevance to
he final 6months of Phase 1, the most promising predictive tests and markers will be selected and will inform twoparallel activities in Phase 2. First, a longitudinal cohort study of older patients undergoing elective surgery willbe conducted to validate predictors in a more diverse population. The Phase 2 cohort study will also allow us to
lies. The Phase 2 biological studies will be designed to identify pathways related to one or more Pillars ofAging so that they are likely to underpin multiple types of resilience, and suggest therapeutic targets and novel,resilience-bolstering interventions.

entation, monitoring and reporting activities relating to the MoTrPAC. The CCC will playa
: of the MoTrPAC resources toward achieving the overall research goals. To accomplish these
. The four CCC components comprise the Administrative Coordinating Center (PI Dr. Pahor),
animal exercise studies; (f) sharing resources; (g) publishing results; and (h) leading

PAD who are overweight or obese, aweight loss intervention combined with exercise (WL+EX)
rie restricted DASH-derivedOMNIHeart diet. In a seven week pilot study, our intervention
:WL+ EX vs. EX alone. Participants will be randomized from Northwestern University, Tulane
ity, capillary density, inflammation, and senescent cell abundance. If our hypotheses

Pillars of Aging,? which have been described by the trans-NIH Geroscience Interest Group,
late life health as well as our team's expertise, are: musculoskeletal recovery after
ssess synergy and interactions between different types of predictors (provocative tests, physiologic

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THE UNIVERSITY OF CALIFORNIA, SAN FRANCISCO (UCSF)
Claude D. Pepper Older Americans Independence Center

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Program Administrator

CENTER DESCRIPTION

Established in 2013, the UCSF Claude D. Pepper Older Americans Independence Center focuses on addressing predictors, outcomes, and amelioration of late-life disability in vulnerable populations. Late-life disability, defined as needing help with daily activities, is common, burdensome, and costly to patients, families, and society. Late-life disability is influenced by medical vulnerabilities (including comorbid illnesses, aspects of medical care, medicines, procedures, neuropsychiatric conditions, and behaviors), social vulnerabilities (social supports, financial resources, communication and literacy, and ethnicity), and their interaction. The overriding goal of the UCSF OAIC is to improve the health care and quality of life of vulnerable older adults with or at risk for disability through the following aims:

1. Catalyze research on disability in vulnerable older persons at UCSF by serving as a hub that brings together scholars and leverages resources
2. Provide tangible, high-value support to funded projects at UCSF that stimulates new research on disability, and leads to new research opportunities for senior and junior investigators
3. Support pilot studies that accelerate gerontologic science and lead to research funding in late life disability
4. Identify the future leaders of geriatrics research and support them with career development funding and exceptional mentoring
5. Develop a leadership and administrative structure that spurs interdisciplinary collaboration, making the OAIC greater than the sum of its parts

Our Center supports researchers who share our passion for improving the well-being of older persons. We view our resources as venture capital that will catalyze the careers and research paths of investigators who will do cutting edge research that advances the care, health, and wellbeing of older persons, both within the UCSF community and nationally.

CORES

Leadership and Administrative Core (LAC)

Leader 1:   Ken Covinsky, MD, MPH   covinsky@medicine.ucsf.edu

Leader 2:   Michael Steinman, MD   Mike.Steinman@ucsf.edu

The Leadership Administrative Core (LAC) plays the central role in coordinating the five UCSF OAIC cores, in maintaining communication across programs, and identifying new opportunities, both within and outside the OAIC. The LAC monitors the success of each core based on tangible metrics of productivity: Research leading to publications in the highest impact journals and new NIH grant funding. The LAC monitors, stimulates, evaluates, remediates, and reports progress toward the goals of the OAIC. The LAC also maintains the substantial collaborations with other UCSF research centers, including the UCSF CTSI and RCMAR, and seeks to establish new collaborations which will leverage OAIC resources and develop new and established investigators in aging research. The overall goal of the LAC is to provide the leadership and administration to support the activities of the entire UCSF OAIC.

Research Education Component (REC)

Leader 1:   Louise Walter, MD   Louise.Walter@ucsf.edu

Leader 2:   Kristine Yaffe, MD   kristine.yaffe@ucsf.edu

The Research Education Component (REC) identifies, supports, and nurtures talented junior investigators who will become national leaders in aging research through the REC Scholars Program and Advanced Scholars Program. The REC Scholars Program targets early career faculty and seeks to accelerate their path towards NIA K awards. The Advanced Scholars Program targets current K award recipients and accelerates the path towards their first R01. Both programs provide extensive mentoring and opportunities to participate in an innovative series of seminars designed to develop skills essential to success in aging research, facilitate interdisciplinary communication, build knowledge and relationships that will stimulate translation between basic and clinical research, and accelerate their productivity. The REC leadership also works with leaders of the Resource Cores to provide scholars access to additional support. These mentorship and curricular programs help junior investigators progress along the pathways that lead to high impact publications and grant funding that develops the scholar's national reputation as a leader in their area. Mentoring services, seminar series, resource core services, and programmatic support are also available to Associate Scholars whose goals are to develop careers in aging research. A particular focus of the Associate Scholars Program is junior faculty who have trained outside of geriatric medicine, but seek to incorporate Geriatric principles into their developing research program. The Research Education Component also sponsors a diversity supplement program to increase the number of faculty members from underrepresented and diverse backgrounds conducting aging research at UCSF.

Pilot and Exploratory Studies Core (PESC)

Leader 1:   Alex Smith, MD, MS, MPH   Alexander.Smith@ucsf.edu

Leader 2:   Sei Lee, MD   Sei.Lee@ucsf.edu

The Pilot and Exploratory Studies Core (PESC) facilitates the development and progress of innovative research relating to the Pepper Center focus on the predictors, outcomes and outcomes of late-life disability, especially in vulnerable older populations. We are especially interested in the interaction of serious clinical conditions, disability, and social disadvantage. The goals of the PESC include: 1) Solicit and select innovative proposals from highly qualified applicants; 2) Provide investigators of PESC studies with the support and infrastructure of the OAIC Cores; 3) Integrate PESC studies and investigators with resources from the UCSF Clinical and Translational Science Institute (CTSI) and other relevant resources at UCSF; 4) Monitor the progress of PESC studies; and 5) Provide mentorship and resources to transform PESC funded studies into successful independently-funded projects. The PESC focuses on identifying projects from outstanding investigators who are conducting aging research that is likely to lead to external funding and is aligned with the OAIC theme.

Vulnerable Aging Recruitment and Retention Core (VARC)

Leader 1:   Rebecca Sudore, MD   rebecca.sudore@ucsf.edu
Leader 2:   Krista Harrison   krista.harrison@ucsf.edu

The Vulnerable Aging Recruitment and Retention Core (VARC) was established in the UCSF Pepper Center grant renewal application. It was developed in response to increased demand both within and outside UCSF to support research focused on improving the knowledge base regarding the needs of medically vulnerable (e.g., complex chronic disease, serious illness, profound cognitive or functional impairment) and/or socially vulnerable (e.g., isolated, impoverished, homeless, incarcerated, with limited literacy or limited English proficiency) older adults. Because these older adults are often particularly difficult to recruit and retain in clinical research, their representation in research is often limited. This impairs our knowledge about how to optimize their care. Therefore, the VARC core focuses on supporting OAIC-affiliated investigators to (1) recruit, enroll, and retain vulnerable older adults in research; (2) use appropriate measures to study their healthcare needs; and (3) engage communities in research about medically and/or socially vulnerable older adults.

Data and Analysis Core (DAC)

Leader 1:   Mike Steinman, MD   Mike.Steinman@ucsf.edu
Leader 2:   John Boscardin, PhD   John.Boscardin@ucsf.edu

The Data and Analysis Core (DAC) provides OAIC investigators access to statistical services at all stages of the research lifecycle. Through the establishment of a central hub of statistical expertise, the DAC ensures smooth delivery of statistical knowledge and rigor across the spectrum of scientific research at the OAIC. This improves the quality of OAIC research studies, helps nurture trainees, facilitates interdisciplinary research groups, and ultimately enhances research on prediction, outcomes, and amelioration of late-life disability, especially in vulnerable populations. The DAC promotes wider use of state of the art statistical practice, lowers barriers of access to basic statistical services to all research groups including trainees, provides access to specialized statistical resources (such as state of the art prognostic model development, complex longitudinal and latent class analysis, and causal inference methods), and develops statistical procedures targeted to solving problems in aging research, and more specifically to challenges that commonly arise in research on disability and function.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications

Kenneth Lam, MD
Assistant Professor, Geriatrics / UCSF OAIC
Aging in place: a study of regional variation in risk-adjusted mean home time after hospitalization in older adults

2021-2023 /
5 (total)
3 (1st/Sr)

"Aging in place" is the term used to describe the preference of older persons to remain independent and in communities of their own choosing as they get older. The surge of nursing home deaths during the pandemic has made aging in place an increasing priority, but the lack of robust objective methods to quantify aging in place makes it impossible to systematically improve efforts to support it. Aging in place is threatened by health crises and disability, and these threats often culminate with hospitalization. Regional variability in post-acute care utilization suggests it may be easier to age in place in some places compared to others, but measures counting days in one setting only (e.g., long-term care) fail to capture aging in place from the patient's perspective. Harder still is determining how much lost home time is inevitable. For his project, Dr. Lam worked to identify adults over the age of 65 hospitalized in 2017 using a 5% Medicare sample to advance how to measure and use home time and how it may be applied to policies to help older adults stay independent in the face of disability while also reduce Medicare and Medicaid costs.

Jennifer James, PhD, MSW, MSSP
Assistant Professor, Medicine / UCSF
Centering incarcerated older adults in research
- NIA Diversity Supplement
- Greenwall Scholar

2022-2023 /
4 (total)
2 (1st/Sr)

Anoop Sheshadri, MD, MS
Assistant Professor, Nephrology / UCSF
Understanding Depression, Anxiety, and Caregiver Burden in Exercise Interventions among Older Patients Awaiting Kidney Transplantation
- GEMSSTAR
- KL2
- RAP

2022-2023 /
2 (total)
1 (1st/Sr)

Past Scholars
Lindsey Hampson, MD, UCSF (2019-2020)
Elizabeth (Liz) Whitlock, MD, MS, UCSF (2019-2020)
Lauren Hunt, PhD, RN, FNP, UCSF (2019-2020)
Ashwin Kotwal, MD, UCSF (2019-2021)
Sachin Shah, MD, MPH, UCSF (2019-2020)
Scott Bauer, MD, MS, UCSF (2019-2020)
Willa Brenowitz, PhD, MPH, UCSF (2019-2020)
Sarah Nouri, MD, MPH, General Internal Medicine, UCSF (2020-2021)
Li-Wen Huang, MD , Division of Hematology/Oncology, UCSF (2020-2021)
James Iannuzzi, MD, MPH , Surgery, UCSF (2020-2021)
Tasce Bongiovanni, MD MPP, UCSF OAIC (2021-2022)

Matt Miller, PT, PhD, UCSF OAIC (2021-2022)

PILOT/EXPLORATORY PROJECTS (10 Pilot Projects Listed)

1. Project Title: **Exploring the preferences and values of older adults with limited English proficiency during the hospital to Skilled Nursing Facility (SNF) care transition**

Leader: **James Harrison, MPH, PhD**

Transition care planning remains persistently medicalized, failing to be guided by patients' own preferences for their recovery, and does not incorporate elements that support preferences related to independence, returning home and function, or factors that allow participation in family or community activities that provide a foundation for personal purpose, creativity or fun. Most studies to improve care transitions have focused on discharges to home, and few in comparison have studied the quality of SNF transitions and have not engaged diverse older adults with limited English proficiency (LEP) during this process. For some LEP patients, in addition to language barriers, communication around preferences and values are further complicated by a lack of trust in healthcare providers, perceived racism and differing views on autonomy and decision-making. Mismatched expectations and poorly communicated care plans can not only contribute to adverse clinical outcomes but also compromise trust between patients and clinicians, impair satisfaction, and lead to delivery of care that is discordant with the preferences of patients and caregivers. Although it is often expected that individual clinicians be responsible for optimal care transitions, it is arguably more effective for high quality transitions to be the shared responsibility of all stakeholders -patients, caregivers, hospitals, and SNFs. The aim of Dr. Harrison's PESC study is to explore how patients with limited English Proficiency (LEP) and their caregivers anticipate and are prepared for a SNF discharge including how their preferences are incorporated into transition plans. Specifically, thisstudy will extend a grounded theory qualitative study that he is conducting as part of his National Institute of Aging (NIA) K01 by supporting the inclusion of older adults with LEP who speak Spanish, Cantonese and Russian. Data generated will then directly inform other elements of my work including the development and pilot implementation of a SNF Preparation Tool. Progress to date includes creating a stakeholder informed study protocol and interview guide, a recruitment approach and implementation plan. Interviews are about to commence at the San Francisco Campus for Jewish Living. Interviews were delayed due to the ongoing COVID-19 pandemic including new variants.

2. Project Title: **Opioid Prescribing Trends in Medicare Beneficiaries with Dementia before and after the 2016 CDC Guidelines for Chronic Pain**

Leader: **Ulrike Muench, RN, PhD, FAAN**

Since the peak of the opioid epidemic in 2012, prescription opioids have substantially decreased. One event that contributed to the reduction in opioid use was the release of the CDC guidelines on the management of chronic pain in 2016. The guidelines recommended the daily dose of morphine milligram equivalents (MME) to stay below 50 MME/day, to weigh the benefits and risks when increasing the daily dose to above 50 MME/day, and to increase to greater than 90MME/day only when it can be carefully justified. Research has found that since the release of the guideline clinicians have significantly reduced opioid prescriptions, as intended by the policy. However, evidence suggests that in some cases the recommendations were applied to patients with cancer pain, surgery, or acute sickle cell crises. In other cases, opioids were abruptly stopped or tapered, though mandated tapering is not supported by the

guidelines. It has been suggested that the inappropriate reductions in opioid prescriptions are in part due to fear of scrutiny by law enforcement agencies such as the DEA, which registers prescribers of controlled substances and can obtain information about prescribing practices of most providers. Monitoring by state medical boards and state laws that mandate dose caps or reinforce the 90 MME threshold further contributed to prescribers reducing their MME. One study that interviewed providers reported that clinicians felt that the only way to protect themselves from liability was to stay rigidly at or below the CDC guideline's 90 MME threshold and to disregard the emphasis on individualized patient care and respect for patient consent that are recognized within the guideline. The proposed study examines whether opioid use decreased systematically differently in persons with dementia (PWD) compared to persons without dementia (PWOD) following the 2016 CDC guidelines. Dr. Muench hypothesized that following the 2016 guidelines, providers disproportionally decreased opioids in PWD, a population at a disadvantage to advocate for the pain medications that they need. Through support from the Pepper Center, Dr. Muench was able to build on her analyses proposed to develop an R01 that examines opioid prescribing trends jointly with pain prevalence trends to test if individuals with ADRD no longer able to communicate are experiencing undertreatment of pain. Her hypothesis was that with increased scrutiny of prescription opioids in recent years providers may be more likely to decrease opioids in a population unable to articulate their pain needs. To this end, her long-term goal is to highlight and address potential disparities in pain treatment and provide important information for opioid prescribing guidelines concerning the management of chronic pain in people with ADRD.

3. Project Title: **Post-Intensive Care Unit Outcomes and the Impact of Resilience in Older Adults with Pre-existing Geriatric Conditions**

Leader: **Julien Cobert, MD**

For older patients admitted to the ICU, the presence of frailty, cognitive decline and disability are associated with higher mortality, worse long-term quality of life and accelerated post-discharge cognitive decline. These issues have received attention given the recognition of persistent physical, functional, psychological sequelae following critical illness –called post-intensive care syndrome (PICS) - which is particularly common in older adult survivors. When older patients face critical illness, the complex relationship between these geriatric conditions, the acute stress of critical illness, and the ICU environment places these vulnerable older adults at a higher risk for morbidity and mortality. ICU admission may result in prolonged immobility, malnutrition, swallowing dysfunction, polypharmacy and potentially burdensome invasive interventions. Critical illness itself is associated with a hyperinflammatory state which can decrease muscle mass and physical function. Lines and tubes tethering patients to beds, alarms and other noises, and lack of sunlight place many older adults at high risk of delirium and functional decline. These harms must be weighed against the potential benefits of ICU care in view of patient goals and expectations. A central goal in studying functional outcomes after critical illness is to identify pre-, intra-and post-ICU targets to mitigate functional decline or to help rehabilitate ICU patients and survivors. Most studies of functional impairment in ICU survivors emphasize factors associated with worse outcomes. Important studies in sepsis and acute respiratory distress syndrome showed that pre-illness cognitive impairment, frailty, and disability are associated with cognitive decline and self-rated health in survivors. However, , protective pre-ICU characteristics such as the capacity to navigate adversity or resilience have received little attention. The implications are important because psychological well-being, satisfaction and behavioral interventions are not directly incorporated into ICU treatment

bundles despite evidence that higher levels of resilience buffer the impact of chronic illness on disability later in life. Resilience is also correlated with decreased neuropsychological impairment and better self-care in ICU survivors. Hence, there is a critical need to understand and identify modifiable traits that protect older adults who face critical illness from functional and cognitive decline. These could be targetable and potentially added to existing preventative and rehabilitative strategies in the ICU. In this study, Dr. Cobert seeks to first understand how pre-existing geriatric conditions impact clinical and functional outcomes and end-of-life care process measures for older adults who require an ICU admission. He will then quantify resilience using a validated measure to determine its impact on clinical and functional outcomes. His central hypothesis is that patients with pre-existing disability, frailty, multimorbidity or dementia have increased risk of short-and long-term morbidity and mortality, but certain outcomes may be mitigated by resilience. Through support from the Pepper Center, Dr. Cobert was able to build upon his prior work on trends of pre-ICU geriatric conditions, using a unique ICU cohort from the Health and Retirement Study to evaluate functional, behavioral, and cognitive impairments in older adults who have suffered a critical illness. This project enabled Dr. Cobert to complete analysis and publish his results on trends of pre-existing geriatric conditions in ICU patients using Medicare-linked Health & Retirement Study (HRS) data. This resulted in a publication in Chest (impact factor ~9.5). Dr. Cobert subsequently extended this work with ongoing data analyses to study whether resilience could mitigate post-ICU morbidity and mortality in older adults. In addition, Dr. Cobert plans to apply for R21 or R03 (and the equivalent I21 through the VA) during the 12-month award (November-December) and begin preparation for an R01 . Dr. Cobert intends for his future R01 to create novel electronic health records (EHR) measures of disability and geriatric conditions using natural language processing techniques. The R01 would be focused on the development of improved EHR tools which would allow for better data capture, better tools for patient recruitment for prospective studies, and more robust outcome measures. This future work would require a mixed methods approach to assess how to best design and validate the improved EHR tool.

4. Project Title: **Biological signatures of neurodegeneration and aging associated with delirium in older adults following hip fracture surgery**

Leader: **Sara LaHue, MD**

Identifying the shared mechanisms connecting delirium, cognitive impairment, and aging are of critical importance. Delirium is a life-threatening acute disturbance in mental status affecting more than 2.6 million hospitalized adults in the United States annually, with an estimated attributable cost of $16,303-$64,421 per case. Delirium is associated with functional dependence, new or accelerated cognitive decline, and death. Older adults and those with mild cognitive impairment (MCI), Alzheimer's Disease, or Alzheimer's Disease Related Dementias (AD/ADRD) are at highest risk for delirium. Once viewed as an inevitability for older adults, delirium is preventable in as many as 40% of cases using intensive clinical pathways. While delirium prevention efforts are critical, they fail to prevent 60% of cases. Insufficient knowledge of delirium pathophysiology dramatically hinders advances in personalized delirium risk assessment, prevention, and impedes the development of delirium treatments, which do not currently exist. The complex association between delirium, cognitive impairment, and advanced age is largely based on epidemiology rather than the identification of markers that may indicate biological mechanisms. Recently, there is growing evidence for plasma AD biomarkers, such as plasma phosphorylated tau at residue 181 (pTau181), demonstrated by Dr. Boxer's lab to

differentiate those with AD from healthy controls and those with other ADRD, such as frontotemporal lobar degeneration; as well as pTau217-19 and neurofilament light chain (NfL). While advanced age is a major risk factor for delirium and AD/ADRD, this is based on chronological age – the number of years alive. However, aging is increasingly understood to be driven by biological mechanisms that are more or less advanced in different individuals. The difference between this biological age and chronological age is "age acceleration," which is associated with increased risk of disease, including AD. Dr. LaHue's long-term goal is to become an independent clinician-investigator focused on identifying mechanisms of delirium and delirium-associated cognitive decline, and to apply this knowledge to develop targeted treatments for delirium. In order to address gaps in our understanding of the biological mechanisms of delirium, she proposes to apply novel markers of neurodegeneration and aging to delirium. These results will provide evidence of a pathophysiological basis for the observed association between delirium, cognitive impairment, and advanced age. This is the first application of plasma pTau181, pTau217 and age acceleration in delirious patients. The goal of this project is to identify whether elevated preoperative measures of pTau181, pTau217, NfL, and age acceleration (by way of DNA methylation) in blood, are associated with postoperative delirium in 100 older adults undergoing hip fracture surgery, in order to advance understanding of the pathologic drivers of delirium. Through achieving this goal, she aims to shed light on the pathological basis for the observed association between delirium, neurodegeneration and aging. Through her Pilot and Exploratory Studies Award, Dr. LaHue received support that was integral to her development as an Early-Stage Investigator at the intersection of neurology and geriatrics. The Pepper Center was able to provide not only mentorship but also research staffing support assist Dr. LaHue in executing her research. The work from this pilot study will provide the basis for a future career development award application to investigate how these markers of neurodegeneration and aging influence the trajectory of postoperative cognitive decline in older adults who develop delirium.

5. **Project Title:**   **Palliative Care for Non-English Speaking Gynecology Oncology Patients**

   Leader: **María de Fátima Reyes, MD**

In this retrospective cohort study, Dr. Reyes seeks to explore the current utilization of palliative care, especially as it relates to a patient's primary language, and will elucidate barriers to palliative care referrals and effective palliation of symptoms. Given immigration and acculturation trends, she anticipates that language barriers will be most prominent in older women over 55 as women who immigrate later in life are more likely to be monolingual, and that her findings will highlight current areas for improvement in end-of-life care for the gynecology oncology patient population. By conducting retrospective chart review to define a cohort of aging gynecology oncology patients with advanced disease (i.e., stage 3 and 4) who obtained their care at University of California San Francisco (a large urban academic center) in the Department of Gynecology Oncology over the past 10 years (2010 to 2020), Dr. Reyes aims to accomplish the following. First, she will determine the utilization and timing of palliative care for aging gynecology oncology patients with advanced disease at our institution. Secondly, she will compare the utilization of palliative care between English-speaking versus non-English speaking aging gynecology oncology patients with advanced disease. Through the Pepper Center, Dr. Reyes was able to receive analytic support from the DAC and mentorship from VARC core leader, Dr. Rebecca Sudore, in analyzing her cohort in relation to her aims. Analysis is currently in progress. In addition, through the DAC, Dr. Reyes is able to access

additional data support from UCSF Clinical Translational Science Institute, a partner of the UCSF Pepper Center.

6. Project Title: **Meaningful activities in seriously ill, vulnerable older adults**
   Leader: **Anna Oh, BSN, MSN, MPH**

Engagement in meaningful activities – enjoyable physical, leisure, social, spiritual activities related to personal interests and values – gives life identity and purpose, and is therefore beneficial to the emotional and physical well-being of older adults. As older adults age and become more susceptible to disease, disability, and cognitive impairment, the ability to participate and engage in meaningful activities place the older adult at higher risk of loss of identity and well-being. Dr. Oh's cross-sectional examination published in JAMA IM of meaningful activity engagement in the National Health and Aging Trends Study (NHATS) found functional disability was the leading factor of nonengagement. Yet, diverse racial and ethnic groups of older adults may have varying experiences with meaningful activity engagement over time due to cultural and language barriers as well as limited access to services and resources. Little is known about meaningful activity engagement in diverse groups of older adults from historically disadvantaged backgrounds, its relationship to disability, and barriers and facilitators for engagement, such as social support, neighborhood factors, and socioeconomic and demographic factors. Previous studies have documented concerning racial and ethnic differences in the experience of aging, older Americans and their caregivers in caregiving experiences, access to and use of in-home rehabilitation services, and advance care planning. In addition to reducing racial and ethnic differences and health disparities, culturally-sensitive, community-based interventions have the potential to increase access to high-quality healthcare for diverse older adults. Culturally-sensitive, community-based interventions that include assessments of meaningful activity engagement can guide goals of care conversations, medical treatment recommendations, and target existing services and supports (e.g. home health, hospice, long-term services and supports) for older adults to stay engaged in meaningful activities. The objective of this study is to identify activity engagement in older, community-dwelling African-American/Black, Latinx/Hispanic, Asian, and bi/multiracial NHATS participants before and after the onset of the COVID-19 pandemic. The data and findings from this research will be a springboard for a K23 award where Dr. Oh will examine longitudinally the barriers and facilitators to staying engaged in meaningful activities. Through support from this award, the Pepper Center is helping to catalyze Dr. Oh's long-term goal is to become a clinician leader who improves the quality-of-life of diverse, community-dwelling, seriously ill older adults with home-based models of care.

7. Project Title: **Social relationships and distressing symptoms among older adults**
   Leader: **Ashwin Kotwal, MD, MS**

Social isolation and pain are highly prevalent conditions critical to the quality of life of older adults. Social isolation (an objective deficit in the number of relationships with family, friends, or the community), occurs in 15-20% of older adults and is associated with lower health related quality of life, higher functional impairment, higher health care costs, and death. The lifetime prevalence of chronic pain ranges from 24-45% and is a substantial contributor to reduced quality of life, health care costs, and the U.S. opioid epidemic. Pain also has known links to other symptoms such as fatigue, dyspnea, and insomnia. Although it is generally understood that pain and depression or anxiety can be linked and be more costly and disabling together

than either condition alone, the relationship between pain and social isolation has received little attention. Yet, social isolation may be both a contributor to the onset of pain and amplify existing pain. If a causal relationship between social isolation and pain exists, this could inform efforts to address challenges in pain and symptom distress among older adults, including inadequate symptom control, impacts of pain on function and independence, and contraindications to opioid and non-opioid analgesics due to their adverse effects. The objective of this pilot project is therefore to gain preliminary understanding of the relationship of social isolation to pain and other downstream symptoms among older adults. We will leverage nationally-representative cohorts of older adults, the National Health and Aging Trends Study (NHATS) and the Health and Retirement Study (HRS), which have longitudinal data on social isolation, pain, and opioid use. Questions will determine the cross-sectional association between social isolation and pain and opioid use.

8. Project Title: **Understanding and Improving the Psychosocial Function of Older Adults undergoing Major Surgery**

Leader: **Victoria Tang, MD, MAS**

"In population studies, older adults who are deficient in their psychosocial function have higher mortality rates, rehospitalization rates, and functional decline following a life stressor such as surgery. Little is known about the components of psychosocial function specific to geriatric surgical outcomes (e.g., mortality, functional decline) and treatment targeting these components has been limited to small surgery-specific cohort studies (i.e., cardiac). To address these gaps, our team recruited older surgical patients in the pre-operative setting to begin exploring their surgical experience through one-on-one interviews. Our preliminary findings support that many older surgical patients suffered from low psychosocial function. This was especially true if post-operative symptoms were still present 6 months after surgery. The long-term goal of this project is to understand and improve the psychosocial function of older adults before and after major surgery. The objective of this application is to collect pilot data to support an NIH R01 application focused on describing, quantitatively, the psychological and social challenges older surgical patients experience before and after major surgery. This application will focus on (1) developing a feasible and acceptable psychosocial survey for the older surgical patient and (2) developing and testing a post-operative recruitment strategy of older non-elective surgical patients. Our team has a track-record of successfully recruiting older patients undergoing elective major surgery and in conducting one-on-one interviews. We are well-equipped to achieve these aims. "

9. Project Title: **Assessing inpatient disparities in pain assessment and management for older minority patients**

Leader: **Aksharananda Rambachan, MD, MPH**

"Despite an increased emphasis on identifying pain as the "fifth vital sign," there are shortcomings in our approach to assessing, documenting, and responding to pain. Cognitive impairment in older persons, drugdrug interactions, patient comorbidities, fall-risk, and frailty all present additional challenges for prescribing clinicians. Furthermore racial, ethnic, cultural, and language-based differences across patients are areas where disparities are present. Studies across various health settings have found that older patients and minority patients are at high risk for underassessment and undertreatment of pain. Pain assessment tools are ubiquitous, given regulatory and hospital level requirements, yet their appropriateness and utility remain

understudied in this patient population. Pain is assessed by nursing across various time points using various self-report and behavioral tools. Clinicians often utilize their own individualized bedside approach and review of clinical data in assessing and managing a patient's pain, disconnected from nursing workflows. There is a paucity of guidelines for inpatient pain management for both acute and chronic conditions and minimal research into best practices for elderly minority patients. We do not know how pain is managed quantitatively across common medical diagnoses for these patient groups, and with regards to the interaction between age, race, ethnicity, and language status."

10. Project Title: **Mixed methods evaluation of the Best Case/Worst Case-Geriatric Oncology communication tool**

Leader: **Melisa L. Wong, MD, MAS**

"To promote delivery of goal-concordant care in geriatric oncology, I recently completed a focus group study with 40 stakeholders (14 older adults with lung cancer, 12 caregivers, and 14 medical oncologists) to adapt the innovative Best Case/Worst Case (BC/WC) communication tool to meet the specific needs of older adults with cancer and their caregivers. The original BC/WC tool was developed to improve shared decision making for older adults making non-cancer surgical decisions. BC/WC uses scenario planning—narrative description of plausible futures—to describe the best, worst, and most likely cases for each option. Scenarios are informed by clinical judgement and knowledge of patient risk factors (e.g., frailty, comorbidities). These scenarios plus an accompanying graphic aid help patients formulate and express preferences and concerns about treatment burdens and outcomes. The clinician then provides a goal-concordant recommendation. In our geriatric oncology adaptation study,15 participants believed that the BC/WC tool could help patients understand their cancer care choices, explore tradeoffs and picture potential outcomes, and deliberate about decisions based on their goals and values. Oncologists also reported that the tool could guide conversations to address points that may frequently be skipped (e.g., alternative options, treatment goals). Based on participant input, our adaptations included framing cancer care as a series of decisions, eliciting patient preferences and asking permission before offering the worst-case scenario, and selection of the two most relevant options to present if multiple exist. I now propose a two-part feasibility pilot study with an initial lead-in phase to refine the intervention, training, and study procedures (2 medical oncologists and 4 older patients) followed by a cluster randomized trial (CRT; 6 medical oncologists, 42 older patients, and up to 42 caregivers) to evaluate our adapted BC/WC-Geriatric Oncology (BC/WC-GeriOnc) communication tool for use with older adults with advanced cancer and their caregivers. In the CRT, 6 medical oncologists will be randomized 1:1 to BC/WC-GeriOnc intervention training versus usual care with wait-list control."

DEVELOPMENT PROJECTS (11 Development Projects Listed)

1. Project Title: **Methods with Survey Data**

   Leader: **Grisell Diaz-Ramirez, MS, Bocheng Jing, MS**

   Core(s):

Currently there are no clear methods or best practice guidelines regarding analysis of survey data to support all survey topics ranging from surgery prediction to cognition. There are currently no software packages available, thus creating an issue of no standardized methods in calculations to perform analysis. The aims of this development project were to explore survey data issues from three main aspects: survival prediction (cox model, competing risk), propensity score methods, and linear mixed model.

Since the start of this project, Ms. Diaz-Ramirez and Mr. Jing have been actively disseminating their findings, of note:
1. The following proceeding paper was accepted to SAS Global: "Mixed-Effects Models and Complex Survey Data with the GLIMMIX Procedure"
2. The following proceeding paper was also accepted to SAS Global: "Propensity Score Matching with Survey Data"
3. SAS proceedings papers on mixed model and propensity score were presented at the Virtual SAS Global meeting. They are both now published on the Proceedings of the SAS Global Forum 2020 and also accessible online to reach the a global audience
[Mixed model download link](#)
[Propensity score download link](#)

2. Project Title: **Statistical Harmonization of Two Nationally Representative Data Sets: HRS and NHATS**

   Leader: **Sun Jeon, PhD**

   Core(s):

Dr. Sun Jeon seeks to develop a harmonized coding of ADL/IADL and other functional measures using the Health Retirement Study (HRS) and the National Health Aging Trends Study (NHATS). Through her analysis of the prevalence of disabilities in those two data sets, NHATS showed higher prevalence across ADL/IADL measures than that in HRS. Currently there is a lack of an understanding of whether the NHATS cohort consists of generally sicker people or the discrepancy was derived from the way the questions were asked or the survey is done. From observation of work that UCSF Pepper Center Investigators are engaging in, she has seen great overlap their interests in and demands for this work. Dr. Jeon will be dedicating her effort to further study in this area to get a deeper understanding of NHATS/HRS cohorts, survey design, and of course as well as some statistical tests.

3. Project Title: **Developing an Algorithm to Identify Older Persons with Unmet Need for Equipment in National Datasets**

   Leader: **Kenneth Lam MD, John Boscardin PhD**

   Core(s):

Dr. Kenny Lam (VA Quality Scholar) and DAC collaborated on developing a novel algorithm that has since resulted in a high-profile publication. The team first approached the development of this algorithm by creating a cohort of older adults aged 65 and above from the nationally representative National Health and Aging Trends Study (NHATS) and selecting participants with bathing and toileting equipment needs. Next, they cross referenced this cohort with Medicare claims data. Afterwards, the team examined how many participants did not receive equipment based on the NHATS annual follow up interviews, where interviewers meet annually with participants in person to ask about health, function, living environment, and finances and to conduct an objective assessment of physical performance. Lastly, the team used data from the 2016 to 2019 waves to determine the incidence of equipment acquisition among those with unmet need in 2015. The description of this methodology and the analysis made possible with this novel algorithm has been published in JAMA Internal Medicine, as cited below: Lam K, Shi Y, Boscardin J, Covinsky KE. Unmet Need for Equipment to Help With Bathing and Toileting Among Older US Adults. JAMA Intern Med. 2021 Mar 22:e210204. doi: 10.1001/jamainternmed.2021.0204. Epub ahead of print. PMID: 33749707; PMCID: PMC7985819.

4. Project Title: **Deep Natural Language Processing Identifies Variation in Care Preference Documentation**

Leader: **Rebecca Sudore, MD**

Core(s):

Retrospective chart reviews are one of many methods for researchers and clinicians to extract key information about subjects and patients. However, this is usually a time-intensive process. In the past year, Dr. Sudore and her collaborators have explored the use of natural language processing (NLP) and how it may increase efficiency in performing chart review. NLP (i.e., computer identification of phrases within electronic records) can be combined with deep learning (i.e., computer systems that can access and use information in an adaptive way) to create tools to aid in the rapid identification of care preference documentation. Neural network models are commonly used in deep learning. Similar to the neural networks in the human brain, computational neural networks include a series of statistical algorithms capable of modeling and processing nonlinear relationships between inputs and outputs in parallel and real time. These algorithms generate rules to associate sequences of words or images on a prespecified concept, such as care preferences, and become more accurate (i.e., learn) with more data over time. This adaptive learning process can be used to abstract complex information from clinical data with an accuracy similar to highly trained humans. As an example of this application, Dr. Sudore and her collaborators have developed and validated deep natural language processing in the identification of documentation of care preferences for patients admitted to the ICU. Their methods and findings can be found in the following manuscript: Udelsman BV, Moseley ET, Sudore RL, Keating NL, Lindvall C. Deep Natural Language Processing Identifies Variation in Care Preference Documentation. J Pain Symptom Manage. 2020 Jun;59(6):1186-1194.e3. doi: 10.1016/j.jpainsymman.2019.12.374. Epub 2020 Jan 9. PMID: 31926970.

5. Project Title: **An eHealth platform to facilitate financial understanding and legal preparation for patients with dementia and their caregivers**

Leader: **Rebecca Sudore, MD**

Core(s):

In collaboration with Sarah Hooper, JD and David Farrell, MPH, Dr. Sudore is a Co-I on this new NIA R44 grant. Prior work shows that digital programs can be designed to be usable and effective for patients with dementia and their caregivers. The team will be working to build and test a web-based platform for educating patients and caregivers about financial risks, strategies they can undertake, and the specific legal preparations they can make; facilitating completion of legal documents in coordination with legal professionals; and communicating about financial and legal issues with health professionals. Dr. Sudore is providing ongoing VARC consultation on the development and testing of new interventions for older adults and recruitment and retention of study subjects.

6. **Project Title:**   **Developing an Evidenced-Based, Online and Advance Care Planning Program to Prepare Surrogates for Medical Decision Making**

    Leader: **Rebecca Sudore, MD**

Core(s):

Dr. Sudore obtained funding from the Greenwall Foundation to develop and test a new intervention designed to help caregivers and care partners prepare for their role as a medical decision maker. Dr. Sudore and her research team have obtained surrogate input in focus groups and in-depth interviews and are developing an online PREPARE for THEIR Care Program. Video stories have been produced and co-developed with a community advisory board. They show surrogates how to start advance care planning conversations, how to communicate with medical providers, and how to make informed medical decisions for others.

7. **Project Title:**   **The Effect of Difficult to Read HIPAA forms on the Recruitment and Retention of Older Primary Care Patients in a Pragmatic Trial.**

    Leader: **Rebecca Sudore, MD**

Core(s):

Dr. Sudore is a Co-I on this PCORI project. The parent trial is a 3 UC-site pragmatic trial designed to compare population-based advance care planning interventions. As part of the trial, a subset of these patients was recruited to answer questionnaires. In addition to helping this team create literacy- and culturally appropriate recruitment materials, Dr. Sudore also helped the team simplify the informed consent form to the 5th grade reading level. Unfortunately, the UC system would not allow the HIPAA forms to also be simplified. She mentored her colleagues at UCLA and helped to design a nested study to compare rates of recruitment for patients who were mailed recruitment packets that contained the HIPAA form and those that did not. Preliminary finds show that recruitment rates with the HIPAA forms were 9%, while the recruitment rates without HIPAA forms was 14%, $p < 0.001$. Recruitment was also lower for patients who self-identified as being from a racial/ethnic minority background, and those who spoke Spanish. For the group in which we did not include the HIPAA, we were able to achieve a closer demographic comparator group to the larger patient populations. Dr. Sudore is working with her UCLA colleagues to submit this manuscript and is working with the UCSF IRB to consider how to simplify the HIPAA forms.

8. Project Title: **A Novel Method for Identifying a Parsimonious and Accurate Predictive Model for Multiple Clinical Outcomes**

Leader: **Grisell Diaz-Ramirez, Sei Lee, MD, Alex Smith, MD, Siqi Gan, John Boscardin, PhD**

Core(s):

At present, there has been limited research on how best to develop clinical prognostic models that predict multiple outcomes simultaneously with accuracy and parsimony. Thus, the DAC Statistical Lab led by Dr. Boscardin collaborated with PESC core leaders Drs. Alex Smith and Sei Lee to evaluate a novel computing method for predictor selection in prognostic models of multiple clinical outcomes using the minimum average normalized BIC across outcomes, which they called the Best Average BIC (baBIC). To develop the proposed method, they used the Health and Retirement Study (HRS) data and a common set of health-related and demographic variables to predict time to: 1) Activities of Daily Living (ADL) Dependence, 2) Instrumental Activities of Daily Living (IADL) Difficulty, 3) Mobility Dependence, and 4) Death. Using HRS data, they demonstrated their method and conducted a simulation study to investigate performance. Upon testing, they found the average Harrell's C-statistics across outcomes of the models obtained with the baBIC and Union methods were comparable. Despite the similar discrimination, the baBIC method produced more parsimonious models than the Union method. In contrast, the models selected with the Intersection method were the most parsimonious, but with worst predictive accuracy, and the opposite was true in the Full method. In the simulations, the baBIC method performed well by identifying many of the predictors selected in the baBIC model of the case-study data most of the time and excluding those not selected in the majority of the simulations. This concludes that the proposed method identified a common subset of variables to predict multiple clinical outcomes with superior balance between parsimony and predictive accuracy to current methods. This body of work proves that it is possible to select a common set of variables to predict multiple clinical outcomes while maintaining parsimony and predictive accuracy. Moving forward, researchers will be able to use this algorithm and code to build prognostic models that are both accurate and parsimonious, potentially saving the clinical time and expense associated with gathering additional unnecessary predictors. Full details about this project are found in the following publication: Diaz-Ramirez LG, Lee SJ, Smith AK, Gan S, Boscardin WJ. A Novel Method for Identifying a Parsimonious and Accurate Predictive Model for Multiple Clinical Outcomes. Comput Methods Programs Biomed. 2021 Jun;204:106073. doi: 10.1016/j.cmpb.2021.106073. Epub 2021 Mar 27. PMID: 33831724; PMCID: PMC8098121.

9. Project Title: **A Novel Metric for Developing Easy-to-Use and Accurate Clinical Prediction Models: The Time-cost Information Criterion**

Leader: **Sei Lee, MD, Alex Smith, MD, Grisel Diaz-Ramirez, Ken Covinsky, MD, Siqi Gan, Catherine Chen, John Boscardin, PhD**

Core(s):   Data and Analysis Core (DAC)

Current guidelines recommend that clinicians use clinical prediction models to estimate future risk to guide decisions. For example, predicted fracture risk is a major factor in the decision to initiate bisphosphonate medications. However, current methods for developing prediction models often lead to models that are accurate but difficult to use in clinical settings. The goal of this project was to develop and test whether a new metric that explicitly balances model accuracy with clinical usability leads to accurate, easier-to-use prediction models. The DAC

Statistical Lab, led by Dr. Boscardin, facilitated the cross-center collaboration amongst PESC core leaders, Drs. Alex Smith and Sei Lee, PESC Scholar Dr. Catherine Chen, and UCSF Pepper Center Director Dr. Ken Covinsky to develop and test whether a new metric that explicitly balances model accuracy with clinical usability leads to accurate, easier-to-use prediction models. The project team proposed a new metric called the Time-cost Information Criterion (TCIC) that will penalize potential predictor variables that take a long time to obtain in clinical settings. To demonstrate how the TCIC can be used to develop models that are easier-to-use in clinical settings, we use data from the 2000 wave of the Health and Retirement Study (n=6311) to develop and compare time to mortality prediction models using a traditional metric (Bayesian Information Criterion or BIC) and the TCIC. Through their analysis, they found that the TCIC models utilized predictors that could be obtained more quickly than BIC models while achieving similar discrimination. For example, the TCIC identified a 7-predictor model with a total time-cost of 44 seconds, while the BIC identified a 7-predictor model with a time-cost of 119 seconds. The Harrell C-statistic of the TCIC and BIC 7-predictor models did not differ (0.7065 vs. 0.7088, P=0.11). Accounting for the time-costs of potential predictor variables through the use of the TCIC led to the development of an easier-to-use mortality prediction model with similar discrimination. Although current prediction model development strategies focus on improving predictive accuracy, the lack of attention to the clinical usability of prediction models have led to the development of many accurate models which are difficult to use in clinical settings. Through this project, our center has introduced the concept of using time-costs as a way of identifying predictors that are easier to obtain in clinical practice. This work has shown that prediction models with similar discrimination, but decreased time-costs can be developed, and this may lead to models that are as accurate and easier to use in routine clinical practice. Full details about this project are found in the following publication: Lee SJ, Smith AK, Diaz-Ramirez LG, Covinsky KE, Gan S, Chen CL, Boscardin WJ. A Novel Metric for Developing Easy-to-Use and Accurate Clinical Prediction Models: The Time-cost Information Criterion. Med Care. 2021 May 1;59(5):418-424. doi: 10.1097/MLR.0000000000001510. PMID: 33528231; PMCID: PMC8026517.

10.	Project Title:	**Methods For Advancing The Rigor and Scope of Qualitative Datasets Relevant To Vulnerable Older Adults**
	Leader:	**Dan Dohan, PhD**
	Core(s):	

Multiple NIA-funded PIs affiliated with OAIC and/or Dr. Dohan's Medical Cultures Lab (MCL) have assembled qualitative datasets examining experiences of aging, physical and cognitive disability (e.g.,dementia), and quality of life among patients, care partners, and/or providers in primary, palliative, and end-of-life care. These rich data could be combined to answer new questions and to support OAIC investigators, akin to secondary analysis of quantitative data. Yet, the science and methods of secondary qualitative data analysis are nascent. Aim: To develop novel methods for merging qualitative and mixed methods data across studies involving older adults with disability and their care partners and clinicians. Approach: Drs. Dohan, Harrison, and team will develop standardized techniques to link concepts and narratives across multiple qualitative datasets – analogous to linking variables across quantitative datasets. We will work with OAIC/MCL-affiliated investigators to reach consensus on essential methodologic questions for merging. Examples include procedures for merging raw (e.g., recordings and transcripts) versus annotated data, how to include annotated

data (such as participant demographic information or fieldworker reflections) to inform analysis, and how best to include contextual data such as data collection setting (e.g., nursing home, community). We will use findings from the process of merging our MCL-OAIC datasets to describe standardized conditions under which qualitative data can be concatenated for analysis across studies in accordance with (a) recently updated NIH requirements for data use and sharing; (b) established practices of qualitative research ethics and protection of human participants. This will prepare merged qualitative datasets for secondary analysis using next-generation computer-assisted analysis methods developed through Dr. Dohan's NIA Director's Pioneer Award that exceed human-only qualitative coding in reliability, accuracy and efficiency.430-433

11. Project Title: **Methods for Estimating the Causal Effect of Serious Acute Events on Long-Term Functional Trajectories and Other Longitudinal Measures**

Leader: **W John Boscardin PhD**

Core(s):

Assessing the impact of acute events such as hip fracture or heart failure hospitalization on future outcomes in HRS, NHATS, and other Medicare-linked panel surveys poses substantial challenges, as disruptive events identified through claims can occur continuously in the dates between the annual or bi-annual interviews where function and cognition are assessed.18, 193, 244, 334 To date, we and others have employed a number of statistical methods for estimating the casual effect of the intervening event including (1) mixed effects modeling of the longitudinal outcome in a cohort of subjects, only some of whom experience the intervening event;244 (2) mixed effects modeling of the longitudinal outcome in those who experience the event and then matching them to subjects who have not experienced it;117, 240 (3) multistate modeling with states considering combinations of functional status and whether the intervening event has been experienced.111, 232 For these potential outcomes framings of the causal inference questions, we have found that the predicted before-and-after curves from fitting any of these models have tremendous graphical impact and clinical impact335 and clinical interpretability. We will thus examine the performance of these methods in a range of relevant scenarios. Our aims are: Specific Aim 1: To conduct a series of careful simulation studies to evaluate the relative advantages and disadvantages of these modeling methods in longitudinal studies with interval assessments, for example HRS, NHATS, and many others. Specific Aim 2: To disseminate open-source statistical programming code for the methods we develop. ? Approach: We will follow recently published best practices for simulation studies.336 We will use several primary strategies for generating our simulated data sets as in our recent work226 and others. First, we will assume a true underlying mixed effects model superimposed with possible times of disruptive event and death. We will vary key parameters (numbers of subjects and measures per subject, distribution of covariates, regression and variance components in the longitudinal model, hazard parameters for disruptive event, dropout and death) in a factorial or fractional factorial manner. Next, we will use assume that the data are truly generated from a multistate model where we again vary the key parameters including the observation times and the transition probabilities. Lastly, we will use recent developments in synthetic data generation337-339 to conduct our studies in random instances strongly reflective of our data setting of interest. The target causal estimates of interest are not expressible as single regression model parameters, but can be computed as contrasts in averaged counterfactual predictions. Finally, the code to conduct these analyses will be

distributed through the GitHub for our statistical laboratory.333 ? Selection of Future DPs: The DAC will fund DPs in Years 2 and 4, and the VARC in alternating years. Our method for selecting subsequent DPs is described in the LAC. Briefly, we will disseminate a Request for Applications to the UCSF community and solicit 2-page letters of intent. Final proposals will be reviewed and selected by the LAC Selection Committee. We will give special preference to research on novel measurement approaches to late-life disability or which develop novel methods that can advance the science of analytic approaches to the study of late-life disability.

RESEARCH (6 Projects Listed)

1. Project Title: **PALLIATIVE CARE FOR PEOPLE LIVING AT HOME WITH ADVANCING DEMENTIA AND THEIR CAREGIVERS**

Leader(s): **HARRISON, KRISTA LYN**
UNIVERSITY OF CALIFORNIA SAN FRANCISCO
NIH K01AG059831 / (2019 - 2024)

Core(s):

Project Summary/Abstract This is an application for a K01 award for Krista Lyn Harrison, PhD, whose research focuses on improvinglife for older adults with Alzheimer s disease and related dementias (ADRD) and their informal caregivers. Dr.Harrison is a health services and policy researcher and Assistant Professor in the Division of Geriatrics at theUniversity of California, San Francisco (UCSF). Dr. Harrison has 12-years of experience in qualitative methodsand led the research enterprise of a large hospice prior to completing a UCSF aging research fellowship andimplementation science certificate. Through the activities proposed in this application, Dr. Harrison willstrengthen and address gaps in her experience through a training plan focused on: a) advanced statisticalmethods in linked datasets, b) ADRD clinical care and research, and c) translating mixed-methods data intoADRD interventions. Resources to foster her career development include UCSF s nationally-recognizedDivision of Geriatrics, Memory and Aging Center, Institute for Health Policy Studies, and K Scholar s program,Dr. Harrison has assembled an extraordinary multidisciplinary team with extensive expertise. Alzheimer s disease and related dementias are progressive incurable illnesses causing significant publichealth burden. Palliative care focuses on reducing suffering and improving quality of life by attending to themulti-dimensional sources of distress for seriously ill individuals and families. Evidence for quality palliativecare for advanced ADRD comes primarily from research in nursing homes. For the more than 700,000 olderadults with advanced Alzheimer s disease who die at home each year, clinicians lack population-level evidenceto guide caregivers and patients in anticipating and planning for disease changes. The proposed K01 willaddress critical knowledge gaps and develop a toolkit of resources to support basic palliative care provided byneurologists. Dr. Harrison will first use a nationally-representative dataset to longitudinally examine factorsassociated with mortality and nursing home stay among people living at home with severe and advancingADRD. Second, she will use semi-structured interviews with older adults living at home with ADRD, currentand bereaved caregivers to understand palliative and end-of-life experiences and opportunities to improvepalliative care for ADRD. Third, Dr. Harrison will work with multiple stakeholders to refine and assess thefeasibility of a toolkit of basic palliative care resources for use in neurology clinical practice (such as anassessment checklist, evidence-based strategies for discussing serious illness prognosis and advance careplanning adapted for ADRD, referral and billing guides, and summarized evidence from Aims 1 and 2 on livingat home with ADRD to inform anticipatory guidance). The goal of this toolkit is to improve neurologists communication with older adults living at home with advancing ADRD and/or their informal caregivers. Theproposed research will provide Dr. Harrison with the preliminary data, training, and experience to supportfuture competitive independent R-series applications to test the efficacy and effectiveness of her intervention.

2. Project Title: **IMPROVING OUTCOMES OF OLDER ADULTS WITH PSYCHOSOCIAL VULNERABILITY UNDERGOING MAJOR SURGERY**

Leader(s): **TANG, VICTORIA LAI-YEN**
UNIVERSITY OF CALIFORNIA SAN FRANCISCO
NIH K76AG059931 / (2019 - 2024)

Core(s):

PROJECT SUMMARY / ABSTRACT This application for the Paul B. Beeson Emerging Leaders Career Development Award in Aging (K76)describes the five-year career development plan of Dr. Victoria Tang, a geriatrician and young physician-scientist in the Division of Geriatrics at the University of California, San Francisco. Dr. Tang s long-term careergoal is to develop a research niche that bridges the field of aging and surgery to improve the care of oldersurgical patients. The specific career development goals outlined in this application include developing expertise inimplementation science, intervention development, clinical trial design/analysis, and building a research nichethat bridges the field of aging and surgery to improve the care of older surgical patients at the national level.The primary mentor for accomplishing these career development goals is Dr. Ken Covinsky, Professor ofMedicine at UCSF and Principle Investigator of the UCSF Older Americans Independence Center. Dr.Covinsky will be assisted by co-mentor Dr. Emily Finlayson, Professor of

Surgery and Director of UCSF sCenter for Surgery in Older Adults. The career development plan of Dr. Tang includes individualizedmentorship with her mentorship team, formal coursework, one-on-one tutorials, and leadership training. The overall objective of the research plan is to understand the role of psychosocial vulnerability in post-operative outcomes with the largest cohort of older surgical patients to date and to develop a pilot test apsychosocial intervention to improve depressive symptoms, coping skills, and social support. The centralhypothesis of this project is that preoperative psychosocial vulnerability is associated with post-operativefunctional recovery, and a greater understanding of psychosocial vulnerability and interventions designed tomitigate its effects will improve post-operative outcomes, such functional recovery. The specific aims of theproject include (1) determining the independent association between pre-operative psychosocial vulnerabilitywith 2-year overall mortality and functional decline following major surgery; (2) understanding howpsychosocial vulnerability impacts post-operative recovery in older surgical patients through semi-structuredinterviews with older surgical patients and caregivers; and (3) comparing 6-month functional recoveryoutcomes between those randomized to a psychosocial intervention (navigator-led social support and problemsolving therapy) versus usual care. These aims will permit a better understanding of psychosocial vulnerability,a geriatric-specific risk factor, in older adults that may be especially important in a time of major surgery. Theapplication is relevant to NIH and NIA because Dr. Tang s career goal is to leverage an understanding of thegeriatric-specific risk factors to elucidate potential aspects needing interventions and to improve sharedsurgical decision-making among older adults and their physicians.

3. Project Title: ADVANCING PATIENT-CENTERED DECISION MAKING IN OLDER ADULTS WITH LUNG CANCER: INCORPORATING RISK OF FUNCTIONAL DECLINE INTO TREATMENT DISCUSSIONS

Leader(s): **WONG, MELISA L**
UNIVERSITY OF CALIFORNIA SAN FRANCISCO
NIH K76AG064431 / (2019 - 2024)

Core(s):

PROJECT SUMMARY/ABSTRACTThis is a Beeson K76 career development award for Dr. Melisa Wong, a thoracic oncology clinician-investigator dually trained in medical oncology and aging research. Dr. Wong s long-term goal is to become anational leader in geriatric oncology research, improving cancer care for older adults by aligning treatmentswith individualized patient goals. More than 72% of older adults with cancer report that they would not choosea treatment that results in functional impairment, even if it improves survival. Yet, oncologists traditionally maketreatment decisions based on cancer characteristics, often without discussing how treatment might affectfunction or eliciting patients goals and values. To move from cancer-centered to patient-centered decisionmaking, oncologists must both predict which older adults are at highest risk for functional decline andcommunicate complex information about benefits and harms to patients in a way that aligns treatments withtheir goals for function, quality of life, longevity, and other priorities. This proposal aims to 1) identify risk factorsfor functional decline in daily activities, physical performance, and life-space mobility during chemotherapyand/or immunotherapy in older adults with metastatic lung cancer; 2A) adapt the Best Case/Worst Case(BC/WC) communication tool; and 2B) test its feasibility for use during treatment discussions with older adultswith lung cancer. In Aim 1 s multi-site cohort study, patients age 65 and older with metastatic lung cancer willundergo serial geriatric assessments to measure functional status during chemotherapy and/orimmunotherapy. In Aim 2A s focus group study, older adults with lung cancer, caregivers, and oncologists willparticipate in focus groups to elicit feedback aimed at adapting the BC/WC tool to incorporate function andother patient priorities into patient-centered decision making. In Aim 2B s pre-post pilot study, oncologists willbe trained to use the adapted BC/WC tool; treatment discussions with older adults with lung cancer before andafter training will be analyzed. Dr. Wong s exceptional multidisciplinary mentoring team is led by Dr. LouiseWalter, an internationally recognized expert on individualized decision making for cancer screening in olderadults. This award will support Dr. Wong s transition to research independence through dedicated training in 1)longitudinal modeling and risk prediction for functional decline in older adults with cancer; 2) shared decisionmaking and decision-making interventions for older adults with functional or cognitive impairment; 3) clinicaltrial design to test decision-making interventions for older adults with cancer; and 4) leadership skills to directmulticenter research to transform geriatric oncology care. The results from this proposal will serve as thefoundation for a multicenter cohort study to develop and validate a risk prediction score for functional declineduring lung cancer treatment in older adults and a cluster-randomized trial to test the effect of the adaptedBC/WC tool on communication, shared decision making, and receipt of goal-concordant care.

4. Project Title: TAILORED GERIATRIC ASSESSMENT AND MANAGEMENT FOR HIV CARE SETTINGS

Leader(s):   **GREENE, MEREDITH**
                UNIVERSITY OF CALIFORNIA SAN FRANCISCO
                NIH K76AG064545 / (2019 - 2024)

Core(s):

PROJECT SUMMARY/ABSTRACTDue in large part to the successful development of antiretroviral therapy, adults with HIV infection are livinglonger; in the United States, 47% of all people living with HIV are age 50 and older. This aging populationincreasingly experiences multimorbidity, polypharmacy, and significant mental health and psychosocialchallenges. Older HIV-positive adults also experience a high frequency of geriatric conditions including falls,frailty, and functional impairment. Geriatric assessment and management could help address this medical andsocial complexity. Supporting a role for geriatric assessment, studies show that assessments can predicthospitalization and mortality among older HIV-positive adults and geriatric conditions are associated withpoorer quality of life. Yet little is known on how to best integrate geriatric assessment and management in HIVcare settings. Strategies developed need to be efficient, able to be administered by non-geriatrics trainedclinicians, and also tailored to the unique aging issues that are influenced by HIV infection. Our proposaladdresses this knowledge gap by developing and testing a tailored Geriatric Assessment and InitialManagement guide focused on the needs of older HIV-positive adults, also referred to as G-AIM HIV.Specifically, the objectives of this proposal are to 1) develop G-AIM HIV by incorporating patient and expertperspectives on the most important geriatric assessment domains and initial management steps; 2) examineHIV providers and staff attitudes towards G-AIM HIV and identify facilitators and barriers to its use; and 3) pilotG-AIM HIV in two HIV outpatient settings to evaluate feasibility, acceptability and preliminary patient reportedoutcomes such as quality of life. The objectives of this proposal support the career development activities ofthe PI Dr. Meredith Greene focused on 1) Delphi methodology and stakeholder engagement, 2) qualitativeresearch methods, 3) intervention and clinical trial research with vulnerable populations, and 4) ongoingleadership development. Dr. Greene will conduct all work at the University of California, San Francisco with anexceptional mentoring team, led by Dr. Kenneth Covinsky. This K76 Beeson proposal will advance ourknowledge of how to integrate geriatric principles into HIV care to improve quality of life for older HIV-positiveadults. It will also provide advanced research skills and valuable data to launch Dr. Greene s career as anindependent investigator and leader at the intersection of HIV and geriatric medicine.

5. Project Title: **PREDICTING POST-TRANSPLANT MORTALITY AND GLOBAL FUNCTIONAL HEALTH BASED ON PRE-TRANSPLANT FUNCTIONAL STATUS IN LIVER TRANSPLANTATION**

Leader(s):   **LAI, JENNIFER C.**
                UNIVERSITY OF CALIFORNIA SAN FRANCISCO
                NIH R01AG059183 / (2018 - 2023)

Core(s):

PROJECT SUMMARYThe decision to proceed with liver transplantation in a patient with end-stage liver disease depends not just onthe risk of death without transplant but the risk of adverse outcomes after it. The transplant clinician's assess-ment of a cirrhotic patient's global functional health which we have conceptualized as his or her vulnerabilityto health stressors is a critical factor (oftentimes the sole factor) in this decision. Yet at the current time, nostandardized, objective criteria for poor global functional health exist to define who is too frail for transplant .Rather, assessment of functional status in transplant is subjective and is applied to decision-making ad hoc,resulting in unequal transplant access and potential denial of otherwise suitable candidates. To facilitatetransplant decision-making, a precise understanding of how pre-transplant functional status impacts post-transplant outcomes is needed to inform prediction of who will not regain excellent global functional health aftertransplant. We have demonstrated that tools to quantify frailty and functional status in older adults have provenvaluable to measure global functional health in cirrhotic patients and have developed an objective Liver FrailtyIndex, consisting of a composite of performance-based tests (grip strength, chairs stands, and balancetesting), to capture longitudinal changes in functional status specifically for use in the pre- and post-transplantsettings. Building logically upon this work, we propose to determine the impact of pre-transplant functionalstatus on 1-year post-transplant mortality and global functional health and develop/validate clinical predictionrules for these outcomes that incorporate pre-transplant functional status. To accomplish these goals, we willleverage our existing Multi-center Functional Assessment in Liver Transplantation Study, consisting of 5 USliver transplant centers (UCSF, Johns Hopkins, Columbia, Baylor, and Duke) with a track record ofcollaboration and high-impact research to obtain data on a minimum of 1,300 liver transplant recipients withassessments of functional status pre-transplantation and assessments of global functional health (including theLiver Frailty Index, disability, and quality of life) 1-year post-transplantation. These data will be used to developand validate clinical prediction rules that incorporate both pre-transplant functional status, patient and donorcharacteristics to predict death, functional status, disability, and quality of

life 1-year after transplantation. Thisproject will positively impact the field by expanding our ability to measure the benefit of transplant both by howlong a recipient will live as well as by how well a recipient will live after liver transplantation. Importantly, thisproject will facilitate clinical decision-making for patients and their clinicians through the precise understandingof how functional status impacts outcomes and what patients can expect after liver transplantation with respectto functional recovery. Given that functional status is modifiable in cirrhotic patients, our data will also supportfuture investigations to develop effective strategies to improve pre-transplant functional status with the goal ofreducing mortality and optimizing post-transplant functional health.

6. Project Title: **TRANSFORMING RESEARCH AND CLINICAL KNOWLEDGE IN GERIATRIC TRAUMATIC BRAIN INJURY (TRACK-GERI)**

Leader(s):   **GARDNER, RAQUEL C.**
                UNIVERSITY OF CALIFORNIA SAN FRANCISCO
                NIH R01NS110944 / (2019 - 2024)

Core(s):

PROJECT SUMMARY / ABSTRACTSome 2.8 million Americans seek medical attention for traumatic brain injury (TBI) annually, resulting inestimated annual costs of over $75 billion. Older adults have the highest and fastest rising rate of TBI of anyother age-group, with 1 in 50 adults age =75y seeking medical attention for TBI in 2013. Older adults with TBIexperience higher mortality, slower recovery, worse outcomes, and may be at especially high risk for post-TBIdementia. There are few evidence-based guidelines for management, no tools to provide patients and familieswith reliable estimates of prognosis, and few proven treatments. Progress has been limited by: 1. systematicexclusion of older disabled patients from most prior prospective TBI studies, and 2. lack of age-appropriate TBIresearch tools. The overall objective is to launch a 2-site prospective geriatric TBI cohort study that will directlyaddress these barriers by applying state-of-the-art geriatric research methods to the field of TBI to improverepresentation of older patients in TBI research, and to develop a novel approach to measuring age-appropriate TBI predictors, outcomes, blood-based biomarkers, and neuropathology. The approach rests on 2foundational concepts: 1. Geriatric TBI is different from TBI in younger patients and will require a targeted age-appropriate approach. 2. Baseline health status including comorbidities/polypharmacy, physical frailty,functional status, and brain structure is recognized as a key predictor of outcome in the field of geriatrics butis not systematically measured in TBI research. The central hypothesis is that pre-injury health will beextremely heterogeneous in geriatric TBI and will be a key predictor of outcome in this population. Anoutstanding team of experts in TBI and aging research will achieve these Aims: Aim 1: Assemble a prospectivecohort of patients age =65y presenting to the Emergency Department =72h after TBI who underwent CT. Enroll270 TBI patient/study-partner dyads and 90 controls; perform baseline assessments and blood draws, andassess longitudinal outcomes at 2wk, 3mo, 6mo (primary endpoint) and 12mo; offer enrollment in a braindonation program. Aim 2: Develop and validate optimized geriatric TBI predictor and outcome assessments:2a: Systematically measure apolipoprotein E allele and pre-injury comorbidities/polypharmacy, physical frailty,and multi-domain functional status via detailed patient and study partner interviews using validated geriatricinstruments and assess association of these predictors with outcome after TBI. 2b: Describe the natural historyof geriatric TBI using validated TBI and geriatric outcomes and then use data-driven analytics to identify themost parsimonious set of measures for longitudinal outcome assessment in this population. 2c (exploratory):Measure pre-injury brain structure (atrophy/white matter disease of uninjured brain visualized on baseline CT)and explore association with outcome after TBI. Aim 3: Identify age-appropriate diagnostic and prognosticblood-based biomarkers. This work will directly inform design of large-scale age-appropriate geriatric TBIclinical trials that are urgently needed to improve care and outcomes in this vulnerable population.

PUBLICATIONS

2023

1. **Clinical Outcomes of Intensive Inpatient Blood Pressure Management in Hospitalized Older Adults.**
   Anderson TS, Herzig SJ, Jing B, Boscardin WJ, Fung K, Marcantonio ER, Steinman MA
   JAMA Intern Med, 2023 Jul 1, 183(7): 715-723
   https://doi.org/10.1001/jamainternmed.2023.1667 | PMID: 37252732 | PMCID: PMC10230372
   Citations: 34 | AltScore: 526.38

2. **Longitudinal Associations between Concurrent Changes in Phenotypic Frailty and Lower Urinary Tract Symptoms among Older Men.**
   Bauer SR, McCulloch CE, Cawthon PM, Ensrud KE, Suskind AM, Newman JC, Harrison SL, Senders A, Covinsky K, Marshall LM
   J Frailty Aging, 2023, 12(2): 117-125
   https://doi.org/10.14283/jfa.2022.33 | PMID: 36946708 | PMCID: PMC10149140
   Citations: 56 | AltScore: 2.5

3. **Response by Brubaker et al to Letter Regarding \A Randomized**
   Brubaker PH, Nelson WB, Kitzman DW
   Controlled Trial of Resistance Training Added to Caloric Restriction Plus Aerobic Exercise Training in Obese Heart Failure With Preserved Ejection Fraction\., Circ Heart Fail, 2023 May(16): 5
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44. **Can markers of disease severity improve the predictive power of claims-based multimorbidity indices?**

Rizzo A, Jing B, Boscardin WJ, Shah SJ, Steinman MA
J Am Geriatr Soc, 2022 Dec 10, 71(3): 845-857
https://doi.org/10.1111/jgs.18150 | PMID: 36495264 | PMCID: PMC10023343
Citations: 38 | AltScore: 21.03

45. **Association of Social Support With Functional Outcomes in Older Adults Who Live Alone.**
Shah SJ, Fang MC, Wannier SR, Steinman MA, Covinsky KE
JAMA Intern Med, 2022 Jan 1, 182(1): 26-32
https://doi.org/10.1001/jamainternmed.2021.6588 | PMID: 34779818 | PMCID: PMC8593829
Citations: 49 | AltScore: 127.95

46. **Change in four measures of physical function among older adults during lung cancer treatment: A mixed methods cohort study.**
Singhal S, Walter LC, Smith AK, Loh KP, Cohen HJ, Zeng S, Shi Y, Boscardin WJ, Presley CJ, Williams GR, Magnuson A, Mohile SG, Wong ML
J Geriatr Oncol, 2022 Sep 1, 14(2): 101366
pii: S1879-4068(22)00206-5. https://doi.org/10.1016/j.jgo.2022.08.015 | PMID: 36058839 | PMCID: PMC9974579
Citations: 58 | AltScore: 9.95

47. **Examining the Impact of the Golden Compass Clinical Care Program for Older People with HIV: A Qualitative Study.**
Tan JY, Greene M, Blat C, Albers A, Grochowski J, Oskarsson J, Shiels M, Hsue P, Havlir D, Gandhi M, Myers J
AIDS Behav, 2022 May, 26(5): 1562-1571
https://doi.org/10.1007/s10461-021-03509-0 | PMID: 34705153 | PMCID: PMC8548856
Citations: 30 | AltScore: 1

48. **KIBRA, MTNR1B, and FKBP5 genotypes are associated with decreased odds of incident delirium in elderly post-surgical patients.**
Terrelonge M, LaHue SC, Tang C, Movsesyan I, Pullinger CR, Dubal DB, Leung J, Douglas VC
Sci Rep, 2022 Jan 11, 12(1): 556
https://doi.org/10.1038/s41598-021-04416-z | PMID: 35017578 | PMCID: PMC8752781
Citations: 32 | AltScore: 0.75

49. **The epidemiology of preexisting geriatric and palliative conditions in older adults with poor prognosis cancers.**
Tsang M, Gan S, Boscardin WJ, Wong ML, Walter LC, Smith AK
J Am Geriatr Soc, 2022 Dec, 70(12): 3402-3412
https://doi.org/10.1111/jgs.18039 | PMID: 36259424 | PMCID: PMC9772051
Citations: 45 | AltScore: 324.65

50. **Changes in older adults' life space during lung cancer treatment: A mixed methods cohort study.**
Wong ML, Shi Y, Smith AK, Miaskowski C, Boscardin WJ, Cohen HJ, Lam V, Mazor M, Metzger L, Presley CJ, Williams GR, Loh KP, Ursem CJ, Friedlander TW, Blakely CM, Gubens MA, Allen G, Shumay D, Walter LC
J Am Geriatr Soc, 2022 Jan, 70(1): 136-149
https://doi.org/10.1111/jgs.17474 | PMID: 34611887 | PMCID: PMC8742783
Citations: 50 | AltScore: 124.99

EXTERNAL ADVISORY BOARD MEMBERS

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RECOGNITION AND AWARDS (2022-2023)

<u>Kenneth Lam, MD, MAS</u> (2022)

- NIA Administrative Supplement

MINORITY RESEARCH

General Brief Description of Minority Activities:
Not defined.

Minority Trainee(s):

- Aksharananda Rambachan, MD, MPH, Assistant Professor, Medicine
  "Despite an increased emphasis on identifying pain as the "fifth vital sign," there are shortcomings in our approach to assessing, documenting, and responding to pain. Cognitive impairment in older persons, drugdrug interactions, patient comorbidities, fall-risk, and frailty all present additional challenges for prescribing clinicians. Furthermore racial, ethnic, cultural, and language-based differences across patients are areas where disparities are present. Studies across various health settings have found that older patients and minority patients are at high risk for underassessment and undertreatment of pain. Pain assessment tools are ubiquitous, given regulatory and hospital level requirements, yet their appropriateness and utility remain understudied in this patient population. Pain is assessed by nursing across various time points using various self-report and behavioral tools. Clinicians often utilize their own individualized bedside approach and review of clinical data in assessing and managing a patient's pain, disconnected from nursing workflows. There is a paucity of guidelines for inpatient pain management for both acute and chronic conditions and minimal research into best practices for elderly minority patients. We do not know how pain is managed quantitatively across common medical diagnoses for these patient groups, and with regards to the interaction between age, race, ethnicity, and language status."

- Anna Oh, BSN, MSN, MPH , former VAQS fellow, now nurse scientist at Stanford
  Engagement in meaningful activities – enjoyable physical, leisure, social, spiritual activities related to personal interests and values – gives life identity and purpose, and is therefore beneficial to the emotional and physical well-being of older adults. As older adults age and become more susceptible to disease, disability, and cognitive impairment, the ability to participate and engage in meaningful activities place the older adult at higher risk of loss of identity and well-being. Dr. Oh's cross-sectional examination published in JAMA IM of meaningful activity engagement in the National Health and Aging Trends Study (NHATS) found functional disability was the leading factor of nonengagement. Yet, diverse racial and ethnic groups of older adults may have varying experiences with meaningful activity engagement over time due to cultural and language barriers as well as limited access to services and resources. Little is known about meaningful activity engagement in diverse groups of older adults from historically disadvantaged backgrounds, its relationship to disability, and barriers and facilitators for engagement, such as social support, neighborhood factors, and socioeconomic and demographic factors. Previous studies have documented concerning racial and ethnic differences in the experience of aging, older Americans and their caregivers in caregiving experiences, access to and use of in-home rehabilitation services, and advance care planning. In addition to reducing racial and ethnic differences and health disparities, culturally-sensitive, community-based interventions have the potential to increase access to high-quality healthcare for diverse older adults. Culturally-sensitive, community-based interventions that include assessments of meaningful activity engagement can guide goals of care conversations, medical treatment recommendations, and target existing services and supports (e.g. home health, hospice, long-term services and supports)

for older adults to stay engaged in meaningful activities. The objective of this study is to identify activity engagement in older, community-dwelling African-American/Black, Latinx/Hispanic, Asian, and bi/multiracial NHATS participants before and after the onset of the COVID-19 pandemic. The data and findings from this research will be a springboard for a K23 award where Dr. Oh will examine longitudinally the barriers and facilitators to staying engaged in meaningful activities. Through support from this award, the Pepper Center is helping to catalyze Dr. Oh's long-term goal is to become a clinician leader who improves the quality-of-life of diverse, community-dwelling, seriously ill older adults with home-based models of care.

- Jennifer E. James, PhD, MSW, MS, Assistant Professor, Institute for Health & Aging at UCSF

Incarceration and the health of currently and formerly incarcerated individuals was highlighted as an important social determinant of health in Healthy People 2020. Individuals with a history of incarceration report more chronic health problems after incarceration than before (Schnittker & John, 2007), in many cases regardless of the length of time served (Schnittker & John, 2007; Massoglia, 2008). Compared to the general population, incarcerated persons are more likely to have high blood pressure, asthma, cancer, arthritis and infectious diseases (Healthy People 2020) and studies have shown that women with a history of incarceration face a greater disease burden than men with a history of incarceration (Healthy People 2020; Covington, 2007). Ninety percent of recently released women have chronic medical, mental health, or substance use disorders, which is significantly higher than the general population (Mallik-Kane & Visher, 2005; Schnittker, Massoglia & Uggen, 2012). Additionally, within the first two weeks after release, recently released individuals have a 12.7 times higher mortality rate than the general population and that relative risk is higher for women than men (Binswanger et al., 2007). Being Black, being a woman, being poor and having a history of incarceration each confer serious health risks (Braithwaite, Treadwell, & Arriola, 2008). The overall goal of this study is to use interviews and ethnographic observation to better understand the intersection of these interconnected forms of risk. Dr. James will use a novel qualitative interview approach called "collective dialogue", grounded in Black Feminist Epistemology, that engages participants in the analysis of the data they produce with the researcher over the course of open-ended interviews about their lives. This method, which Dr. James developed and piloted in her dissertation, enables her to center the lived experience of older, formerly incarcerated Black women and enables the women to participate in the production of knowledge about themselves. These interviews, combined with ethnographic observations of organizations advocating for the health and welfare of currently and formerly incarcerated women, will produce a multi-faceted and multilayered account of post-incarceration experiences of women with chronic disease and how they access healthcare. Currently, she is continuing to recruit participants for interviews. Her interviews to date have produced incredibly rich data. She is currently working with two research assistants to analyze the data, and have submitted abstracts based on preliminary findings to four conferences, and have been invited to present at two conferences this summer. However, attendance for conferences have been placed on hold due to COVID 19 safety protocols.

- Linda Park, RN, PhD, FNP, Associate Professor

UCSF RCMAR (Center for Aging in Diverse Communities or CADC) has been dedicated to eliminating health disparities in minority aging populations. Their goal is to support work that focuses on understanding health disparities and building and testing community-engaged interventions to reduce disparities among older adults. Like the UCSF Pepper Center, one of

our most important missions is to train and mentor talented, underrepresented junior investigators to develop independent research careers focused on health disparities and aging issues. During this year, CADC and UCSF Pepper Center have provided joint support for the following project and investigator: Improving Health Disparities by Promoting Physical Activity Among Asian American Older Adults with Cardiovascular Disease: A Pilot Study Cardiovascular disease (CVD) is the leading cause of mortality, affecting 43.7 million older adults age 60 and over. To ameliorate this, cardiac rehabilitation (CR) is a highly effective, Class I level guideline-recommended 12-week group program that offers supervised physical activity (PA) after cardiac events (e.g., myocardial infarction, revascularization, valve replacement). It has been shown to improve physical function and decrease morbidity and mortality in older adults. Thus, maintaining PA after CR is essential in older adults to gain and maintain the critical benefits of improved physical function (balance, gait, strength, and endurance). PA maintenance after CR is also linked to reduced adverse geriatric outcomes such as falls and mobility impairment but thereby increases susceptibility to adverse secondary cardiac events, functional decline, and depression. Although it is estimated that minority individuals from diverse racial/ethnic backgrounds will comprise ~50% of the total U.S. population, minority older adults have more CVD burden than non-Hispanic Whites and have disproportionately lower rates of enrollment and adherence to CR (20% enrollment in Whites vs.8% in non-Whites). Asian Americans (AA) have been identified as a high-risk population for CVD based on genetic predisposition, coronary risk factor profile, and behaviors (e.g., PA and diet). In general, AA are less physically active than non-Hispanic Whites. Specific for CR participation, barriers may include cultural, socioeconomic, and linguistic challenges but it is unknown what the perceived barriers and facilitators are to continue PA behaviors after CR completion. Modifiable targets related to sustained PA may include depression and anxiety and slower self-efficacy, motivation, and social support. Tailored, accessible, and culturally appropriate interventions are urgently needed for AA older adults to promote sustained PA after CR to reduce future cardiac events. The objective of this mixed-methods proposal is to conduct a pilot study that will collect the critical data needed for a clinical trial to promote sustained PA through digital coaching after CR completion with a focus on improving physical function for AA older adults. This pilot work will reduce persistent health disparities that exist for ethnic minorities so we can target modifiable factors for sustained PA after CR. The under lying hypothesis is that there are distinct differences in barriers, facilitators, and preferences for interventions that aim to sustain PA after CR, thus requiring cultural tailoring for AA. My long-term career goal is to become a leading academic investigator who develops and tests behavioral interventions to improve older adults' health and well-being with CVD. While the COVID-19 pandemic led to delays in the initiation of this project, work on this project has now resumed, and Dr. Park plans to complete the survey distribution and conduct individual interviews by June 2021. Dr. Park and her team are IRB approved to achieve the study aims.

No minority grant information specified.

UNIVERSITY OF FLORIDA
Claude D. Pepper Older Americans Independence Center

Karyn Esser, PhD   352-294-5800   kaesser@ufl.edu
Principal Investigator

Todd Manini, PhD   352-294-5800
Principal Investigator

Connie Caudle   352-294-5800   ccaudle@ufl.edu
Program Administrator

CENTER DESCRIPTION

The mission of the University of Florida Older Americans Independence Center (OAIC) is twofold: 1) to optimize older persons' physical performance and mobility through interdisciplinary approaches; and 2) to train new investigators in aging and disability research while developing their leadership qualities. Our goal is to enhance late-life health and independence, with a special focus on mobility. To accomplish our mission, our strategy is to attract studies and inventive investigators from diverse behavioral, clinical, basic, and technological science disciplines with a common research focus: "mobility and prevention of disability." Traversing the entire spectrum of biomedical investigation, including molecular biology, animal studies, clinical research, behavioral sciences, epidemiology, and engineering, our research effort addresses the OAIC's general goal: to increase scientific knowledge that leads to better ways to maintain or restore independence of older people. Our research objectives are to: 1) assess, using translational research (among diverse disciplines), the biological, co-morbid, psychosocial, behavioral, and other factors that contribute to physical function decline, loss of mobility, and progression toward disability; and 2) develop and reliably test, in clinical and preclinical studies, interventions that target mobility to prevent, delay, or recover the age-related declines in physical function. Our educational objective is to train future leaders in clinical translational research on aging. To meet these objectives the proposed OAIC trains Junior Scholars and supports investigators, resources, services, external studies, development projects, and pilot/exploratory studies through seven integrated cores: *Leadership and Administrative Core; Research Education Core; Pilot/Exploratory Studies Core; Clinical Research Core; Metabolism and Translational Science Core; Biostatistics Core; Data Science and Applied Technology Core; and Circadian Rhythms Core*. A relevant strength of the proposed OAIC is the concerted action of the interdisciplinary cores, projects, and investigators who address one common research focus spanning the entire spectrum of biomedical investigation.

Research hypotheses:

- Multiple biological, co-morbid, psychosocial, cognitive, and behavioral factors contribute to agerelated physical function decline, loss of mobility, and progression to disability.
- Interventions that target individual or multiple biological, co-morbid, psychosocial, cognitive, and behavioral risk factors of physical function decline avert the loss of mobility and prevent disability.

Research objectives:

- Assess, by taking advantage of a bidirectional translation between basic and clinical research, the multiple factors that contribute to physical function decline, loss of mobility, and progression to disability.

- Develop and test pharmacological, nutritional, and behavioral interventions for preventing decline in physical function, loss of mobility, and progression to disability.

Educational objectives:

- Educate and train new investigators in research on aging and disability in older adults.
- Develop leadership qualities and roles in Junior Scholars supported by the OAIC.
- Develop skills for translating findings between basic and clinical research.

Operational objectives:

- To provide outstanding investigators and state-of-the-art resources, environment, and services to support the above-mentioned research and educational objectives.

CORES

Leadership and Administrative Core (LAC)

<u>Leader 1:</u>   Marco Pahor, MD   mpahor@ufl.edu

<u>Leader 2:</u>   Karyn Esser, PhD   kaesser@ufl.edu

The Leadership and Administrative Core (LAC) is responsible for strategic planning, organization, administrative operations, and evaluation of the Older Americans Independence Center (OAIC) research and training program. A special effort is devoted to ensure the cohesion of the Center and maintain an interdisciplinary and translational research focus on the common research theme, which is "mobility and prevention of disability." The Core Leader and three committees achieve the key LAC tasks. The Executive Committee, which is composed of the OAIC core leaders, administers, governs, provides scientific guidance, and sets productivity benchmarks for the OAIC. The External Advisory Board, which is composed of experts external to the institution, reviews all OAIC activities and provides overall scientific guidance to the OAIC. The Independent Review Panel, which is composed of ad hoc experts (at least one third external to the institution), reviews proposed support for development projects, and pilot/exploratory studies. Taken together, the LAC provides support for planning, organizational, evaluation, and administrative activities relating to the other cores and to the OAIC as a whole. The LAC monitors, stimulates, sustains, evaluates, and reports progress toward the overall goals of the OAIC.

Research Education Component (REC)

<u>Leader 1:</u>   Christiaan Leeuwenburgh, PhD   cleeuwen@ufl.edu

<u>Leader 2:</u>   Roger Fillingim, PhD   RFillingim@dental.ufl.edu

The REC promotes the development of independent investigators in interdisciplinary research on aging relevant to the independence of older Americans. One of our major goals is to identify the most promising Junior Scholars with research relevant to the OAIC theme at UF & VA and to provide them with mentorship, training activities, access to OAIC Core resources and funding and enable them to become independent investigators in interdisciplinary aging research. Furthermore, this core emphasizes the development of leadership, and research skills for translating basic findings into clinical research and clinical findings into basic research. The REC supports the research training of OAIC Junior Scholars that span the spectrum from beginning trainees who are not yet funded to advanced trainees who already have competed successfully for career development grants that provide substantial salary support.

Pilot and Exploratory Studies Core (PESC)

<u>Leader 1:</u>   Yenisel Cruz-Almeida, Ph.D.   cryeni@ufl.edu

<u>Leader 2:</u>   Marco Pahor, MD   mpahor@ufl.edu

The Pilot/Exploratory Studies Core serves to develop key information needed to select and design future, original and independently funded studies that can advance our insight into sarcopenia and prevention of disability in older Americans. Specifically, the core fosters the Pilot and Exploratory studies by ensuring the availability of optimal infrastructure, environment, funding, expertise, and instrumentation. Pilot and Exploratory studies foster Junior Scholars in their efforts to develop research careers in aging by providing opportunities for meaningful participation in well-designed research studies and by collecting the needed preliminary data for independent research applications. Furthermore, these studies will allow investigators already accomplished in aging

research to gather data that will extend and broaden their focus of research. Finally, these studies will also be a vehicle to encourage and facilitate experienced investigators traditionally working in other research fields to focus on aging.

Clinical Research Core (RC1)

<u>Leader 1:</u>   Stephen Anton, PhD   santon@ufl.edu

<u>Leader 2:</u>   Marco Pahor, MD   mpahor@ufl.edu

The Clinical Research Core (RC1) is a key resource for the UF OAIC in providing the infrastructure and investigators for conducting clinical research -- randomized controlled trials and observational studies. The clinical research core has four primary goals: 1) optimal selection and utilization of measures for clinical trials and observational studies 2) understanding the physiological and biomechanical mechanisms contributing to changes in walking speed, 3) in collaboration with the Biostatistics Core, conduct secondary analyses of randomized clinical trials and observational studies to provide preliminary data to support the rationale for future clinical trials, and 4) development of behavioral and pharmacological interventions to improve physical function and quality of life of older adults. The RC1 offers state-of the art infrastructure and experienced personnel to support the conduction of observational studies, and Phase 2 and 3 randomized controlled trials that involve behavioral and pharmacological interventions. Senior researchers with NIH and/or VA funding, who also have established track records as mentors for career development, lead each one of these goals.

Biostatistics Core (RC 3) (Biostats)

<u>Leader 1:</u>   Peihua Qiu, PhD pqiu@ufl.edu

The Biostatistics Core is one of five research cores in the OAIC at UF. The mission of the UF OAIC is to assess risk factors of physical disability in older adults, to develop and test effective prevention and rehabilitation therapies, and to train new investigators in research on aging and disability. The Biostatistics Core is a key cog in the interaction among scientists from many disciplines to accomplish this mission. The core provides data coordination including: developing data collection forms, designing web-based capture systems, and managing the data (including quality control) for studies conducted within the OAIC. The core is also involved in all phases of these studies including initial study design and sample size calculations when preparing a grant proposal, randomization, and state-of-the-art statistical analyses once the data are collected. For study designs and data for which current methodology is lacking, the core has the expertise to develop new statistical methodology to perform appropriate analyses. The Biostatistics Core will also be involved in preparation of manuscripts for dissemination within the research community. The Core also conducts research using The UF & Shands Academic Health Center's new electronic medical record system (EPIC), which has gone live with new modules planned through the next few years. This includes the implementation of a clinical data warehouse (CDW). The CDW is the foundation for the development of a research data repository whereby researchers and junior scholars and faculty may have unfettered access to anonymized data for clinic research.

Circadian Rhythms Core (RC5)

<u>Leader 1:</u>   Karyn Esser, PhD kaesser@ufl.edu

The new Circadian Rhythms research core within the UF OAIC provides the specialized resources and expertise to support scientists that want to incorporate circadian and sleep concepts into their aging research program. This includes new investigators, early-stage investigators and current investigators in aging. The core supports research through; 1) in vivo rodent circadian phenotyping across age; 2) resources to implement time restricted feeding with unique automated cages; 3) methods to test the robustness and resilience of the circadian system across ages; 4) non-invasive analysis of rodent sleep parameters; 5) statistical support for analysis of circadian data from rodents and humans. 6) ongoing development of an in vitro assay to analyze human circadian clock function using primary cells from subjects of different ages and health status. 7) work with the Data Science Core (RC4), the Biostatistics core to leverage UF machine learning strengths to define a blood marker assay as a biomarker of human circadian health.

Data Science and Applied Technology Core (RC 4) (Data Science)

 Leader 1:   Todd Manini, PhD   tmanini@ufl.edu

 Leader 2:   Sanjay Ranka, PhD   ranka@cise.ufl.edu

The Data Science and Applied Technology (DSAT) Core (RC4) provides an interactive data and technology ecosystem for preserving mobility and preventing disability. Big data initiatives, applied technologies, and new methodological approaches for data science have exploded in many various environments, and the world is moving toward a connected system of computing and sensing components. Additionally, mobile health (mHealth, smartphones and smartwatches) technologies are changing the landscape for how patients and research participants communicate about their health in real time. DSAT investigators provide OAIC leadership to assure that researchers in Geriatrics in general, mobility and disability are prepared for the rapid advances in these expanding technologies. The RC4 provides many unique attributes, such as developing software for interactive mobile technology (e.g., wearable sensors that are programmable in real time); validating new sensing technology; warehousing data; repurposing data; and applying machine learning techniques to domain problems. DSAT provides a central hub of expertise in computer science, biomedical engineering, biomedical informatics, data science, applied technology, epidemiology, and content expertise in the assessment of mobility. There is a growing demand for data science and applied technology for meeting the challenge of preserving mobility and preventing disability. The DSAT Core adds a highly innovative aspect to this challenge that will lead it into the future of connected systems of computing, sensing and biomedical informatics.

Metabolism and Translational Science (RC2) (Metabolism and Translational Science)

 Leader 1:   Christiaan Leeuwenburgh, PhD   cleeuwen@ufl.edu

The Metabolism and Translational Science Core (RC2), in collaboration with other UF OAIC cores, supports biochemical analyses for preclinical, human interventional, or observational clinical studies. By measuring a selected set of biomarkers, we can determine how targeted interventions influence the rate of aging, as well as loss of mobility and independence. This core thereby provides the support for the Research Education Core (REC) Scholars and pilot study investigators. Aging and disease feature progressive deterioration of various physiological and metabolic processes. This is associated with altered functions or contents of protein, RNA, and DNA, which provide biomarkers to monitor aging. Multiple pathways and domains have been associated with aging, such as genomic instability (including telomere attrition, mutations, and deletions); epigenetic alterations; loss of proteostasis (including dysfunctional autophagy); deregulated nutrient sensing; mitochondrial (Mt) dysfunction; inflammation and cellular senescence; stem cell

exhaustion, disrupted circadian clock rhythms; and dysfunctional nicotinamide adenine dinucleotide (NAD+) homeostasis. The specific analyses of protein, RNA, and DNA biomarkers that this core will provide are related to major biological and metabolic pathways known to regulate aging and focus on: (i) Mt function; (ii) inflammation and senescence; (iii) autophagy; (iv) circadian clock biology; and (v) NAD+ homeostasis. We use innovative analytical tools and standard high-throughput analysis to determine the fundamental biological mechanisms of aging. The Metabolism and Translational Science Core (RC2) supports the overarching hypothesis that knowledge of specific protein, RNA, and DNA biomarkers, as well as measurements of metabolism of isolated mitochondria and white blood cells (WBCs), are critical for understanding the trajectory of healthy aging and the underlying biological causes of mobility loss. The core also supports extraction of proteins, RNA, and DNA, analysis of biomarkers, isolation of cells (WBCs) and organelles (mitochondria), and assessments of Mt function. The RC2 provides investigators across UF OAIC cores and REC scholars with established methodologies, scientific data, infrastructure, highly qualified personnel, and consultative and collaborative expertise and pursues the following aims: Aim 1: To support protein, RNA, and DNA isolation and analysis of specific biomarkers of aging. Aim 2: To support analysis of Mt respiration, Mt enzyme activities, and NAD coenzymes. Aim 3: To facilitate and provide consultation on analyses and sample storage, and collaborate synergistically with the other OAIC cores to pursue the common OAIC theme of promotion of mobility and independence.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications
Lakeshia Cousin, PhD, APRN, AGPCNP-BC	2022-2024 /
Assistant Professor / College of Nursing	1 (total)
<u>A Pilot Feasibility Study of a Gratitude Journaling Intervention to enhance Well-being and Exercise Readiness in Older African American Female Breast Cancer Survivors</u>	0 (1st/Sr)
Feng Yue, PhD	2022-2024 /
Assistant Professor / Department of Animal Sciences	3 (total)
<u>Mechanisms of sepsis-induced myopathy in aging: insights from a new modified surgical sepsis model by single cell analysis</u>	0 (1st/Sr)
• NIDDKD 1R01DK136722-01	
Clayton Swanson, PhD, MS	2022-2024 /
Assistant Professor / Department of Aging & Geriatric Research	0 (total)
<u>Development of a Home-based Self-delivered Prehabilitation Intervention to Proactively Reduce Fall Risk in Older Adults</u>	0 (1st/Sr)

Past Scholars
Rui Xiao, PhD, Department of Aging & Geriatric Research (2015-2017)
Hyochol "Brian" Ahn, PhD, ARNP, ANP-BC, College of Nursing, Department of Family, Community and Health System Science (2015-2017)
Scott Brakenridge, MD, College of Medicine, Department of Surgery (2015-2017)
Andrew Bryant, MD, College of Medicine, Department of Internal Medicine Pulmonary, Critical Care and Sleep Medicine (2015-2016)
Sara Burke, PhD, College of Medicine, Department of Neuroscience (2015-2017)
Huaihou Chen, PhD, Department of Biostatistics (2015-2017)
Sooyeon Lee, PhD, College of Medicine, Department of Surgery (2015-2016)
Joshua Brown, PhD, MS, Department of Pharmaceutical Outcomes & Policy (2017-2019)
Robert Mankowski, PhD, Department of Aging & Geriatric Research (2017-2019)
Yu-Jung "Jenny" Wei, PhD, MS, Department of Pharmaceutical Outcomes and Policy (2017-2019)
Joseph McQuail, PhD, Department of Neuroscience (2018-2019)
Terence Ryan, PhD, Department of Applied Physiology & Kinesiology (2018-2020)
Sung Min Han, PhD , College of Medicine Department of Aging and Geriatric Research (2019-2021)
Carolina Maciel, MD, Department of Neurology, Division of Neurocritical Care (2019-2021)
Scott Vouri, PharmD, MSCI, PhD, Department of Pharmaceutical Outcomes and Policy (2019-2021)
Matthew R. Burns, MD, PhD, Department of Neurology (2020-2022)

Sudeshna A. Chatterjee, BPTh, MS, PhD, Department of Aging & Geriatric Research (2020-2022)
Mamoun Al Mardini, PhD, Health Outcomes and Biomedical Informatics (2020-2022)
Samir K. Shah, MD, MPH, Department of Surgery (2020-2022)

PILOT/EXPLORATORY PROJECTS (7 Pilot Projects Listed)

1. Project Title: **Probing metabolomics of pancreatic cancer and skeletal muscle in elderly patients**

Leader: **Ashwin S. Akki, MD, PhD**

The overall goal of this research project is to increase the understanding of metabolic alterations in the skeletal muscle of elderly patients with cachexia and accelerated sarcopenia in pancreatic ductal adenocarcinoma (PDAC). Since skeletal muscle metabolism and strength are intricately linked to tumor metabolism, simultaneously probing PDAC metabolism is crucial. This knowledge will enable us to decipher the impact of a rapidly proliferating tumor on aggressive cachexia, accelerated sarcopenia and impaired mobility in elderly PDAC patients and help identify novel metabolic targets that could potentially be modulated to curb tumor growth, preserve skeletal muscle mass/strength, and prevent disability in the aging population. Consequently, the proposed project is highly relevant to the OAIC theme of "Mobility and Prevention of Disability". This proposal is extremely relevant to the interests of the "Clinical and Translational Research of Aging Review Committee (NIAT)" and/or the "Aging Systems and Geriatrics Study Section"

2. Project Title: **Pain Resilience and Inflammatory Marker Expression (PRIME)**

Leader: **Emily J. Bartley, PhD**

The overarching goal of this study is to elucidate the immunological and resilience mechanisms underlying self-reported and functional disability in older adults with cLBP. This project expands an existing community-based study (Adaptability and Resilience in Aging Adults [ARIAA]) whereby 60 adults (ages 60+ years) with cLBP completed clinical (psychological and pain measures), functional (tests of mobility), and somatosensory pain assessments. The study supplements the parent project through the inclusion of biomarker assays to assess pro- and anti-inflammatory function. These findings will provide novel and important information regarding the mechanisms underpinning pain and disability and will be a step toward the development of therapeutic modalities aimed at mobility preservation in older adults with cLBP.

3. Project Title: **Impact of Pain and Exercise on Mobility in Older Adults with Opioid Use Disorder**

Leader: **Meredith S. Berry, PhD and Danielle E. Jake-Schoffman, PhD**

This study aims to determine the effects of the exercise intervention versus control on (i) self-reported pain and pain catastrophizing, (ii) objective and self-reported mobility ratings (iii) biologically verified urinalysis results of illicit drug-use, and (iv) craving, withdrawal, and behavioral economic demand for opioids. The study directly aligns with the central OAIC themes of enhancing mobility, and reducing pain through an exercise intervention. This project has tremendous potential for public health impact with possibility for wide deployment for those in need. Our multidisciplinary team is uniquely suited to advance understanding of shared mechanisms underlying pain, mobility, craving and withdrawal, and to complete the proposed project with expertise in (i) OUD (ii) PA promotion (iii) pain (iv) exercise physiology (v) cardiology and (vi) biostatistics.

4. Project Title: **Prevention of Cancer-Induced Immobility and Dysfunction**

Leader: **Daria Neyroud, PhD and Andrew D'Lugos, PhD**

This study aims to 1. Quantify the extent to which cancer impacts mobility and skeletal muscle dysfuction; and 2. Determine the efficacy of exercise training for preventing cancerinduced disability and cachexia. The project is therefore highly aligned with the mission of the National Institute on Aging (NIA), in particular with goal C of the current NIA Strategic Direction for Research, "to develop effective interventions to maintain health, well-being, and function and prevent or reduce the burden of age-related diseases, disorders, and disabilities".

5. Project Title: **Role of skeletal muscle Bmal1 on healthspan and survival**

Leader: **Miguel Gutierrez-Monreal, PhD (Karyn Esser, PhD)**

The goal of this pilot study is to provide feasibility and supporting data for a NIH grant application. This pilot is aimed to examine the effect of skeletal muscle molecular clock on systemic metabolism and inflammation during aging. We have recently identified there is a progressive age-related decline in circadian function in skeletal muscle. Disruptions in circadian rhythms have profound negative consequences on several pathways that comprise the hallmarks of aging including metabolism and inflammation.

6. Project Title: **Sleep, pain and aging: potential underlying mechanisms**

Leader: **Soamy Montesino Goicolea, MD (Yenisel Cruz-Almeida, PhD)**

This study will quantify the levels of the GABA neurotransmitter after oral administration, regardless of the direct or indirect route that mediates its function in the brain. This constitutes the starting point in the development of cost-effective over-the-counter GABA treatments aiming at improving the currently costly and often co-morbid problems of sleep dysfunction and chronic pain in the aging population. The project addresses an existing knowledge gap and may potentially identify GABA.

7. Project Title: **Design of Printable Gelatin Microgel and Stem Cell-based Composite Bioink for Repairing Degenerated Intervertebral Discs**

Leader: **Yong Huang, PhD, Christiaan Leeuwenburgh, PhD, Brian Harfe, PhD, Kyle Allen, PhD**

The overarching goal of this pilot study is to design and evaluate a gelatin microgel and stem cellbased printable bioink as a delivery system for the repair and regeneration of age-related degenerative intervertebral discs (IVDs) for personal mobility and independence. Intervertebral disc degeneration (IDD) is an age-related condition that happens when one or more of the discs between the vertebrae of the spinal column deteriorate or even break down. As a natural occurrence that comes with aging, it may lead to lower back pain and even immobility due to weakness, numbness, and pain that radiates down the leg, resulting in disability. As a minimally invasive approach, the cell-therapy approach aims to address disc inflammation by inhibiting aberrant cytokine production as well as disc rehydration and height restoration by initiating matrix anabolism and repopulating native cells. While the cell-therapy approach needs a unified understanding of the disease mechanism of degeneration and useful interpretation of clinical evaluations, clinical trials also call for effective delivery systems of therapeutic cells, which is the subject of the study. Accordingly, two specific aims are proposed: Aim 1: Repair

of degenerative IVD using a gelatin microgel and mesenchymal stem cell-based printable composite bioink. Aim 2: Evaluation of the mechanical properties and formation of fibrocartilage-like intervertebral disc tissue of IVDs repaired using the proposed cell delivery system. This pilot study provides a novel gelatin microgel-based self-supported cell delivery system to repair degenerated IVDs for their better regeneration by integrating engineering and biology to create a costeffective and safe cell therapy for IVD regeneration. Such a printable stem-cell therapy will help improve the mobility and independence of seniors who are disabled due to IDD-induced weakness, numbness, and back pain that radiates down the leg. We further envision that the delivery system using the proposed printable self-supporting cellular bioink can be explored as a much-needed reliable and costefficient stem-cell therapy to facilitate in situ tissue repair and wound healing applications, to name a few.

DEVELOPMENT PROJECTS (2 Development Projects Listed)

1. Project Title:		**Time restricted feeding to improve aging circadian clocks and healthspan in rodents**
Leader:		**Karyn Esser, PhD, Thomas Foster, PhD, Andrew Liu, PhD, Christiaan Leeuwenburgh, PhD**
Core(s):		Biostatistics Core (RC 3) (Biostats)
		Circadian Rhythms Core (RC5)
		Metabolism and Translational Science (RC2) (Metabolism and Translational Science)

Aging is associated with changes in circadian rhythms including patterns of locomotor activity and sleep/wake states (114-120). Underlying circadian rhythms is a molecular clock mechanism that is found in virtually all cells throughout the body. Research has demonstrated that disruption of circadian timekeeping leads to increases in pathology, morbidity, and mortality (121-129). The purpose of this project is to implement a circadian-based intervention, time-restricted feeding, for its potential to enhance circadian function across organs and improve healthspan in aging mice. This preclinical study will complement the clinical DP-1 (described in RC1) with the ability to carefully control the times of feeding the mice, and to assess the health impact on organs such as brain, heart, and skeletal muscle.

2. Project Title:		**Assessment of Fuel Utilization and Circadian Rhythms in Overweight, Older Adults Following Time Restricted Eating - Phase 2 (FAR Phase 2)**
Leader:		**Stephen Anton, PhD, Christiaan Leeuwenburgh, PhD, Todd Manini, PhD, Bhanuprasad Sandesara, MD**
Core(s):		Clinical Research Core (RC1)
		Biostatistics Core (RC 3) (Biostats)
		Data Science and Applied Technology Core (RC 4) (Data Science)
		Metabolism and Translational Science (RC2) (Metabolism and Translational Science)

Both fuel metabolism and circadian rhythms have emerged as important targets to improve cellular and mitochondrial health and ultimately affect function in older adults. Thus, the purpose of this study is to develop minimally invasive measures that will allow us to accurately assess and detect changes in fuel metabolism and circadian rhythms in older adults following time-restricted eating. A growing body of evidence indicates the mitochondria have an important role in the etiologies of many chronic diseases as well as the onset of physical disability in older adults. Although it is recognized that the mitochondria have an important role in many functions relevant to healthy aging, the direct assessment of mitochondrial function in humans is complicated and typically involves a muscle biopsy. Muscle tissue obtained from a biopsy can be used to provide an index of mitochondrial function, but only at a single time point. Some individuals may be discouraged from participating in research studies involving biopsies due to the perceived pain and risk involved. Why there is a decrease in mitochondrial function with aging remains under debate, but emerging science indicates that there is a clear connection between mitochondrial biogenesis and function with fuel metabolism and circadian rhythms. Thus, the purpose of this development project is to develop relatively non-invasive measures that are sensitive to fuel metabolism and circadian health which can serve studies

conducted within the University of Florida's Pepper Center in the coming years. In the proposed project, we will investigate the extent to which our measures of fuel utilization and circadian health markers are time stable and also sensitive to change following an intervention of time restricted eating, which is expected to impact these variables. To our knowledge, no study has assessed fuel utilization patterns or circadian health markers in overweight older adults. Measurements of altered mitochondrial oxidation with a preference toward fat metabolism obtained from a blood sample would provide a sensitive biomarker that is relatively easy to obtain from participants for future interventions studies. The use of continuous glucose monitoring may also be used as surrogate measure of adherence to lifestyle interventions involving calorie restriction and/or intervention fasting, in future studies. In addition to fuel utilization, there is growing recognition that age-related disease conditions and functional decline are associated with disruption of circadian rhythms. These observations raise the possibility that targeting circadian rhythms through timing lifestyle cues, such as meal timing, could be health promoting and may also reduce age associated declines in mobility. The ability to assess markers of circadian and metabolic health in minimally invasive ways through temperature and glucose monitoring, will provide potential valuable measures for explanatory or outcome measures in future studies. In specific aim 1, we will develop a new measure to detect shifts in fuel utilization at the cellular level using Seahorse XF Technology to measure fuel utilization within white blood cells. We will also measure 24-hour fluctuations in plasma glucose levels using a continuous glucose monitor. In specific aim 2, we will develop a new measure to detect the expression of circadian clock genes, as well as non-invasive measures, from which circadian health parameters can be extracted. These measures include activity levels, body temperature, and heart rate, using Wearable Technology. The reliability and variability in measures of fuel utilization and circadian health markers will be assessed in relation to changes in some of our standard Clinical Research Core measures of physical function.

RESEARCH (25 Projects Listed)

1. Project Title: **CEREBRAL NETWORKS OF LOCOMOTOR LEARNING AND RETENTION IN OLDER ADULTS**

Leader(s): **CLARK, DAVID J**
VETERANS HEALTH ADMINISTRATION
VA I01RX003115 / (2019 - 2023)

Core(s):

Aging often leads to substantial declines in walking function, especially for walking tasks that are more complex such as obstacle crossing. This is due in part to a lack of continued practice of complex walking (sedentary lifestyle) combined with age-related deficits of brain structure and the integrity of brain networks. Neurorehabilitation can contribute to recovery of lost walking function in older adults, but major and persistent improvements are elusive. A cornerstone of neurorehabilitation is motor learning, defined as an enduring change in the ability to perform a motor task due to practice or experience. Unfortunately, in most clinical settings, the time and cost demands of delivering a sufficiently intensive motor learning intervention is not feasible. There is a need for research to develop strategies for enhancing motor learning of walking (locomotor learning) in order to improve the effectiveness of neurorehabilitation. The objective of this study is to use non-invasive brain stimulation to augment locomotor learning and to investigate brain networks that are responsible for locomotor learning in mobility-compromised older adults. We have shown that frontal brain regions, particularly prefrontal cortex, are crucial to control of complex walking tasks. Our neuroimaging and neuromodulation studies also show that prefrontal cortex structure and network connectivity are important for acquisition and consolidation of new motor skills. However, a major gap exists regarding learning of walking tasks. The proposed study is designed to address this gap. Our pilot data from older adults shows that prefrontal transcranial direct current stimulation (tDCS) administered during learning of a complex obstacle walking task contributes to multi-day retention of task performance. In the proposed study we will build upon this pilot work by conducting a full scale trial that also investigates mechanisms related to brain structure, functional activity, and network connectivity. We will address the following specific aims: Specific Aim 1: Determine the extent to which prefrontal tDCS augments the effect of task practice for retention of performance on a complex obstacle walking task. Specific Aim 2: Determine the extent to which retention of performance is associated with individual differences in baseline and practice-induced changes in brain measures (working memory, gray matter volume, task- based prefrontal activity, and brain network segregation). Specific Aim 3: Investigate the extent to which tDCS modifies resting state network segregation. We anticipate that prefrontal tDCS will augment retention of locomotor learning, and that our data will provide the first evidence of specific brain mechanisms responsible for locomotor learning/retention in older adults with mobility deficits. This new knowledge will provide a clinically feasible intervention approach as well as reveal mechanistic targets for future interventions to enhance locomotor learning and rehabilitation.

2. Project Title: **INVESTIGATING MOVEMENT-EVOKED PAIN IN OSTEOARTHRITIC CONDITIONS (IMPACT): AN OBSERVATIONAL STUDY TO INFORM CULTURALLY-TAILORED INTERVENTION DEVELOPMENT**

Leader(s): **BOOKER, STAJA**
UNIVERSITY OF FLORIDA
NIH K23AR076463 / (2020 - 2023)

Core(s):

Knee osteoarthritis (OA) is one the most problematic sources of persistent musculoskeletal pain, impaired function and mobility, and reduced quality of life in older adults. Although these are common outcomes associated with OA, they are disproportionately worse in older African Americans. These threats to healthy aging demand further investigation into the most significant driver of OA pain and disability, which is movement. The experience of pain due to movement, known as movement-evoked pain (MEP), often prohibits full participation in daily living activities and self-management actions such as physical activity/exercise. MEP is consequently a substantial contributor to high-impact chronic pain and disability in people with OA; yet, our understanding of the mechanisms contributing to MEP and its management in older African Americans is severely limited. Therefore, the overall goals for this two-phased Mentored Patient-Oriented Research Career Development Award (K23) is to fill this knowledge gap by (1) characterizing the biopsychosocial-behavioral mechanisms of MEP and function and (2) develop a mechanism-based self-management intervention (Pain Relief for OsteoArthritis using Culturally-Tailored InterVentions for Black Elders [PROACTIVE]). This intervention will address the most pivotal and

culturally-relevant predictors of MEP and impaired function in older African Americans. Our methods represent a new and substantive departure from current static pain assessments in chronic musculoskeletal disorders by measuring pain with movement. This K23 proposes training and research activities that will launch a program of research which advances the science of pain and disability in African American older adults. To this end, I have assembled an interdisciplinary team of senior scientists representing nursing, psychology/pain science, aging, and epidemiology/community engagement who will provide mentorship to help me achieve proposed training goals and facilitate my transition to an independent research career. Primary training goals essential to my research program include: (1) advance understanding of biopsychosocial and behavioral- environmental mechanisms of OA pain, (2) develop a comprehensive knowledge base in the application of community-engaged participatory research within experimental designs, and (3) enhance translational research skills to function as an independent investigator capable of conducting rigorous clinical trials testing the effectiveness of non-pharmacological, behavioral chronic pain self-management interventions within a cultured community (e.g., southern African Americans). Phase 2 of the K23 will apply community-based participatory mixed-methods to collaboratively create the PROACTIVE intervention. The University of Florida and University of Connecticut are strong incubators for pain research and provide ideal environments to extend the PI s prior work and forge a path towards understanding multiple biopsychosocial and behavioral mechanisms uniquely involved in the intra-ethnic experience of chronic pain, which are key to the discovery of better therapeutic interventions and self-management behaviors.

3. Project Title: **Natural language processing (NLP) to connect social determinants and clinical factors for outcomes research**

Leader(s): **WU, YONGHUI**
UNIVERSITY OF FLORIDA
PCORI ME-2018C3-14754 / (2020 - 2024)

Core(s):

People interact with the environment at different levels in a large social system. Individuals health outcomes are determined through a complex interplay of multilevel factors, including both social determinants of health (e.g., education, employment, social cohesion) and behavioral determinants of health (e.g., smoking). For example, cancer, the second leading cause of death in the U.S., presents multiple causation and outcomes related to its biological, clinical, behavioral, and social influences. Nonetheless, these important variables are scarcely documented in structured medical codes but are often available in narrative clinical text. Clinical natural language processing (NLP) is the key technology to extract information from unstructured clinical text to support downstream applications that depend on structured data. However, NLP methods to extract social determinants of health have been understudied. Existing NLP systems for behavioral determinants and adverse events are suboptimal. Current clinical outcomes studies in PCORI communities are often limited to only structured medical codes due to a lack of NLP systems to identify and extract the necessary information and populate it into the national Patient-Centered Clinical Research Network (PCORnet) Common Data Model (CDM). This proposal seeks to develop NLP methods and systems to extract and connect social/behavioral information and adverse events with clinical factors (medical concepts that are directly generated by clinical practice, e.g., diseases, medications) for clinical outcomes research. The proposed NLP system will unlock mentions of social determinants, behavioral determinants, and adverse events from narrative clinical notes and populate them into structured PCORnet CDM databases. The NLP methods proposed in this project will also advance the extraction of general medical concepts from clinical narratives. This project will leverage the informatics infrastructure and clinical data at two PCORnet Clinical Data Research Network (CDRN) sites--the University of Florida affiliated with OneFlorida Clinical Research Consortium (OneFlorida CRC) and Weill Cornell Medicine affiliated with the New York City CDRN (NYC-CDRN). If successful, this project will provide an easy-to-use package to bridge the gap of using clinical narratives for PCORI and other communities. To develop a successful NLP tool for extracting social determinants (SDoH), behavioral determinants (BDoH), and adverse events (AEs) from clinical narratives, the involving of clinicians, patients, researchers, and data managers is very important. The clinician and patient representatives will provide suggestions on how the information was mentioned and documented in electronic health record systems (EHR) during patient-provider communications. This information can help us determine where different social and behavioral variables are documented to guide the development of methods and systems. The researchers will provide suggestions on identifying and categorizing the SDoH, BDoH, AEs, and other clinical factors that are priorities for their own studies. The representatives of data managers and analysts will provide feedback on pipelines to populate information to structured databases (e.g., PCORnet CDM) and how to use NLP extracted information to form queries that were not available before. We will form an advisory panel of all stakeholders and evaluate the system using cancer patients as cancer outcomes are known to relate with various social and behavioral influences and adverse events.

4. Project Title: **UNIVERSITY OF FLORIDA RESOURCE CENTER FOR MINORITY AGING RESEARCH**

Leader(s):   **FILLINGIM, ROGER B**
UNIVERSITY OF FLORIDA
NIH P30AG059297 / (2018 - 2023)

Core(s):

PROJECT SUMMARYChronic pain conditions represent arguably the most prevalent and costly public health problem in the UnitedStates, and they are the leading cause of disability worldwide. While pain affects individuals throughout thelifespan, older adults are disproportionately impacted and are at particularly increased risk for chronic pain andpain-related disability. Surprisingly, knowledge regarding the biopsychosocial mechanisms underlying age-related increases in pain remains quite limited, therefore, increased research is needed to elucidate social andbehavioral contributions to pain and disability among older adults. A critical barrier to progress in this area ofresearch is the limited availability of investigators with appropriate interdisciplinary training in addressing laterlife pain and disability. With strong institutional support, the University of Florida (UF) Resource Center forMinority Aging Research (RCMAR) will be established to address these scientific and workforce developmentneeds. The UF RCMAR has an educational objective to provide outstanding training and career developmentopportunities to promising investigators from underrepresented backgrounds. The UF RCMAR's researchobjective is to conduct innovative and impactful transdisciplinary social and behavioral research addressing painand disability among older adults, including health disparities in later life pain and disability (e.g. racial and ethnicdifferences, sex and gender differences, and socioeconomic influences). The UF RCMAR will accomplish theseobjectives through the synergistic efforts of four Cores: an Administrative Core (AC), a Research EducationComponent (REC), an Analysis Core (AnC), and a Community Liaison and Recruitment Core (CLRC). Inaddition, the UF RCMAR will benefit from extensive collaborations with other UF entities, including The UF PainResearch & Intervention Center of Excellence (PRICE), the UF Institute on Aging (IOA), and the UF Clinical andTranslational Science Institute (CTSI). The UF RCMAR boasts an outstanding interdisciplinary group of CoreFaculty with expertise spanning the spectrum of clinical and translational research related to our theme ofbiopsychosocial contributions to pain and disability among older adults. In order to accomplish its objectives, theUF RCMAR will recruit and retain outstanding early stage investigators from unrepresented backgrounds andprovide them with excellent mentoring and career development support. Through its research activities, the UFRCMAR will produce novel and important information regarding social and behavioral contributors to pain anddisability in older adults, and will develop and test innovative interventions to reduce later life pain and disability.

5. Project Title: **ESTROGEN AND COGNITION OVER THE LIFESPAN**

Leader(s):   **FOSTER, THOMAS C; KUMAR, ASHOK ;**
UNIVERSITY OF FLORIDA
NIH R01AG037984 / (2010 - 2023)

Core(s):

AbstractSex differences are evident in vulnerability to age-related cognitive decline and diseases of aging. Estradiol(E2) is protective against neurodegenerative diseases, including Alzheimer s disease, implicating sexhormone effects on sex differences in vulnerability. However, obstacles to sex steroid treatments includeclosing of the therapeutic window observed as decreased effectiveness of E2 treatment with advanced age.The goal of the proposed research is to provide an understanding of the mechanisms for E2 effects onmemory and the closing of the therapeutic window. Closing of the therapeutic window is marked by a decreasein E2-responseive transcription and an inability of E2 treatment to enhance N-methyl-D-aspartate receptor(NMDAR)-mediated synaptic transmission examined several days after treatment. Aim 1 will test thehypothesis that E2 treatment, several days prior to testing, specifically influences NMDAR-dependentepisodic memory, such that it can rescue an age-related decline in episodic memory examined on the watermaze and novel object recognition tasks. Aim 2 will test the hypothesis that E2 effects on memory andNMDAR function are mediated by reversal of NMDAR hypofunction, mediated by redox regulation ofphosphatase/kinase activity, similar to that previously described in aging males. Thus, it is predicted that priorto closing of the therapeutic window (i.e. in animals in which E2 treatment improves cognition and increasesNMDAR function), E2 treatment will promote antioxidant enzyme activity, reduce oxidative stress, andminimize redox-mediated decrease in CaMKII activity and NMDAR function. Further, following closing of thetherapeutic window (i.e. for animals in which E2 does not rescue cognition and NMDAR function), E2treatment will not promote antioxidant enzyme activity or reduce oxidative stress, and the NMDAR responseand CaMKII activity will be decreased due to an oxidized redox state. Aim 3 will test the hypothesis that age-related changes in transcriptional

responsiveness to E2 are due, at least in part, to epigenetic regulationthrough DNA methylation. It is predicted that decreased responsiveness of E2-sensitive genes will beassociated with DNA hypermethylation, particularly in gene body regions (introns), and specific to CpG,relative to non-CpG methylation sites. The proposed studies will employ a powerful combination of behavioraltests that are sensitive to NMDAR function, patch-clamp recording of NMDAR synaptic responses, measuresof oxidative stress and enzyme activity, transcription, and DNA methylation.

6. Project Title: SENESCENCE AND GROWTH DIFFERENTIATION FACTORS AS MODIFIERS OF AGING

Leader(s): **LEBRASSEUR, NATHAN K**
MAYO CLINIC
NIH R01AG055529 / (2018 - 2023)

Core(s):

PROJECT SUMMARY/ABSTRACTAging is the primary risk factor for the majority of chronic diseases. Studies in mice have implicated specificgrowth and differentiation factors (GDFs) and proteins secreted by senescent cells as potential modifiers ofaging. The objective of this proposal is to establish the rationale and provide robust clinical evidence for GDF8,GDF11, and senescence-related proteins eotaxin (CCL11), intracellular adhesion molecule 1 (ICAM1), activinA (AA), and plasminogen activator inhibitor 2 (PAI2), as indicators of biological age and age-related conditionsin humans. The central hypothesis is that circulating concentrations of GDFs and senescence-related proteinsare associated with, and predictive of, clinically important health outcomes and can be altered by physicalactivity. Samples from the Lifestyle Interventions and Independence for Elders (LIFE) Study; the largest andlongest randomized trial of a physical activity intervention in older adults, will be used to test this hypothesis,and samples from the Health, Aging, and Body Composition (HABC) Study will be used to validate studyfindings. A novel multiplexed liquid chromatography-tandem mass spectrometry assay will be leveraged toaccurately quantify GDFs, and an advanced multiplexing platform will be used to measure senescence-relatedproteins in LIFE and HABC biospecimens. In Specific Aim 1, a multidisciplinary team will first determine theextent to which baseline concentrations of GDF8, GDF11, CCL11, ICAM1, AA and PAI2 are associated withbaseline measures of physical (i.e., gait speed, Short Physical Performance Battery (SPPB) score),cardiopulmonary (i.e., blood pressure, forced expiratory volume), and cognitive (i.e., processing speed,memory) function, inflammation, and prevalence of multimorbidity (based on the ICD-9 codes for 20 chronicconditions). In Specific Aim 2, the degree to which baseline concentrations of GDFs and senescence-relatedproteins predict longitudinal changes in a) gait speed and SPPB score, b) major mobility disability (i.e., theinability to walk 400m), c) combined cardiovascular events (e.g., myocardial infarction, heart failure, stroke); d)adjudicated falls and injurious falls, e) cognitive function (as Aim 1), and f) the number of chronic conditions (asin Aim 1), at 1 and 2 years in LIFE and at 2 and 4 years in HABC will be determined. Finally, Specific Aim 3 willaddress whether a structured physical activity intervention impacts longitudinal changes in GDF8, GDF11,CCL11, ICAM1, AA, and PAI2, compared to a health education control intervention, and the degree to whichchange in the concentrations of these proteins parallel change in the health outcomes described in Aim 2. Thesuccessful completion of the proposed research will fill an important translational gap in our understanding ofhow GDFs and senescence-related proteins predict and, therefore, potentially mediate aging related disabilityand disease in older women and men. Ultimately, these proteins may be viable targets for innovative therapiesto extend human healthspan.

7. Project Title: INTERMITTENT PNEUMATIC COMPRESSION FOR DISABILITY REVERSAL IN PAD: THE INTERCEDE TRIAL

Leader(s): **MCDERMOTT, MARY MCGRAE**
NORTHWESTERN UNIVERSITY AT CHICAGO
NIH R01AG057693 / (2018 - 2023)

Core(s):

PROJECT SUMMARY Our work and that of others has established that people with lower extremity peripheral artery disease(PAD) have greater functional impairment and faster rates of functional decline than people without PAD.However, few therapies improve functioning or prevent functional decline in people with PAD. Intermittent pneumatic compression (IPC) is a non-invasive intervention, consisting of an air pumpinside inflatable cuffs that are wrapped around the feet, ankles, and calves and worn for two hours daily. Every20 second, the cuffs rapidly inflate, followed by rapid deflation. During deflation, arterial blood return into thearteriovenous pressure gradient generates shear stress and stimulates nitric oxide production. Preliminaryevidence suggests that IPC improves lower extremity blood flow and walking endurance in people

with PADand that benefits persist for up to 12 months after intervention completion. However, evidence is limited bysmall sample sizes, high loss to follow-up, lack of blinding, and lack of sham controls. Clinical practiceguidelines do not mention IPC as a therapeutic option in PAD. A definitive randomized trial is needed. Walking exercise is first-line therapy for PAD. However, many PAD patients are unable or unwilling toexercise. Therefore, in people with PAD, we will determine whether IPC augments the benefits of exercise onwalking endurance and whether IPC alone improves walking endurance compared to sham control. We willconduct a randomized trial (2 x 2 factorial design) of 230 PAD participants randomized to one of four groups:Group A: IPC + exercise; Group B: IPC + no exercise control; Group C: sham control + exercise; and GroupD: sham control + no exercise control. The IPC and sham interventions will be delivered for six months. Inour primary specific aims, we will determine whether IPC combined with exercise improves the 6-minute walkat 6-month follow-up compared to exercise alone and whether IPC alone improves the 6-minute walk at 6-month follow-up, compared to sham control. In secondary aims, we will determine whether benefits of IPCpersist by re-measuring study outcomes at twelve-month follow-up, six months after the IPC intervention iscompleted. We will also delineate mechanisms by which IPC affects walking performance, by measuringchanges in MRI-measured calf muscle perfusion, physical activity (measured with ActiGraph), and calf musclebiopsy measures of angiogenesis, muscle regeneration, mitochondrial biogenesis, mitochondrial activity, andautophagy. Based on preclinical evidence that IPC increases nitric oxide abundance and promotesvasodilation in skeletal muscle distant from the lower extremities, we will determine whether IPC improvessystemic endothelial function, by measuring changes in brachial artery flow-mediated dilation. If the IPC intervention with and without exercise improves functional performance and preventsfunctional decline in PAD, this non-invasive and well tolerated intervention will have a major impact onpreventing mobility loss and improving quality of life in the large and growing number of people with PAD.

8. Project Title: MECHANISMS OF OXYTOCINS ANALGESIA IN OLDER ADULTS

Leader(s):   **CRUZ-ALMEIDA, YENISEL; EBNER, NATALIE C ;**
UNIVERSITY OF FLORIDA
NIH R01AG059809 / (2018 - 2023)

Core(s):

ABSTRACTOsteoarthritis (OA) represents a significant cause of disability worldwide in individuals aged 65 and older, arapidly growing segment of our population. The knee is the most commonly affected joint with pain being theprimary symptom, negatively impacting physical, cognitive, and emotional functioning. Symptomatic knee OAhas been traditionally attributed to peripheral mechanisms, but measures of joint damage only modestly accountfor the presence or severity of OA-related pain. The neuropeptide oxytocin (OT) has been recognized as amediator of endogenous analgesia in animal and human studies. However, little is known about theneurobiological mechanisms underlying OT's pain-relieving properties. This proposal is based on a mechanisticmodel of OT's analgesic effects leveraging pilot data supporting efficacy and safety of self-administeredintranasal OT over 4-weeks in older individuals. Relative to placebo (P), daily administration of intranasal OTdiminished self-reported pain intensity, reduced experimental pain sensitivity, and increased self-reportedphysical and emotional functioning. Further, participants treated with OT, compared to P, showed decreases inbrain metabolite concentrations associated with inflammation. Thus, our overarching goal is to evaluate theeffects of intranasal OT on pain and function in aging and to determine the extent to which central and peripheralinflammatory mechanisms contribute to these analgesic responses. We aim to 1) determine the effect ofintranasal OT administration on clinical and experimental pain sensitivity in older adults with symptomatic kneeOA and 2) characterize inflammatory mechanisms contributing to the inter-individual variability in analgesicresponses to OT. Older adults with symptomatic knee OA will self-administer intranasal OT or P over 4 weeksusing a double-blinded, parallel study design. With strong support from the University of Florida and the McKnightBrain Institute, our interdisciplinary project, using a comprehensive multi-methods approach, will be the first todetermine the potential benefit of OT as a novel analgesic therapy for knee OA pain in aging. OT is currentlyused in obstetrics and may be an inexpensive, effective method for pain management in older adults with littlepotential for addiction. Embedded in a biopsychosocial framework, our proposal will help pave the way for futureinvestigations using a mechanism-based treatment optimization strategy for individuals suffering from chronicpain.

9. Project Title: ACTIVE ROLES OF GLIAL CELLS IN OLFACTION AND AGE-RELATED OLFACTORY DECLINE

Leader(s):   **XIAO, RUI**
UNIVERSITY OF FLORIDA
NIH R01AG063766 / (2019 - 2024)

Core(s):

Project SummaryAge-dependent olfactory decline (presbyosmia) is widely present in many species, including humans. At leastfifteen million Americans over 55 years old suffer from presbyosmia. By affecting the well-being, quality of life,and overall health, presbyosmia presents a significant challenge to public health. Patients with presbyosmiaoften show a decreased interest in food, can withdraw socially, and exhibit higher rates of depression.Furthermore, many age-related neurological diseases, including Parkinson's disease and Alzheimer's disease,are commonly associated with olfactory dysfunction. In fact, olfactory loss often precedes various motoricsymptoms in these deadly neurological diseases. Despite the importance of olfaction to human physiology andhealth, the cellular and molecular mechanisms underlying presbyosmia are poorly understood (knowledgegap).As a major cell type in the nervous system, glial cells are typically considered as passive modulators duringneural development and synaptic transmission. Whether glial cells play active roles in sensory transductionand brain aging is not well understood. C. elegans is a well-established model organism for neuroscience andaging research due to its simple nervous system, short lifespan, and powerful genetic tools. Very importantly,genetic studies from multiple model organisms have shown that the evolutionarily conserved genetic programsand signaling pathways play pivotal roles in regulating sensory transduction and aging process across species.This proposal will bring together in vivo calcium imaging, optogenetics, molecular genetics, and behavioralanalysis to investigate and discover the molecular mechanisms through which the olfactory glial cells playactive roles in odorant detection and age-dependent olfactory decline. Since both olfaction and aging areregulated by the evolutionarily conserved genes and signaling pathways, our innovative studies on C. elegansglial cells in olfaction and age-associated olfactory decline will provide mechanistic insights into similarprocesses in other species.

10. Project Title: **BIOBEHAVIORAL BASIS OF KNEE OSTEOARTHRITIS PAIN**
Leader(s): **CRUZ-ALMEIDA, YENISEL**
UNIVERSITY OF FLORIDA
NIH R01AG067757 / (2020 - 2025)

Core(s):

Discovery and validation of strong candidate biomarkers and clinical endpoints for pain is urgently needed that can be used to facilitate the development of non-opioid pain therapeutics from discovery through Phase II clinical trials. Emerging research using a combination of biomarkers deliver individualized predictions about future brain and body health. Our own findings suggest that behavioral chronic pain characteristics are associated with multiple biological biomarkers where a greater pain burden is associated with accelerated detrimental biological processes. However, prospective research is urgently needed to determine pain s impact on the heterogeneity of these biological processes within an individual to elucidate the underlying patterns of biological changes using a biobehavioral perspective which is needed for predicting future health and to be able to use as clinical endpoints for interventions. The proposed study will prospectively address biobehavioral factors (i.e., cognitive, psychological, social and cultural) affecting the experience and interpretation of knee pain and physical function across racial/ethnic groups over time. We will prospectively assess pain along with multiple biomarkers as predictors of cognitive, psychological and physical functional progression among middle-aged and older non- Hispanic Blacks and non-Hispanic Whites with knee pain and controls over a four-year study period. With strong support from the University of Florida, our interdisciplinary project, using a comprehensive biobehavioral multi- methods approach, we will be the first to prospectively determine the trajectory and interactions among pain, biological biomarkers and multiple domains of function within race/ethnic groups in OA pain. Findings will contribute towards increased understanding of pain and its biobehavioral basis, with the potential to reduce race/ethnic group disparities and improve pain-related health and functional outcomes.

11. Project Title: **THE BENEFITS AND HARMS OF LUNG CANCER SCREENING IN FLORIDA**
Leader(s): **BIAN, JIANG; GUO, YI ;**
UNIVERSITY OF FLORIDA
NIH R01CA246418 / (2020 - 2023)

Core(s):

Lung cancer is the leading cause of cancer related death in both men and women in the United States. Currently, approximately 70% of lung cancer patients are diagnosed at advanced stages, and the 5-year survival rate of advanced stage lung cancer is very low, at only 16%. Investigators have been searching for effective screening modalities for the early detection of lung cancer so that patients can receive curative treatments at an early stage. When the National Lung Screening Trial (NLST) demonstrated the effectiveness of using low-dose computed tomography (LDCT) scan for lung cancer screening (LCS), researchers and physicians hope to save lives from lung cancer by screening high-risk population who aged 55 to 77 years and have a 30 pack years making history or former smokes who have quitted within the past 15 years. Since the release of the landmark NLST results, many medical associations published guidelines to recommend LDCT-based screening for individuals at high risk for lung cancer and the Centers for Medicare and Medicaid Services (CMS) also decided to cover the LCS for Medicare beneficiaries who are at high risk for lung cancer. While many efforts have been made to accelerate the dissemination the beneficial LCS, the concerns over the high false positive rates (96.4% of the positive results), invasive diagnostic procedures, postprocedural complications and health care costs may hinder the utilization of lung cancer screening. This concern was magnified as researchers and policy makers started questioning whether the complication rate and false positives in real-world settings would be even higher than the rates reported in the NLST, which was conducted in a setting with well-established facilities and proficiency in cancer care. Therefore, we propose to understand the contemporary use of lung cancer screening and associated health care outcomes and costs using data from a real-world setting. Our study has three goals: 1) to develop an innovative computable phenotype algorithm to identify high-risk and low-risk individuals for LCS from both structured and unstructured (i.e., clinical notes) electronic health record (EHR) data and to develop advanced natural language processing (NLP) methods to extract LCS related clinical information from clinical notes such as radiology reports; 2) to determine the appropriate and inappropriate use of LDCT among high-risk and low-risk individuals in Florida and to examine the test results of LDCT, the rates of invasive diagnostic procedures, postprocedural complications, and incidental findings in real-world settings; and 3) to develop and validate a microsimulation model of the clinical courses of LCS incorporating the real-world data in LCS to estimate the long-term benefits and the cost-effectiveness of LCS. Our proposed study has the potential to reduce lung cancer incidence and mortality by informing policymakers and practitioners on the appropriateness of contemporary use of LCS. This knowledge will help both patients and physicians better understand the harm- benefit tradeoff of lung cancer screening and transform such knowledge into practice to prevent avoidable postprocedural complications.

12. Project Title: Evaluation of an Adaptive Intervention for Weight Loss Maintenance

Leader(s):   ROSS, KATHRYN MARIE
   UNIVERSITY OF FLORIDA
   NIH R01DK119244 / (2019 - 2024)

Core(s):

Obesity remains a substantial public health challenge in the United States. Behavioral weight management programs have demonstrated effectiveness for weight loss, but long-term maintenance of these weight losses after the end of treatment tends to be poor. Evidence has demonstrated that individuals who can maintain their changes in eating and activity can successfully maintain their weight loss; thus, attempts to improve weight loss maintenance have often involved provision of continued support through monthly extended-care intervention sessions. While these interventions have demonstrated significant improvements in weight loss maintenance, effects have been modest. A key challenge is continued participant engagement (often assessed as attendance at intervention sessions). Attendance has been closely tied to weight outcomes, but rates tend to be poor and decline over time. The once-per-month, static treatment schedules of existing programs may contribute to these suboptimal outcomes; a participant experiencing a small lapse in weight-related behaviors may not receive support for several weeks, by which point they may be experiencing a larger lapse or weight regain. This can lead to feelings of frustration, shame, or embarrassment and disengagement from intervention. In contrast, tailoring intervention delivery such that sessions are provided when individuals are at high risk for weight regain offers potential to disrupt this cycle and significantly improve program engagement, adherence to program goals, and long-term weight maintenance outcomes. We propose to evaluate an innovative method of providing phone-based extended-care adaptive to participant needs. We have built a smartphone application that can be used by participants to track weight, dietary intake, and physical activity (key self-monitoring behaviors in traditional behavioral weight management programs) and can further query participants throughout the week regarding self-report factors (e.g., ratings of hunger and the importance of staying on track with weight management goals) that indicate high risk for weight regain. We have also developed a predictive algorithm that uses this data to identify when individuals are at high risk of weight regain. We propose to conduct a randomized controlled trial evaluating the impact of ADAPTIVE (delivered only when indicated by our algorithm or when initiated by participants via an in-app support request) versus STATIC (the monthly, pre-scheduled format used in existing extended-care programs) treatment provision on weight regain at 24 Months in 258 adults who successfully lose = 5% of

initial weight during a gold-standard 16-week behavioral weight management program. Results of this study have clear treatment implications for the timing/frequency of sessions within extended-care weight maintenance programs, and this study will result in an innovative, low-cost, and easily scalable intervention for weight loss maintenance. Further, the proposed research will fill a critical gap in the weight management literature by building a foundational evidence base of proximal predictors of weight-related behaviors for future adaptive intervention development.

13. Project Title: THE ROLE AND MECHANISMS OF LIPID AND LIPOPROTEIN DYSREGULATION IN SEPSIS

Leader(s): **GUIRGIS, FAHEEM W**
UNIVERSITY OF FLORIDA
NIH R01GM133815 / (2020 - 2025)

Core(s):

Sepsis is a dysregulated response to infection that has both fatal and non-fatal morbid consequences. Unfortunately, initial survival does not provide relief from morbidity for most sepsis survivors. Initial clinical trajectories include rapid recovery, early in-hospital death, and progression to chronic critical illness (ICU stay = 14 days with organ dysfunction). Late complications include sepsis readmission and late death, both of which have rates of approximately 40% at 90 days and 6 months, respectively. Circulating lipids play an important role in sepsis and cholesterol levels of both high density lipoproteins (HDL-C) and low density lipoproteins (LDL-C) are dynamically regulated in sepsis. HDL and LDL are both thought to play protective roles in sepsis via several mechanisms (antioxidant/anti-inflammatory function, bacterial toxin clearance, steroid synthesis), but the exact mechanisms by which HDL and LDL protects against sepsis are not known. Lipid and lipoprotein dysregulation occurs in early sepsis, leading to failure to protect against sepsis. We have shown that: 1) HDL becomes dysfunctional (pro-oxidant and pro-inflammatory) in early sepsis (Dys-HDL); 2) elevated Dys-HDL levels positively correlate with and predict organ failure severity and are associated with poor outcomes including 28-day mortality; 3) HDL from older septic patients exhibits impaired cholesterol efflux capacity (required for toxin clearance and steroidogenesis); 4) HDL and LDL levels drop precipitously during sepsis, and the severity of the drop is predictive of death; and 5) low baseline LDL levels are associated with increased long-term community-acquired sepsis risk. Highly biologically active lipid metabolites are also present in the circulation during sepsis that may propagate and promote inflammation resolution and contribute to cholesterol dysfunction. Our data strongly suggest that lipid and lipoprotein dysregulation occurs in sepsis and leads to altered function, oxidation, and reduced levels that may influence clinical outcomes. We hypothesize that specific functional, lipidomic, and genomic changes in lipid and lipoprotein metabolism occur in early sepsis and relate to relevant clinical trajectories (rapid recovery, early death, and chronic critical illness and sepsis recidivism). To test our hypothesis, we will capitalize on an established and experienced sepsis research team and the opportunity provided by an existing bank of samples from a diverse cohort of 80 community-acquired (CA) and 85 hospital-acquired (HA) sepsis patients from two-centers. This approach has several advantages: 1) cost-savings from use of existing samples with isolated mRNA, 2) a recent cohort of sepsis patients (2016-2018) consistently treated with institutional evidence-based management bundles, 3) availability of serial samples over time (enrollment, 48h, 28d, and 90d), sepsis readmission samples, and mRNA for the CA cohort, 4) age/gender matched control samples, 5) available clinical and outcomes data. We also propose two-site prospective enrollment of a small cohort of sepsis readmission patients to study this novel and important outcome. This project satisfies the NIGMS mission of researching biological mechanisms that underlay the foundation for advances in treatment of diseases such as sepsis.

14. Project Title: TRANSCRIPTIONAL REGULATION OF KCNH2

Leader(s): **DELISLE, BRIAN P**
UNIVERSITY OF KENTUCKY
NIH R01HL141343 / (2019 - 2023)

Core(s):

SummaryCircadian rhythms help to match the optimal function of the cardiovascular system to the daily changes in theenvironment. Normal cardiovascular rhythms provide a physiological advantage to people. Unfortunately,normal circadian signaling can also unmask a time-of-day pattern in adverse events like heart attack, stroke,and sudden death in patients with underlying cardiovascular disease.Emerging data now show that abnormal or unhealthy daily rhythms can create a negative impact on normalhealth too. For example shiftwork, which repeatedly causes shifts in endogenous circadian rhythms, is anindependent risk factor for cardiovascular disease.In mammals the suprachiasmatic nucleus (SCN) in the brain is the primary circadian pacemaker that helps toentrain endogenous rhythms to the environment. SCN rhythms are synchronized to the environment via light,and its signaling helps to coordinate the molecular rhythms in cells throughout the body. What is new aboutthis application is we determine how repeated changes in light cycle will impact molecular circadian signaling inthe heart.Most cells have a molecular clock signaling mechanism that cycles with a periodicity of ~24 hours. We foundgenetic disruptions in the molecular clock mechanism of heart cells (cardiomyocytes) primarily causesabnormal changes in cardiac electrophysiology by disrupting the regulation of ion channel function.The goal of this application is to determine how repeated shifts in the light cycle impact molecular clocksignaling in the mouse heart and its regulation on ion channel function.Aim 1. To identify new mechanisms with which the cardiac molecular clock regulates different ion channels.Aim 2. To determine how repeated changes in light impact molecular clock signaling in the heart and ionchannel regulation.This project creates new knowledge at the interface between chronobiology and cardiac electrophysiology.

15. Project Title: IMPAIRED MITOCHONDRIAL ENERGETICS IS A DRIVER OF HEMODIALYSIS ACCESS RELATED HAND DYSFUNCTION

Leader(s):   SCALI, SALVATORE T.
UNIVERSITY OF FLORIDA
NIH R01HL148597 / (2019 - 2024)

Core(s):

PROJECT SUMMARYCurrently, in the United States, there are ~425,000 patients receiving hemodialysis (HD) and it is estimated that30-60% of this population have some element of hand dysfunction after hemoaccess surgery. The underlyingpathophysiologic mechanisms responsible for this devastating problem are poorly understood. The renaldysfunction (RD) milieu causes a variety of physiologic derangements in HD patients including increasedoxidative stress (OS) and chronic inflammation that have been implicated as major contributors to acceleratedatherosclerosis and elevated mortality. Profound changes in OS contribute to skeletal muscle and neuromuscularjunction dysfunction associated with muscle atrophy and frailty in this population. AVF surgery causes significanthemodynamic changes in the extremity which presents an adaptive challenge to the skeletal muscle andneuromotor end-plate. Supported by our previous work, as well as preliminary data on RD associated skeletalmuscle mitochondrial phenotypic changes, we propose that RD driven mitochondrial dysfunction alters skeletalmuscle and neuromuscular junction responses to AVF induced ischemia leading to clinically apparent handdysfunction. Further, these pathways can be modified either prior to AVF creation or at first evidence of handdysfunction to reverse/prevent the functional impairment. Our hypothesis is that the RD milieu disruptsmitochondrial and cellular energetics resulting in elevated OS predisposing patients undergoing AVF surgery todeveloping skeletal muscle and neuromuscular junction perturbations causing clinically significant handdysfunction. RD mediated mitochondrial impairments are further exacerbated by local hemodynamic changesfollowing AVF creation through maladaptive OS metabolic responses that drives the diversity of clinicallyapparent hand dysfunction. Aim 1 will establish how RD impacts mitochondrial and cellular energetics that areexacerbated by AVF-induced limb ischemia. Using a series of in vitro experiments, we will uncover thebiochemical mechanisms by which RD impacts mitochondrial energetics leading to impaired oxidativephosphorylation and increased OS. Aim 2 will determine the efficacy of global or mitochondrial-targetedantioxidant therapies delivered prior to- and following AVF surgery in mice. Using a novel RD murine AVF model,we will determine whether global (N-acetylcysteine) or mitochondrial-targeted (AAV delivery of mitochondrialtargeted catalase) antioxidant therapy have therapeutic potential for AVF-induced muscle dysfunction. Aim 3will evaluate the association between mitochondrial health and AVF-induced hand dysfunction in humanpatients. Mitochondrial health will be examined in-situ using permeabilized myofibers prepared from RD patientsbefore and after AVF surgery: mitochondrial phenotypic changes will be evaluated and their association withchanges in serial hemodynamic, neurophysiological and biomechanical outcomes modulating the spectrum ofhand function will be determined.

16. Project Title: MOLECULAR MECHANISMS REGULATING PERIPHERAL ARTERIAL DISEASE PATHOBIOLOGY IN CHRONIC KIDNEY DISEASE

Leader(s):   RYAN, TERENCE E
UNIVERSITY OF FLORIDA
NIH R01HL149704 / (2019 - 2024)

Core(s):

Peripheral artery disease (PAD) is caused by atherosclerosis in the lower extremities which leads to a spectrum of life-altering symptomatology, including claudication, ischemic rest pain, and gangrene requiring limb amputation. Complicating the etiology of PAD, patients typically present with comorbid conditions or risk factors that accelerate disease evolution and substantially worsen pathology contributing to increased mortality risk. Among these, chronic kidney disease (CKD) accelerates the development of atherosclerosis, decreases functional capacity, and increases risk of amputation or death, however the underlying biologic mechanism(s) are poorly understood and vastly understudied compared with other comorbidities (i.e. smoking and diabetes). We have uncovered a novel molecular pathway that may link CKD and PAD pathobiology. We find that many uremic metabolites, which accumulate in CKD, cause chronic activation of the aryl hydrocarbon receptor (AHR) which leads to disruption of the mitochondrial electron transport system that exacerbates ischemic muscle injury and impairs angiogenesis. Preliminary experiments demonstrate that genetic knockdown of the AHR is protective against uremic toxicity, whereas expression of a constitutively active AHR causes mitochondrial dysfunction. Thus, we propose to test the novel hypothesis that the chronic activation of the AHR pathway results in ischemic muscle injury and impaired angiogenesis, thereby linking CKD and PAD pathobiology. This hypothesis will be tested using muscle- and vascular-specific inducible knockout of the AHR as well as adeno- associated virus-mediated expression of the a constitutively active AHR in pre-clinical models of CKD/PAD. Finally, our recent human data indicate elevated AHR signaling in PAD patients with CKD. We propose to extend these findings to establish a clinical link between muscle health/function, mitochondrial energetics, and AHR signaling in human PAD patients. Success in these studies will provide mechanistic insight into the impact of CKD on PAD pathobiology, and would provide a novel target for therapeutic development aimed to treat a patient population that currently has few available options.

17. Project Title: CIRCADIAN CLOCK REGULATION OF MYOCARDIAL ION CHANNEL EXPRESSION AND FUNCTION

Leader(s):   ESSER, KARYN A; DELISLE, BRIAN P ;
UNIVERSITY OF FLORIDA
NIH R01HL153042 / (2020 - 2024)

Core(s):

The overall objectives of this proposal are to 1) define the genomic and transcriptomic mechanisms by which the cardiomyocyte clock regulates ion channels that contribute to cardiac excitability; and 2) disrupt the cardiomyocyte clock to link changes in circadian-ordered gene expression with electrophysiological properties of atrial and ventricular cardiomyocytes. The outcomes will address significant gaps in our understanding for how the myocardial circadian clock regulates the expression of key cardiac ion channels and how abnormal cardiac clock function contributes to arrhythmia vulnerability. The mechanism regulating circadian timing, the molecular clock, exists in virtually all cell types in the body. A critical function of the molecular clock is to link time of day with a large-scale transcriptional program to support cellular homeostasis To date, our labs have used an inducible cardiomyocyte specific mouse model to knock out the core clock gene, Bmal1 (iCS Bmal1). These studies showed that disruption of the myocardial clock is sufficient to decrease ventricular K+ and Na+ channel gene expression, disrupt current levels, disrupt cardiac excitability, and increase arrhythmia susceptibility. These studies establish a critical role for the cardiomyocyte clock, independent of the central clock, in regulating the expression of different families of ion channel genes that impact the ionic balance needed for normal excitability. One goal of this project is to utilize large scale genomic and transcriptomic approaches with our mouse model system to define the circadian clock dependent control of temporal gene expression in both atrial and ventricular tissues. To address abnormal circadian clock function, our lab has used different models of circadian disruption, such as chronic phase advance or time restricted feeding to test links between circadian disruption and arrhythmia vulnerability in mouse models. We have found that disrupting either light or feeding time cues is sufficient to induce pathological changes in cardiac rhythms in normal mice and to accelerate sudden cardiac death in a genetic mouse model of arrhythmia susceptibility. These studies support our premise that disruption of day- night rhythms through environmental factors leads

to altered myocardial clock function with outcomes that include modified ion channel expression, cardiac excitability and arrhythmia vulnerability. The aims of this proposal are designed to test the following hypotheses: 1) The molecular clocks in both atrial and ventricular cardiomyocytes are necessary to direct daily chromatin accessibility and transcriptional output including expression of key ion channel and ion channel regulatory genes. 2) Chronic disruption of the cardiomyocyte clock using altered time of feeding is sufficient to cause dysregulation of the cardiac clock resulting in an imbalance in cardiac ion channel expression and currents leading to altered excitability and increased arrhythmia vulnerability.

18. Project Title: BIOBEHAVIORAL MECHANISMS UNDERLYING SYMPTOMS AND HEALING OUTCOMES IN OLDER INDIVIDUALS WITH CVLU

Leader(s): **STECHMILLER, JOYCE K.; LYON, DEBRA E ;**
UNIVERSITY OF FLORIDA
NIH R01NR016986 / (2018 - 2023)

Core(s):

ABSTRACT Our long-term goal is to elucidate the complex biobehavioral mechanisms responsible for symptoms andhealing outcomes for older adults with venous leg ulcers (VLUs) for the development of targeted therapies thataddress both the patient-oriented outcomes and healing outcomes in this growing group of affected individuals.VLUs, which account for 70 90% of ulcers found in the lower leg, affect 2 million persons annually, includingnearly 4% of people over age 65 years. To date, the basic biology underlying the development and persistenceof VLUs and the influence of aging and multiple disease conditions on wound healing are generally not wellunderstood. Individuals living with chronic VLU (CVLU) have a high symptom burden of both wound-relatedsymptoms and symptoms of pain, depression, anxiety, fatigue and cognitive dysfunction, collectively labeled as psychoneurologic symptoms (PNS). Guided by the National Institutes of Health Symptom Science Model(NIH-SSM) framework, the central hypothesis of this application is that there are interrelated molecularmechanisms by which the immune activation that contributes to the development and persistence of CVLUalso leads to the development, persistence and severity of PNS. The specific aims of the proposed study areto: (1) Characterize the strength of the associations at baseline among patient-host factors, systemicinflammation, and wound microenvironment with wound area and symptoms (PNS and wound-related); and,(2) Test associations and models over time for: (a) Patient-host factors and systemic inflammation with woundmicroenvironment; (b) Patient-host factors and wound microenvironment with systemic inflammation; (c)Patient-host factors, systemic inflammation, and wound microenvironment with wound healing; (d) Patient-hostfactors, systemic inflammation, and wound microenvironment with symptoms (PNS and wound-related) and (e)Patient-host factors, systemic inflammation, wound microenvironment and wound healing with symptoms (PNSand wound-related). To achieve the specific aims, we will longitudinally examine 200 older adults (age >60)who are receiving state of the art, standardized wound treatment biweekly across eight weeks time. We willfully characterize patient-host characteristics (age, comorbidities, sex, race/ethnicity, BMI, nutritional status,lifestyle habits, and wound treatment [pressure therapy, debridement, antibiotics]); systemic inflammatoryactivation (C-reactive protein and cytokines); wound microenvironment factors (local inflammation [Matrixmetalloproteinase (MMP) enzymes C-reactive protein, cytokines], biofilm, and micro RNAs); symptoms (PNS[cognitive dysfunction, pain, fatigue, and depressive/anxiety symptoms] and wound-related); and woundcharacteristics and healing trajectory at the five timepoints. This knowledge is critical to provide a foundationfor developing targeted interventions to address this critical health problem from a holistic perspective and toprovide a basis for preventing or reversing the adverse health outcomes of CVLUs, a condition thatdifferentially affects older and minority individuals.

19. Project Title: ETHNIC DIFFERENCES IN RESPONSES TO PAINFUL STIMULI

Leader(s): **FILLINGIM, ROGER B**
UNIVERSITY OF FLORIDA
NIH R37AG033906 / (2009 - 2024)

Core(s):

No abstract provided

20. Project Title: **THE INTEGRATIVE AND MULTIDISCIPLINARY PAIN AND AGING RESEARCH TRAINING (IMPART) PROGRAM**

Leader(s): **FILLINGIM, ROGER B**
UNIVERSITY OF FLORIDA
NIH T32AG049673 / (2015 - 2025)

Core(s):

DESCRIPTION (provided by applicant): As detailed in a recent Institute of Medicine (IOM) report, chronic pain represents a major public health concern, affecting 100 million U.S. adults and costing more than $500 billion annually. Aging confers increased risk for chronic pain, with half of older adults reporting persistent or recurring pain, and aging is associated with greater pain-related loss of physical and psychosocial function. Current knowledge regarding pain and aging is surprisingly limited, and future progress in the field hinges on the availability of well-trained scientists who have an appreciation for preclinical and clinical research approaches to the study of both aging and pain. At present, there are no existing NIH-funded T32 programs devoted to training in pain and aging. To address this unmet need, we propose to develop a new postdoctoral training program: the Integrative and Multidisciplinary Pain and Aging Research Training (IMPART) Program. The overall goal of the IMPART program is to develop outstanding independent investigators capable of sustaining productive clinical and translational research careers addressing the biopsychosocial mechanisms underlying age-related changes in the experience of pain and/or designing clinical interventions to ameliorate acute and chronic pain among older adults. In order to accomplish this overarching goal, the specific aims of this new postdoctoral training program in pain and aging research are to: 1) Recruit and train promising junior investigators to conduct mechanistically-based and clinically relevant translational research in pain and aging; 2) Implement an integrated didactic and experiential training program, which will equip trainees with new research skills and the knowledge and expertise to apply these skills to address important and unanswered questions regarding pain and aging; and 3) Create a culture of research excellence in order to ensure that trainees aspire to the high standards of scientific integrity and quality, which will set the tone for their futurecareers in pain and aging research. IMPART leverages two excellent and collaborative research programs at the University of Florida - the aging research community represented by the Institute on Aging (IOA), and the pain research community, organized under the Pain Research and Intervention Center of Excellence (PRICE). Each member of the training faculty boasts an excellent track record of both research funding and mentoring experience. The proposed program requests support for four postdoctoral trainees from a variety of training backgrounds, each of whom will work with their multidisciplinary mentoring team to create and implement a tailored independent development plan as the blueprint for their training. Trainees will achieve their research and career development objectives through a combination of didactic, research, and professional development activities, and program evaluation will be ongoing and multimodal. The IMPART Program is committed to promoting diversity among our trainees, and the program will provide a training experience that emphasizes excellence in research integrity and ethics.

21. Project Title: **TRANSLATIONAL RESEARCH TRAINING ON AGING AND MOBILITY (TRAM)**

Leader(s): **MANINI, TODD**
UNIVERSITY OF FLORIDA
NIH T32AG062728 / (2020 - 2025)

Core(s):

Preserved mobility is one of hallmarks of geriatric care, gerontology and geroscience. The loss of mobility with aging is progressive, caused by multiple factors and does not have a simple cure. Unfortunately, mobility loss continues to lack clinical attention, robust biomedical targets, objectively-measured surveillance systems, and effective treatments. As a result, mobility difficulties have remained persistently high and stagnant since it was systematically measured in the late 1980's. Currently, 30% of Americans aged 60-69, 40% of individuals aged 70-79, and 55% of individuals age 80 or older report difficulties with their mobility (e.g. walking and climbing stairs). To address this unmet need, we propose the Translational Research training on Aging and Mobility (TRAM) postdoctoral training program to train 4 post-doctoral fellows per year (2 in year one). The overall goal of the TRAM program is to develop outstanding independent investigators capable of sustaining productive multi-disciplinary and translational research careers addressing the multi-factorial causes and consequences of age-related changes in mobility and/or designing multi-modal interventions to prevent and rehabilitate mobility impairments in older adults. The goals are to: 1) Provide a 2-3 year integrated training program for PhD/MD fellows to create a career pathway for conducting mechanistic and clinically relevant translational research in mobility and aging; 2) Implement a cross-fertilized training program based on the Experiential Learning

Theory; 3) To equip trainees with new research skills along with the knowledge and expertise to address impactful and unanswered questions regarding mobility and aging; 4) Closely monitor and track trainee-related experiences and outcomes for making continuous quality improvements; 5) Create a culture for professional excellence and development based on enhancing rigor, reproducibility and transparency in trainee-related research and; 6) To attract, recruit and enroll minorities, and those with disabilities and disadvantaged backgrounds. TRAM program faculty are collaborators on each other's projects, bring strong mentorship experience and successful commitment to research related to mobility and/or aging. Program faculty are grouped into either Aging or Mobility Research Clusters based on research focus and expertise. TRAM will use a mosaic mentoring approach that will employ dual primary mentors one from aging and another from mobility expertise a third mentor will serve as an advocate/sponsor. Mentees will also receive support from other archetypes like coaches, connectors and senior peer mentors. This unified mentoring team will guide trainees through an individual development plan, didactic coursework (e.g. mechanistic and clinical-based research on aging and/or mobility, ethics, responsible conduct of research), directed research training, and professional development activities (e.g. strategic planning, innovative leadership) that will be tailored according to the educational needs and research interests of the trainee. At completion, TRAM fellows will fulfill the scientific needs and grow the research workforce for meeting the growing population of mobility impaired older adults.

22. Project Title: MOLECULAR BIOLOGY IN BURNS AND TRAUMA
Leader(s): MOLDAWER, LYLE L
UNIVERSITY OF FLORIDA
NIH T32GM008721 / (1999 - 2024)

Core(s):

This Ruth Kirschstein NRSA training Program proposes to take primarily surgeons and other critical caremedicine physicians during the second or third year of their general residency programs, and expose them totwo, three and even four years of mentored research in inflammation biology with highly productive basic sciencementors focused on inflammation-related topics. Four training positions are requested. The overall researchprogram will focus on mastery of molecular biology, functional genomics and gene regulation, as it appliesbroadly to inflammation research. Although the bulk of the training program will be in the laboratory of anexperienced research mentor, trainees will be expected to participate in didactic experiences that complementtheir research experience. Select trainees will have the opportunity to complete a Ph.D. program in the GraduateSchool in three to four years. Other trainees can participate in graduate certificate programs which are formalcollections of courses that together form a coherent program of study offered through an academic unit. Thistraining program takes advantage of the unique strengths of the College of Medicine in the expanding field offunctional genomics and molecular biology, as well as the existing collaborations between basic scientists andclinicians committed to the training of future clinical academicians. The interface between molecular biology andinflammation research will be targeted to trauma, sepsis syndromes, ischemia/reperfusion injury, vascular injury,delayed wound healing and the burn wound. The faculty will be drawn from funded basic and clinical scientistsin the Surgery, Medicine, Pathology, Aging and Geriatric Research and Molecular Genetics and MicrobiologyDepartments, who will serve as research mentors to the trainees. Clinical mentors from the Surgery, Medicineand Pathology Departments will interact with the trainees and the research faculty to assure that the traineesare being exposed to clinically-important issues in inflammation research. Overall direction of the program willrest with the Program Director and an Executive Committee. Candidates for the fellowship are recruitednationally and from the University of Florida College of Medicine (Gainesville, Jacksonville). Successfulapplicants with the Executive Committee will identify a research and clinical mentor who will help formulate aformal training program and periodic review of the trainee s progress. Furthermore, trainees are expected toparticipate in basic science seminars in the Institute on Aging, Emerging Pathogens Institute and GeneticsInstitute, and in their own basic science departments, as well as laboratory research meetings. They will also beexpected to attend clinical seminars, including Surgery and Critical Care Medicine Grand Rounds and theDepartment of Surgery Academic Research Conference. Based on our past experiences, it is anticipated thatsuccessful graduates of this training program will possess sufficient research skills to successfully compete fortransitional funding in inflammation research and become leaders in academic surgery.

23. Project Title: MULTIMODAL IMAGING OF BRAIN ACTIVITY TO INVESTIGATE WALKING AND MOBILITY DECLINE IN OLDER ADULTS
Leader(s): MANINI, TODD; CLARK, DAVID J. ; SEIDLER, RACHAEL D ;

UNIVERSITY OF FLORIDA
NIH U01AG061389 / (2018 - 2023)

Core(s):

Project Description: Mobility impairments in older adults decrease quality of life and are associated with highsocietal and economic burden. NIH RFA-AG-18-019 solicits applications to investigate the central neuralcontrol of mobility in older adults using innovative and cutting-edge methods. Current approaches to studythe neural control of walking are limited by either the inability to measure people during walking (functionalmagnetic resonance imaging, fMRI) or the inability to measure activity below the cortex (functional near-infrared spectroscopy, fNIRS). We assert that a full and accurate understanding of the neural control of walkingin older adults requires real time measurement of active regions throughout the brain during actual walking. Wewill achieve this by using innovative mobile brain imaging with high-density electroencephalography (EEG).This approach relies upon innovative hardware and software to deliver three-dimensional localization of activecortical and subcortical brain regions with high spatial and temporal resolution during walking. The result isunprecedented insight into the neural control of walking. Here, our overarching objective is to determine thecentral neural control of mobility in older adults by collecting EEG during walking and correlating these findingswith a comprehensive set of diverse mobility outcomes (clinic-based walking, complex walking and communitymobility measures). Our first aim is to evaluate the extent to which brain activity during actual walking explainsmobility decline. In both cross sectional and longitudinal designs, we will determine whether poorer walkingperformance and steeper trajectories of decline are associated with the Compensation Related Utilization ofNeural Circuits Hypothesis (CRUNCH). CRUNCH is a well-supported model of brain activity patterns that areseen when older individuals perform tasks of increasing complexity. CRUNCH describes the over-recruitmentof frontoparietal brain networks that older adults exhibit in comparison to young adults, even at low levels oftask complexity. CRUNCH also describes the limited reserve resources available in the older brain. Thesefactors cause older adults to quickly reach a ceiling in brain resources when performing tasks of increasingcomplexity. When the ceiling is reached, performance suffers. The RFA also calls for proposals to Operationalize and harmonize imaging protocols and techniques for quantifying dynamic gait and motorfunctions . In accordance with this call, our second aim is to characterize and harmonize high-density EEGduring walking with fNIRS (during actual and imaged walking) and fMRI (during imagined walking). This willallow us to identify the most robust CRUNCH-related hallmarks of brain activity across neuroimagingmodalities, which will strengthen our conclusions and allow for widespread application of our findings. Ourthird aim is to study the mechanisms related to CRUNCH during walking. Thus, our project will address amajority of the objectives in NIH RFA-AG-18-019 and will identify the neural correlates of walking in olderadults, leading to unprecedented insight into mobility declines and dysfunction.

24. **Project Title:**   **PRagmatic EValuation of evENTs And Benefits of Lipid-lowering in oldEr Adults (PREVENTABLE)**

Leader(s):   **ALEXANDER, KAREN; AMBROSIUS, WALTER T; HERNANDEZ, ADRIAN; WILLIAMSON, JEFF DOUGLAS**
DUKE UNIVERSITY
NIH U19AG065188 / (2019 - 2026)

Core(s):

There is an urgent need for evidence to guide clinical care of older adults due to demographic shifts, including longer life expectancy and a recent doubling of the older adult population. Statins reduce recurrent CVD events and prevent initial events in patients younger than 75 years. However, clinical research has often excluded persons older than 75 years due to a higher prevalence of comorbidity and frailty so little to no evidence is available to guide care in this population. For older adults living longer, the promise of preventing cognitive impairment is as compelling as preventing a CVD event, but some evidence suggests statins may contribute to memory difficulty or muscle symptoms. There is equipoise regarding the usefulness of statins for primary CVD, dementia, and disability prevention in adults older than 75 years, especially in the setting of multiple chronic conditions, advanced age, or frailty. Evidence to improve cognitive and functional outcomes in older populations with diverse race/ethnicity and health status will require new clinical trial approaches with sustainable methodology and infrastructure. We propose PREVENTABLE (PRagmatic EValuation of evENTs And Benefits of Lipid-lowering in oldEr adults), the first statin trial with a non-CVD primary outcome survival free of dementia or persisting disability. Using a placebo-controlled pragmatic clinical trial (PCT) design across PCORnet and VA network, the trial will be under the leadership of Dr. Karen Alexander at DCRI, Dr. Jeff Williamson at WFSM, Dr. Adrian Hernandez at DCRI, and Dr. Walter Ambrosius at WFSM. This team has established experience and track-record of accomplishment in the design and conduct of PCTs, trial expertise in ascertaining cognitive and disability outcomes in older adults, and is supported by a robust administrative infrastructure for coordinating these shared responsibilities for

success. The overarching goal of PREVENTABLE is to generate knowledge about the role of statins in older adults, a population in which risk/benefit for primary prevention has been under studied. The hypothesis is that a large trial conducted in an older adult population will demonstrate the benefit of statins for reducing dementia, disability, and CV events. We further hypothesize that extensive genomic, biochemical and imaging ancillary studies will offer unique insights into these key outcomes. PREVENTABLE has the following specific aims: AIM 1: Determine the role of a moderate-intensity statin in preventing dementia and prolonging disability-free survival in patients 75 years and older without clinically evident coronary heart disease, including those with frailty, impaired physical function, mild cognitive impairment, polypharmacy, and multi-morbidity. AIM 2: Determine the role of moderate- intensity statin in preventing hospitalization for myocardial infarction/acute coronary syndrome, stroke, heart failure, revascularization or cardiovascular-related death, and preventing either mild cognitive impairment or dementia. AIM 3: Test the safety and tolerability of statins in older adults and collect 17,000 bio-specimens to advance precision health.

25. Project Title: TOGETHER: TRANSFORMING AND TRANSLATING DISCOVERY TO IMPROVE HEALTH

Leader(s):   MITCHELL, DUANE A.
UNIVERSITY OF FLORIDA
NIH UL1TR001427 / (2015 - 2024)

Core(s):

Florida is a demographically and geographically diverse state. The University of Florida (UF) and Florida StateUniversity (FSU) CTSA hub will work within this environment to further the mission to improve human health byaccelerating the translation of scientific discoveries and the implementation of evidence-based best practicesfor the diagnosis, treatment, prevention and cure of human diseases across the lifespan. The UF-FSU hubvision is think globally, act locally , offering research opportunities to underserved participants in North andNorth Central Florida, creating innovative career development and training opportunities, as well ascollaborating across the country with the Accelerated Clinical Trials Network and PCORnet. Researchstrengths include precision medicine, team science, community engagement, implementation science andinformatics which are conducted in diverse settings through the OneFlorida Clinical Research Consortium. The2019-2024 period represents the next phase of evolution from creating a clinical and translational scienceinfrastructure to enhancing the local, state and national impact of CTSI-led science. During this period, FSUwill be integrated across all components and will engage six additional colleges. Hub activities will be centeredaround four strategic goals: (1) chart new pathways for developing the translational workforce by taking UF ssuccess in career development and translating this success to the FSU and historically black colleges anduniversities; (2) strengthen the capacity of the learning health system environment and develop transferablemodels for embedding translational science into the clinical enterprise by further integrating data and software,developing multi-site pilots in healthcare institutions serving unique patient populations and building on thesuccess of the personalized medicine program to use genomics data to improve patient outcomes; (3) expandstatewide collaborations and opportunities to advance a participant-centered research agenda that reflects thehealth priorities and diversity of the catchment area by continuing to strengthen stakeholder engagement andtrust in research through the HealthStreet Program and enhance collaboration with policy stakeholders fromFlorida Medicaid, Florida surgeon general and others; and (4) strengthen regional and national collaborationsto accelerate the collective impact of the CTSA network through continued work with ACT, PCORnet, genomicmedicine, aging and metabolomics. Throughout this important work, the UF-FSU hub will remain dedicated tosupporting the recruitment, retention and career development of underrepresented minority and disabledtrainees and faculty. Integral to the success of the proposed work, the UF-FSU hub will further integrate healthcare and research in Florida guided by four keys to success: (1) organizational alignment, (2) clinicalinformatics, (3) clinician and stakeholder engagement, and (4) strong support from implementation andimprovement science expertise.

PUBLICATIONS

2023

1. **Genetic Testing for Cancer Risk and Perceived Importance of Genetic Information Among US Population by Race and Ethnicity: a Cross-sectional Study.**
   Hong YR, Yadav S, Wang R, Vadaparampil S, Bian J, George TJ, Braithwaite D
   J Racial Ethn Health Disparities, 2023 Jan 23 1-13
   https://doi.org/10.1007/s40615-023-01526-4 | PMID: 36689121 | PMCID: PMC9870197
   Citations: 42 | AltScore: 1.5

2. **Sex differences in body composition, voluntary wheel running activity, balance performance, and auditory function in CBA/CaJ mice across the lifespan.**
   Kim MJ, Carmichael PB, Bose U, Honkura Y, Suzuki J, Ding D, Erfe SL, Simms SS, Avaiya KA, Milani MN, Rymer EJ, Fragnito DT, Strom N, Salvi R, Someya S
   Hear Res, 2023 Feb, 428: 108684
   https://doi.org/10.1016/j.heares.2022.108684 | PMID: 36599258
   Citations: | AltScore: NA

3. **The role of mitochondria in the recovery of neurons after injury.**
   McElroy T, Zeidan RS, Rathor L, Han SM, Xiao R
   Neural Regen Res, 2023 Feb, 18(2): 317-318
   https://doi.org/10.4103/1673-5374.343907 | PMID: 35900413 | PMCID: PMC9396508
   Citations: 12 | AltScore: 0.5

4. **Relationship between Mitochondrial Quality Control Markers, Lower Extremity Tissue Composition, and Physical Performance in Physically Inactive Older Adults.**
   Picca A, Triolo M, Wohlgemuth SE, Martenson MS, Mankowski RT, Anton SD, Marzetti E, Leeuwenburgh C, Hood DA
   Cells, 2023 Jan 2, 12(1):
   https://doi.org/10.3390/cells12010183 | PMID: 36611976 | PMCID: PMC9818256
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5. **Conscious connected breathing with breath retention intervention in adults with chronic low back pain: protocol for a randomized controlled pilot study.**
   Pratscher SD, Sibille KT, Fillingim RB
   Pilot Feasibility Stud, 2023 Jan 24, 9(1): 15
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   Citations: 185 | AltScore: 1

6. **Disease correction in mucopolysaccharidosis type IIIB mice by intraparenchymal or cisternal delivery of a capsid modified AAV8 codon-optimized NAGLU vector.**
   Rouse CJ, Hawkins K, Kabbej N, Dalugdug J, Kunta A, Kim MJ, Someya S, Herbst Z, Gelb M, Dinelli I, Butterworth E, Falk DJ, Rosenkrantz E, Elmohd H, Khaledi H, Mowafy S, Ashby F, Heldermon CD
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   https://doi.org/10.1093/hmg/ddac209 | PMID: 35997776 | PMCID: PMC9851742
   Citations: 36 | AltScore: 0.75

7. **Feasibility of a Smartwatch Platform to Assess Ecological Mobility: Real-Time Online Assessment and Mobility?Monitor.**
   Smail EJ, Alpert JM, Mardini MT, Kaufmann CN, Bai C, Gill TM, Fillingim RB, Cenko E, Zapata R, Karnati Y, Marsiske M, Ranka S, Manini TM
   J Gerontol A Biol Sci Med Sci, 2023 May 11, 78(5): 821-830

https://doi.org/10.1093/gerona/glad046 | PMID: 36744611 | PMCID: PMC10172974
Citations: 49 | AltScore: NA

8. **Media Consumption and COVID-19-Related Precautionary Behaviors During the Early Pandemic: Survey Study of Older Adults.**
Smail EJ, Livingston T, Wolach A, Cenko E, Kaufmann CN, Manini TM
JMIR Form Res, 2023 May 22, 7: e46230
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9. **Exercise and Behavior: Adjuncts to Pro-Myogenic Compounds for Enhancing Mobility in Older Adults.**
Storer TW, Pahor M, Woodhouse LJ, Lachman ME, Fielding RA
J Gerontol A Biol Sci Med Sci, 2023 Jun 16, 78(Supplement_1): 61-66
https://doi.org/10.1093/gerona/glad041 | PMID: 37325956 | PMCID: PMC10272978
Citations: 40 | AltScore: NA

10. **Defining the age-dependent and tissue-specific circadian transcriptome in male mice.**
Wolff CA, Gutierrez-Monreal MA, Meng L, Zhang X, Douma LG, Costello HM, Douglas CM, Ebrahimi E, Pham A, Oliveira AC, Fu C, Nguyen A, Alava BR, Hesketh SJ, Morris AR, Endale MM, Crislip GR, Cheng KY, Schroder EA, Delisle BP, Bryant AJ, Gumz ML, Huo Z, Liu AC, Esser KA
Cell Rep, 2023 Jan 31, 42(1): 111982
https://doi.org/10.1016/j.celrep.2022.111982 | PMID: 36640301 | PMCID: PMC9929559
Citations: 63 | AltScore: 50.1

11. **Reducing tobacco-associated lung cancer risk: a study protocol for a randomized clinical trial of AB-free kava.**
Xing C, Malaty J, Malham MB, Nehme AMA, Freeman B, Huo Z, Firpi-Morrel R, Salloum RG
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Citations: 37 | AltScore: 2

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Akinyemiju T, Ogunsina K, Gupta A, Liu I, Braithwaite D, Hiatt RA
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Citations: 104 | AltScore: 0.5

2. **Using Machine Learning To Define the Impact of Beta-Lactam Early and Cumulative Target Attainment on Outcomes in Intensive Care Unit Patients with Hospital-Acquired and Ventilator-Associated Pneumonia.**
Alshaer MH, Maranchick N, Bai C, Maguigan KL, Shoulders B, Felton TW, Mathew SK, Mardini MT, Peloquin CA
Antimicrob Agents Chemother, 2022 Jul 19, 66(7): e0056322
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3. **Ineffective Erythropoietin Response to Anemia in Sepsis.**
Apple CG, Kelly LS, Kannan KB, Ungaro RF, Moore FA, Brakenridge SC, Moldawer LL,

Efron PA, Mohr AM
Surg Infect (Larchmt), 2022 Mar, 23(2): 142-149
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Citations: 40 | AltScore: NA

4. **Differential DNA methylation in Black and White individuals with chronic low back pain enrich different genomic pathways.**
Aroke EN, Jackson P, Meng L, Huo Z, Overstreet DS, Penn TM, Quinn TL, Cruz-Almeida Y, Goodin BR
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https://doi.org/10.1016/j.ynpai.2022.100086 | PMID: 35243180 | PMCID: PMC8885563
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5. **Are Machine Learning Models on Wrist Accelerometry Robust against Differences in Physical Performance among Older Adults?**
Bai C, Wanigatunga AA, Saldana S, Casanova R, Manini TM, Mardini MT
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Citations: 68 | AltScore: 1.5

8. **Multicomponent intervention to prevent mobility disability in frail older adults: randomised controlled trial (SPRINTT project).**
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10. **Personalised Lung Cancer Screening (PLuS) study to assess the importance of coexisting chronic conditions to clinical practice and policy: protocol for a multicentre observational study.**
Braithwaite D, Karanth SD, Slatore CG, Zhang D, Bian J, Meza R, Jeon J, Tammemagi M, Schabath M, Wheeler M, Guo Y, Hochhegger B, Kaye FJ, Silvestri GA, Gould MK
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Citations: 62 | AltScore: 0.25

11. **Evaluation of a Multivalent Transcriptomic Metric for Diagnosing Surgical Sepsis and Estimating Mortality Among Critically Ill Patients.**
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12. **A wrinkle in time: circadian biology in pulmonary vascular health and disease.**
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13. **Objective and subjective sleep measures are associated with neurocognition in aging adults with and without HIV.**
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Carmichael ED, Apple CG, Kannan KB, Gardener A, Anton S, Efron PA, Moldawer LL, Moore FA, Brakenridge SC, Mohr AM
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Citations: 30 | AltScore: 0.25

15. **Post-meeting report of the 2022 On-site Padua Days on Muscle and Mobility Medicine, March 30 - April 3, 2022, Padua, Italy.**
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17. **Relationships Between Cognitive Screening Composite Scores and Pain Intensity and Pain Disability in Adults With/At Risk for Knee Osteoarthritis.**
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Citations: 206 | AltScore: 5.65

20. **SEX DIFFERENCES ASSOCIATE WITH LATE MICROBIOME ALTERATIONS AFTER MURINE SURGICAL SEPSIS.**
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Citations: 38 | AltScore: 1

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Hernandez AR, Hoffman JM, Hernandez CM, Cortes CJ, Jumbo-Lucioni P, Baxter MG, Esser KA, Liu AC, McMahon LL, Bizon JL, Burke SN, Buford TW, Carter CS
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Johnson AJ, Buchanan T, Laffitte Nodarse C, Valdes Hernandez PA, Huo Z, Cole JH, Buford TW, Fillingim RB, Cruz-Almeida Y
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RECOGNITION AND AWARDS (2022-2023)

<u>Karyn Esser, PhD</u> (2022)

- Basic Science Faculty Research Award, University of Florida
- Organizing Committee, International Biochemistry of Exercise meeting
- NIA workshop: Understanding Heterogeneity of Responses to, and Optimizing Clinical Efficacy of, Exercise Training in Older Adults: Workshop, April 2022

<u>Karyn Esser, PhD</u> (2023)

- External Advisory Board member for the Indiana Center for Musculoskeletal Health 2017-present
- Executive Committee for NIH, Molecular Transducers of Physical Activity in Humans 2016-present
- External Advisory Panel, Michigan Integrative Musculoskeletal Health P30 Core Center (MiMHC), University of Michigan, 2016- present
- External Advisory Board, Baylor University, Department of Physiology 2016- present
- Editorial Board, Physiological Reviews, 2018- present

<u>Peihua Qiu, PhD</u> (2022)

- Elected Fellow, American Association for the Advancement of Science (AAAS)

<u>Peihua Qiu, PhD</u> (2023)

- Keynote Speaker, 2023 INFORMS Conference on Quality, Statistics, and Reliability

<u>Stephen Anton, PhD</u> (2022)

- Associate Editor: journal Obesity 2012-2022
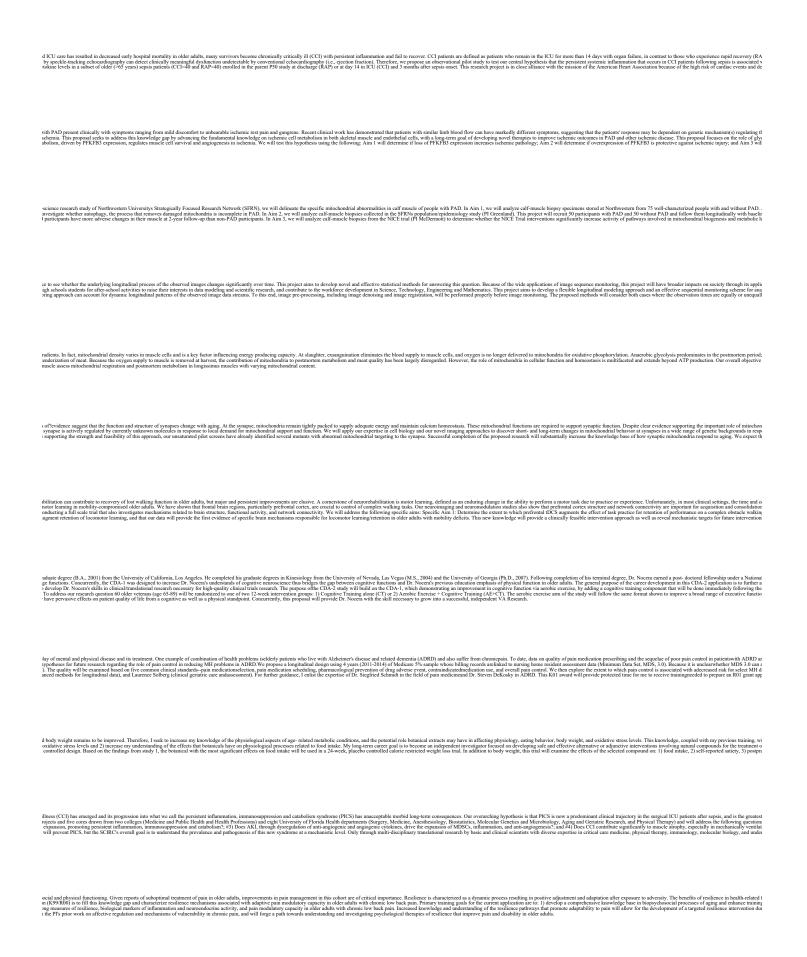
<u>Stephen Anton, PhD</u> (2023)

- Editorial Board Member: Journal Nutrients

MINORITY RESEARCH

General Brief Description of Minority Activities:

1. **Project Title:**

   Cardiac Dysfunction in Older Sepsis Survivors

   Leader(s):

   MANKOWSKI, ROBERT TOMASZ

   UNIVERSITY OF FLORIDA

   American Heart Association (AHA) 18CDA34080001 / (2018-2021)

   As a result of sepsis, approximately 30% of older Americans (age >65 years) have elevated levels of systemic inflammation at discharge from the intensive care unit (ICU) and die from cardiovascular (CV) events, including congestive heart failure, within 12 months. Although recently improved implementation of evidence-base high-risk new population for cardiac disease and death within 12 months post-sepsis. Cardiac dysfunction after discharge (i.e., impaired cardiac contractility) that may lead to cardiomyopathy and heart failure after sepsis, however, has not been characterized in this high-risk population. Novel measures of myocardial contractility the infrastructure of the NIH-funded project (P50GM11115202) at the University of Florida that is currently successfully enrolling and following sepsis patients for up to 12 months. For the proposed pilot study, we will perform biventricular myocardial contractility analyses and peripheral blood analyses for pro-inflammatory cy and help develop anti-inflammatory interventions to lower the CV risk in older sepsis survivors. (AHA Program: Career Development Award)

2. **Project Title:**

   Role of PFKFB3 in peripheral artery disease

   Leader(s):

   RYAN, TERENCE

   UNIVERSITY OF FLORIDA

   American Heart Association (AHA) 18CDA34110044 / (2018-2021)

   Peripheral artery disease (PAD) is a leading cause of atherosclerotic cardiovascular disease death which is estimated to affect more than 20% of individuals older than age 60 (~200 million people worldwide). PAD is defined as a blockage in the peripheral arteries which results in decreased blood flow to the lower legs. Patients w interventions aimed to improve blood flow to the leg, but mortality rates in PAD remain high (50% within 10 years of diagnosis). The low success rate of PAD therapies indicates that restoration of blood flow alone is not sufficient to rescue the limb, implying that factors other than limb perfusion regulate the limb's response to i systemic glycolytic flux display complete protection from ischemic muscle necrosis; (ii) among the genes responsible for elevated glycolytic flux, PFKFB3 is required for ischemic protection; and (iii) PFKFB3 protein expression is decreased in severe PAD patients. Based on these discoveries, we hypothesize that glycolytic met through metabolomics/proteomics experiments. This work will advance fundamental knowledge on ischemic cell metabolism, develop novel gene therapies, and offer mechanistic insight applicable to multiple diseases and tissues.

3. **Project Title:**

   Calf Muscle Mitochondrial Dysfunction and Impaired Autophagy in Peripheral Artery Disease

   Leader(s):

   LEEUWENBURGH, CHRISTIAAN

   UNIVERSITY OF FLORIDA

   American Heart Association (AHA) 18SFRN33900136 / (2018-2022)

   Lower-extremity peripheral artery disease (PAD) results in ischemia-reperfusion-induced oxidative stress in calf skeletal muscle and reduced skeletal muscle metabolic activity, but the specific mitochondrial defects and their association with functional impairment and decline in people with PAD are not established. In this basic- transport chain (ETC) proteins have greater damage, resulting in poorer ETC function in PAD compared to those without PAD. In Aim 1B, we will investigate the D-loop region of mtDNA involved in regulating mtDNA replication, to determine if the increased mtDNA abundance in PAD is due to oxidative stress. Aim 1C will i of >0.20 between their legs. We will investigate whether: a) the leg with lower ABI (more ischemia) has greater mitochondrial abnormalities than the leg with higher ABI (less ischemia); b) mitochondrial abnormalities are associated with greater functional impairment and faster functional decline in PAD participants; and c) PAD associated with skeletal muscle pathophysiologic changes in PAD. Results are expected to identify new potential targets for interventions that may improve functional performance and prevent functional decline in PAD. (AHA Program: Strategically Focused Research Network)

4. **Project Title:**

   Longitudinal Modeling and Sequential Monitoring of Image Data Streams

   Leader(s):

   QIU, PEIHUA

   UNIVERSITY OF FLORIDA

   National Science Foundation 1914639 / (2019-2022)

   In imaging applications related to earth and environmental monitoring, manufacturing industries, medical studies and many others, collected image data are often in the form of data streams in the sense that new images are acquired sequentially over time. In such applications, one fundamental task is to monitor the image seque distributed freely for convenient use by practitioners. A web portal will also be developed for individual researchers to try the proposed methods. The PI plans to integrate the research results into educational activities, including the development of new curriculum modules, the mentoring of Ph.D. students, and outreach to local h model for describing observed images in a given time interval is flexible, and its estimation procedure has the edge-preservation property while removing noise. It can accommodate both geometric misalignments among observed images and spatio-temporal data correlation in the observed image data. The proposed image monito

5. **Project Title:**

   Mitochondrial Function in Postmortem Muscle

   Leader(s):

   SCHEFFLER, TRACY

   UNIVERSITY OF FLORIDA

   United States Department of Agriculture 2017-67017-26468 / (2017-2021)

   Our goal is to understand how mitochondria influence postmortem metabolism and tenderization, in order to optimize meat quality and value. Living muscle relies primarily on mitochondria and aerobic metabolism for energy; ATP is necessary for muscle contraction and relaxation, and to fuel active transport and maintain ion g and result in pH declining to a final or ultimate pH (pHu) near 5.6. At this point, ATP is exhausted and no longer generated, and rigor is complete and additional ATP is not generated by metabolism. The rate and extent of metabolic processes postmortem significantly impact water holding capacity, color, and protease-mediated t properties influence mitochondria function and integrity. Our objectives are to evaluate changes in mitochondrial function in oxidative and glycolytic muscles during the first 24h postmortem determine mitochondrial function in oxidative and glycolytic muscles under pH and oxygen tension conditions that simulate postmortem m

6. **Project Title:**

   Identifying Genes That Regulate Mitochondrial Positioning at the Synapse During Aging

   Leader(s):

   HAN, SUNG MIN

   UNIVERSITY OF FLORIDA

   American Federation for Aging Research (AFAR) AGR00015406 / (2019-2021)

   A decline in the functions of the nervous system is a hallmark of aging, and can lead to many age-related changes in balance, mobility, hearing, vision, smell, and taste. The function of the nervous system depends on the maintenance of synapses-the special contact area where neurons communicate with other neurons. Many line mediate mitochondrial positioning at synapses and how aging affects this regulation remain unclear. Our goal is to uncover the underlying mechanisms that regulate mitochondrial positioning and function at the synapse during the aging process. My proposed aims are based on my hypothesis that mitochondrial localization at the mitochondrial localization at the synapse, we have established an innovative visual genetic screen for assessing mitochondrial distribution in the AIY interneuron of Caenorhabditis elegans. We anticipate that these screens will identify novel molecules that regulate mitochondrial targeting or anchoring at the synapse. As evidence understanding the maintenance of synaptic function in aging and other neuronal diseases associated with abnormal mitochondrial positioning and function.

7. **Project Title:**

   CEREBRAL NETWORKS OF LOCOMOTOR LEARNING AND RETENTION IN OLDER ADULTS

   Leader(s):

   CLARK, DAVID J

   VETERANS HEALTH ADMINISTRATION

   VA I01RX003115 / (2019-2023)

   Aging often leads to substantial declines in walking function, especially for walking tasks that are more complex such as obstacle crossing. This is due in part to a lack of continued practice of complex walking (sedentary lifestyle) combined with age-related deficits of brain structure and the integrity of brain networks. Neurorehab is a need for research to develop strategies for enhancing motor learning of walking ('locomotor learning') in order to improve the effectiveness of neurorehabilitation. The objective of this study is to use non-invasive brain stimulation to augment locomotor learning and to investigate brain networks that are responsible for locor proposed study is designed to address this gap. Our pilot data from older adults shows that prefrontal transcranial direct current stimulation (tDCS) administered during learning of a complex obstacle walking task contributes to multi-day retention of task performance. In the proposed study we will build upon this pilot work by c with individual differences in baseline and practice-induced changes in brain measures (working memory, gray matter volume, task- based prefrontal activity, and brain network segregation). Specific Aim 3: Investigate the extent to which tDCS modifies resting state network segregation. We anticipate that prefrontal tDCS will a

8. **Project Title:**

   AEROBIC EXERCISE AND COGNITIVE TRAINING IN OLDER ADULTS

   Leader(s):

   NOCERA, JOE ROBERT

   VETERANS HEALTH ADMINISTRATION

   VA IK2RX000744 / (2012-2018)

   DESCRIPTION This proposal, 'Aerobic Exercise and Cognitive Training in Older Adults', is resubmission for a Career Development Award- Level 2 with Dr. Joe R. Nocera as the Principal Investigator and a mentoring team of Drs. Bruce Crosson, Ron Shorr, Marco Pahor and Michael Marsiske. Dr. Nocera received his undergr Florida. Dr. Nocera then received a CDA-1 aimed at studying the effects aerobic exercise on executive language function in older adults. It was hypothesized, and demonstrated in the preliminary CDA-1 work, that the robust documented benefits of aerobic exercise on cognition could carry over to more specific executive langua purpose of designing interventions aimed at improving function and quality of life in older veterans. Specific training components in the proposal include; skills in cognitive neuroscience with specific training in cognitive aging, measurement, neuroanatomy, and basic imaging approaches. Additionally, the proposal is designed to generalizability of the cognitive training. Importantly, this study will focus on older veterans at-risk for mobility disability. This area is of particular importance for he VA system, considering a large percentage of veterans are entering old age and therefore likely to suffer from age-related cognitive decline and mobility disability. arm will consists of a popular commercially-available brain fitness program that has demonstrated specific cognitive improvements and high adherence. Ultimately, this investigation will substantially advance the development of treatments for cognitive impairment because these goals explore an intervention that may potentially

9. **Project Title:**

   PHARMACOLOGICAL MANAGEMENT OF PAIN IN ALZHEIMER'S DISEASE AND RELATED DEMENTIA

   Leader(s):

   WEI, YU-JUNG

   UNIVERSITY OF FLORIDA

   NIH K01AG054764 / (2017-2022)

   Summary: My career goal is to become an independent geriatric pharmacoepidemiologist with expertise inpharmacotherapy quality measurement and outcomes evaluation in the fields of pain and aging. The clinicalfocus of my research has centered on the management of multi-morbidity in older adults and particularly, theinterp hasattempted to establish the effect of adequate pain control on preventing mental health (MH) disorders. Thegoal of my K01 proposed research is to provide preliminary data that improve our understanding of currentpain medication prescribing and potential discrepancies between practices and pain guidelines, and toformulate l validating MDS-based pain, depression, and behavioral symptoms against medical records at two nursinghomes (Aim 1). With the nationally representative Medicare-MDS data, we explore the quality ofpharmacological pain management and its determinants among ADRD and non-ADRD residents with non-cancer pain (Aim 2 3). This project is well tailored for me to apply the knowledge and skills that will beobtained from training activities with my Primary Mentor, Dr. Almut Winterstein (pharmacoepidemioloy, qualitymeasurement and outcome assessment) and Co-Mentors: Drs. Roger Fillingim (pain), Marco Pahor (aging),Babette Brumback (adv results from this line of research are expected to lead to better pharmacological painmanagement and improved pain and health outcomes in older adults with cognitive impairments.

10. **Project Title:**

    INVESTIGATIONS OF BOTANICALS ON FOOD INTAKE, SATIETY, WEIGHT LOSS, AND OXIDATIVE

    Leader(s):

    ANTON, STEPHEN D

    UNIVERSITY OF FLORIDA

    NIH K23AT004251 / (2009-2014)

    DESCRIPTION (provided by applicant): My training to date has provided me with a solid understanding of the behavioral, psychosocial, and environmental factors that contribute to eating behavior and weight management; however, my understanding of physiology and the biological mechanisms regulating eating behavior an research investigating alternative and adjunctive treatments involving botanicals for age-related metabolic conditions (obesity, type 2 diabetes). My immediate career goals are to 1) obtain a R01 grant to further examine the potential effects of different doses of the selected botanical compounds on food intake, body weight, and that botanical compounds have in affecting food intake, neuroendocrine signals, satiety, weight loss, and oxidative stress levels. Study 1 will investigate the effects of two promising botanicals (garcinia cambogia derived hydroxycitric acid, and glucomannan) on food intake, satiety, and weight loss using a double-blind, placebo (i.e., DNA and RNA oxidation). PUBLIC HEALTH RELEVANCE: Botanicals represent important sources of potential new adjunctive therapies for obese and insulin resistant individuals and may enhance the health benefits of weight loss interventions by reducing systemic oxidative stress levels.

11. **Project Title:**

    PICS: A NEW HORIZON FOR SURGICAL CRITICAL CARE

    Leader(s):

    MOORE, FREDERICK A

    UNIVERSITY OF FLORIDA

    NIH P50GM111152 / (2014-2019)

    DESCRIPTION (provided by applicant): Despite 30 years of intensive research, morbidity and mortality of sepsis in surgical intensive care unit (ICU) patients remain unacceptably high. Although recent advances in early ICU care have reduced in-hospital mortality, with the aging population a new epidemic of chronic critical i least in part, by dysregulated myelopoiesis and expansion of myeloid-derived suppressor cells (MDSCs), aggravated by aging and largely driven by acute kidney injury (AKI), resulting in imbalance of angiogenic and anti-angiogenic factors. This Sepsis and Critical Illness Research Center (SCIRC) application comprises four p ICU patients and what are the long-term cognitive and functional consequences? #1b) Can novel biomarkers predict, early, which patients will develop CCI, and, later, which CCI patients will have morbid long-term outcomes (i.e., PICS)? #2) Is PICS inherently driven by dysregulation in myelopoiesis and inappropriate MDSC reduce inflammation, and alter the trajectory of CCI away from the PICS phenotype? We will study 400 surgical ICU patients who develop sepsis for at least one year, and use murine models of chronic polymicrobial sepsis for mechanistic studies and interventional methods. We recognize that no single therapeutic intervention understood and novel therapies developed.

12. **Project Title:**

    ADAPTABILITY AND RESILIENCE IN AGING ADULTS (ARIAA)

    Leader(s):

    BARTLEY, EMILY J.

    UNIVERSITY OF FLORIDA

    NIH R00AG052642 / (2016-2021)

    Growing evidence supports the presence of dysregulated pain modulation in older adults, an effect which may heighten age-associated risk for chronic pain. While persistent pain is common in older adults, chronic low back pain is the leading cause of disability in this population and results in significant impairments in psychos fostering adaptive physiological and affective responses to pain. Given this, capitalizing on positive resources is a promising target for enhancing pain adaptation, and is especially salient to older adults given the burden of high-impact pain in this group. Therefore, the overall goal for this mentored career development applicati and assessment of psychosocial and biological (i.e., inflammatory, neuroendocrine) markers associated with pain and resilience; and 3) augment training in the design, implementation, and analysis of randomized clinical trials. The proposed study is delineated into two phases. Study 1 (K99 Phase) will examine associations amon effects on pain modulatory function and patterns of pain- evoked recovery in physiological and affective systems, and will establish whether a resilience-oriented intervention confers benefits in psychosocial and physical functioning in older adults with chronic low back pain. The proposed career development plan extends from

13. **Project Title:**

    ESTROGEN AND COGNITION OVER THE LIFESPAN

d ICU care has resulted in decreased early hospital mortality in older adults, many survivors become chronically critically ill (CCI) with persistent inflammation and fail to recover. CCI patients are defined as patients who remain in the ICU for more than 14 days with organ failure, in contrast to those who experience rapid recovery (RA... by speckle-tracking echocardiography can detect clinically meaningful dysfunction undetectable by conventional echocardiography (i.e., ejection fraction). Therefore, we propose an observational pilot study to test our central hypothesis that the persistent systemic inflammation that occurs in CCI patients following sepsis is associated w... rtokine levels in a subset of older (>65 years) sepsis patients (CCI=40 and RAP=40) enrolled in the parent P50 study at discharge (RAP) or at day 14 in ICU (CCI) and 3 months after sepsis onset. This research project is in close alliance with the mission of the American Heart Association because of the high risk of cardiac events and de...

with PAD present clinically with symptoms ranging from mild discomfort to unbearable ischemic rest pain and gangrene. Recent clinical work has demonstrated that patients with similar limb blood flow can have markedly different symptoms, suggesting that the patients' response may be dependent on genetic mechanism(s) regulating th... ischemia. This proposal seeks to address this knowledge gap by advancing the fundamental knowledge on ischemic cell metabolism in both skeletal muscle and endothelial cells, with a long-term goal of developing novel therapies to improve ischemic outcomes in PAD and other ischemic disease. This proposal focuses on the role of glyc... abolism, driven by PFKFB3 expression, regulates muscle cell survival and angiogenesis in ischemia. We will test this hypothesis using the following: Aim 1 will determine if loss of PFKFB3 expression increases ischemic pathology; Aim 2 will determine if overexpression of PFKFB3 is protective against ischemic injury; and Aim 3 wil...

-science research study of Northwestern Universitys Strategically Focused Research Network (SFRN), we will delineate the specific mitochondrial abnormalities in calf muscle of people with PAD. In Aim 1, we will analyze calf-muscle biopsy specimens stored at Northwestern from 75 well-characterized people with and without PAD. ... investigate whether autophagy, the process that removes damaged mitochondria, is incomplete in PAD. In Aim 2, we will analyze calf-muscle biopsies collected in the SFRNs population/epidemiology study (PI Greenland). This project will recruit 50 participants with PAD and 50 without PAD and follow them longitudinally with baselin...) participants have more adverse changes in their muscle at 2-year follow-up than non-PAD participants. In Aim 3, we will analyze calf-muscle biopsies from the NICE trial (PI McDermott) to determine whether the NICE Trial interventions significantly increase activity of pathways involved in mitochondrial biogenesis and metabolic h...

ce to see whether the underlying longitudinal process of the observed images changes significantly over time. This project aims to develop novel and effective statistical methods for answering this question. Because of the wide applications of image sequence monitoring, this project will have broader impacts on society through its applic... igh schools students for after-school activities to raise their interests in data modeling and scientific research, and contribute to the workforce development in Science, Technology, Engineering and Mathematics. This project aims to develop a flexible longitudinal modeling approach and an effective sequential monitoring scheme for ana... oring approach can account for dynamic longitudinal patterns of the observed image data streams. To this end, image pre-processing, including image denoising and image registration, will be performed properly before image monitoring. The proposed methods will consider both cases where the observation times are equally or unequall...

radients. In fact, mitochondrial density varies in muscle cells and is a key factor influencing energy producing capacity. At slaughter, exsanguination eliminates the blood supply to muscle cells, and oxygen is no longer delivered to mitochondria for oxidative phosphorylation. Anaerobic glycolysis predominates in the postmortem period; ... enderization of meat. Because the oxygen supply to muscle is removed at harvest, the contribution of mitochondria to postmortem metabolism and meat quality has been largely disregarded. However, the role of mitochondria in cellular function and homeostasis is multifaceted and extends beyond ATP production. Our overall objective ... muscle assess mitochondrial respiration and postmortem metabolism in longissimus muscles with varying mitochondrial content.

s of?evidence suggest that the function and structure of synapses change with aging. At the synapse, mitochondria remain tightly packed to supply adequate energy and maintain calcium homeostasis. These mitochondrial functions are required to support synaptic function. Despite clear evidence supporting the important role of mitochon... synapse is actively regulated by currently unknown molecules in response to local demand for mitochondrial support and function. We will apply our expertise in cell biology and our novel imaging approaches to discover short- and long-term changes in mitochondrial behavior at synapses in a wide range of genetic backgrounds in respo... : supporting the strength and feasibility of this approach, our unsaturated pilot screens have already identified several mutants with abnormal mitochondrial targeting to the synapse. Successful completion of the proposed research will substantially increase the knowledge base of how synaptic mitochondria respond to aging. We expect th...

abilitation can contribute to recovery of lost walking function in older adults, but major and persistent improvements are elusive. A cornerstone of neurorehabilitation is motor learning, defined as an enduring change in the ability to perform a motor task due to practice or experience. Unfortunately, in most clinical settings, the time and c... motor learning in mobility-compromised older adults. We have shown that frontal brain regions, particularly prefrontal cortex, are crucial to control of complex walking tasks. Our neuroimaging and neuromodulation studies also show that prefrontal cortex structure and network connectivity are important for acquisition and consolidation... conducting a full scale trial that also investigates mechanisms related to brain structure, functional activity, and network connectivity. We will address the following specific aims: Specific Aim 1: Determine the extent to which prefrontal tDCS augments the effect of task practice for retention of performance on a complex obstacle walkin... augment retention of locomotor learning, and that our data will provide the first evidence of specific brain mechanisms responsible for locomotor learning/retention in older adults with mobility deficits. This new knowledge will provide a clinically feasible intervention approach as well as reveal mechanistic targets for future interventio...

aduate degree (B.A., 2001) from the University of California, Los Angeles. He completed his graduate degrees in Kinesiology from the University of Nevada, Las Vegas (M.S., 2004) and the University of Georgia (Ph.D., 2007). Following completion of his terminal degree, Dr. Nocera earned a post-doctoral fellowship under a National... ge functions. Concurrently, the CDA-1 was designed to increase Dr. Nocera's understands of cognitive neuroscience thus bridges the gap between cognitive functions and Dr. Nocera's previous education emphasis of physical function in older adults. The general purpose of the career development in this CDA-2 application is to further a... develop Dr. Nocera's skills in clinical/translational research necessary for high-quality clinical trials research. The purpose ofthe CDA-2 study will build on the CDA-1, which demonstrating an improvement in cognitive function via aerobic exercise, by adding a cognitive training component that will be done immediately following th... To address our research question 60 older veterans (age 65-89) will be randomized to one of two 12-week intervention groups: 1) Cognitive Training alone (CT) or 2) Aerobic Exercise + Cognitive Training (AE+CT). The aerobic exercise arm of the study will follow the same format shown to improve a broad range of executive functio... have pervasive effects on patient quality of life from a cognitive as well as a physical standpoint. Concurrently, this proposal will provide Dr. Nocera with the skill necessary to grow into a successful, independent VA Research.

lay of mental and physical disease and its treatment. One example of combination of health problems iselderly patients who live with Alzheimer's disease and related dementia (ADRD) and also suffer from chronicpain. To date, data on quality of pain medication prescribing and the sequelae of poor pain control in patientswith ADRD ar... ypotheses for future research regarding the role of pain control in reducing MH problems in ADRD.We propose a longitudinal design using 4 years (2011-2014) of Medicare 5% sample whose billing records arelinked to nursing home resident assessment data (Minimum Data Set, MDS, 3.0). Because it is unclearwhether MDS 3.0 can a...). The quality will be examined based on five common clinical standards--pain medicationselection, pain medication scheduling, pharmacological prevention of drug adverse event, contraindicatedmedication use, and overall pain control. We then explore the extent to which pain control is associated with adecreased risk for select MH d... anced methods for longitudinal data), and Laurence Solberg (clinical geriatric care andassessment). For further guidance, I enlist the expertise of Dr. Siegfried Schmidt in the field of pain medicineand Dr. Steven DeKosky in ADRD. This K01 award will provide protected time for me to receive trainingneeded to prepare an R01 grant app...

d body weight remains to be improved. Therefore, I seek to increase my knowledge of the physiological aspects of age-related metabolic conditions, and the potential role botanical extracts may have in affecting physiology, eating behavior, body weight, and oxidative stress levels. This knowledge, coupled with my previous training, wi... oxidative stress levels and 2) increase my understanding of the effects that botanicals have on physiological processes related to food intake. My long-term career goal is to become an independent investigator focused on developing safe and effective alternative or adjunctive interventions involving natural compounds for the treatment o... controlled design. Based on the findings from study 1, the botanical with the most significant effects on food intake will be used in a 24-week, placebo controlled calorie restricted weight loss trial. In addition to body weight, this trial will examine the effects of the selected compound on: 1) food intake, 2) self-reported satiety, 3) postpra...

illness (CCI) has emerged and its progression into what we call the persistent inflammation, immunosuppression and catabolism syndrome (PICS) has unacceptable morbid long-term consequences. Our overarching hypothesis is that PICS is now a predominant clinical trajectory in the surgical ICU patients after sepsis, and is the greatest... rojects and five cores drawn from two colleges (Medicine and Public Health and Health Professions) and eight University of Florida Health departments (Surgery, Medicine, Anesthesiology, Biostatistics, Molecular Genetics and Microbiology, Aging and Geriatric Research, and Physical Therapy) and will address the following question... expansion, promoting persistent inflammation, immunosuppression and catabolism?; #3) Does AKI, through dysregulation of anti-angiogenic and angiogenic cytokines, drive the expansion of MDSCs, inflammation, and anti-angiogenesis?; and #4) Does CCI contribute significantly to muscle atrophy, especially in mechanically ventilat... will prevent PICS, but the SCIRC's overall goal is to understand the prevalence and pathogenesis of this new syndrome at a mechanistic level. Only through multi-disciplinary translational research by basic and clinical scientists with diverse expertise in critical care medicine, physical therapy, immunology, molecular biology, and unde...

ocial and physical functioning. Given reports of suboptimal treatment of pain in older adults, improvements in pain management in this cohort are of critical importance. Resilience is characterized as a dynamic process resulting in positive adjustment and adaptation after exposure to adversity. The benefits of resilience in health-related l... on (K99/R00) is to fill this knowledge gap and characterize resilience mechanisms associated with adaptive pain modulatory capacity in older adults with chronic low back pain. Primary training goals for the current application are to: 1) develop a comprehensive knowledge base in biopsychosocial processes of aging and enhance trainin... ong measures of resilience, biological markers of inflammation and neuroendocrine activity, and pain modulatory capacity in older adults with chronic low back pain. Increased knowledge and understanding of the resilience pathways that promote adaptability to pain will allow for the development of a targeted resilience intervention dur... n the PI's prior work on affective regulation and mechanisms of vulnerability in chronic pain, and will forge a path towards understanding and investigating psychological therapies of resilience that improve pain and disability in older adults.

P). Due to persistent inflammation, we believe that older CCI patients represent an extremely
with impaired myocardial contractility over 3 months after sepsis onset. We will capitalize on
aths among older adults after sepsis. A future long-term study may help predict heart failure

e limbs response to decreased blood flow. The current treatments for PAD include surgical
olytic metabolism in the ischemic limb based on the following discoveries: (i) mice with elevated
l identify novel metabolic targets/pathways regulating ischemic pathology in human PAD samples

Aim 1A will test the hypothesis that mitochondrial (mt)DNA regions that encode the electron
e and 2-year follow-up biopsies. Of those with PAD, 30 will have an Ankle-Brachial Index (ABI)
ealth, compared to placebo. This projects overall goal is to identify specific mitochondrial defects

ations in different disciplines and areas. Open source R packages will be developed and
lyzing image data streams, and study their statistical properties. The proposed longitudinal
y spaced.

breakdown of glycogen generates lactate and H+, which accumulate in postmortem muscle
is to define how postmortem conditions and inherent muscle metabolic and contractile

dria at synapses, and the effect aging has on synaptic function, the molecular mechanism(s) that
onse to aging and acute mitochondrial stressors. To reveal new mechanisms that mediate
is research to have widespread implications in the neurobiology of aging, particularly in

ost demands of delivering a sufficiently intensive motor learning intervention is not feasible. There
n of new motor skills. However, a major gap exists regarding learning of walking tasks. The
g task. Specific Aim 2: Determine the extent to which retention of performance is associated
s to enhance locomotor learning and rehabilitation.

l Institute of Health T32 training grant within the Department of Neurology at the University of
nd more substantially develop Dr. Nocera's understanding of cognitive neuroscience for the
aerobic exercise. It is hypothesized that aerobic exercise will potentiate and increase the
ns in older adults in previous research as well as our CDA-1 pilot work. The cognitive training

e scarce. Studies investigating these associations are limited by small sample size, and none
iccurately detect patients with pain and MH disorders, we first conduct a feasibility studyof
isorders, including depression, behavioral symptoms, anxiety, and sleepdisorders in ADRD (Aim
lication to examine pain medication practices and their impact on healthoutcomes in ADRD. The

ll provide an ideal foundation from which I can build a unique and independent line of
f obesity and other metabolic conditions. The proposed line of research will explore the role
ndial neuroendocrine signals (i.e., CCK, GLP-1, insulin, and leptin), and 4) oxidative stress levels

, near-term clinical challenge in surgical ICUs. We further hypothesize that PICS is caused, at
s in four projects: #1a) What is the incidence and early risk factors for CCI in septic surgical
ed patients' diaphragms and extremities, and will resistance exercise improve muscle strength,
standing of muscle, kidney, and aging physiology, can CCI progression into PICS be

iunctioning are manifold, and recent evidence suggests that resilience plays an important role in
g in the assessment and treatment of older adults; 2) increase knowledge in the understanding
ring Study 2 (R00 Phase). This phase will provide the opportunity for examining intervention

Leader(s):

FOSTER, THOMAS C ; KUMAR, ASHOK ;

UNIVERSITY OF FLORIDA

NIH R01AG037984 / (2010-2023)

AbstractSex differences are evident in vulnerability to age-related cognitive decline and diseases of aging. Estradiol(E2) is protective against neurodegenerative diseases, including Alzheimer?s disease, implicating sexhormone effects on sex differences in vulnerability. However, obstacles to sex steroid treatments includecloslin receptor(NMDAR)-mediated synaptic transmission examined several days after treatment. Aim 1 will test thehypothesis that E2 treatment, several days prior to testing, specifically influences NMDAR-dependentepisodic memory, such that it can rescue an age-related decline in episodic memory examined on the watermaze and E2 treatment will promote antioxidant enzyme activity, reduce oxidative stress, andminimize redox-mediated decrease in CaMKII activity and NMDAR function. Further, following closing of thetherapeutic window (i.e. for animals in which E2 does not rescue cognition and NMDAR function), E2treatment will not promote an particularly in gene body regions (introns), and specific to CpG,relative to non-CpG methylation sites. The proposed studies will employ a powerful combination of behavioraltests that are sensitive to NMDAR function, patch-clamp recording of NMDAR synaptic responses, measuresof oxidative stress and enzyme activity, tran

14. **Project Title:**   **SENESCENCE AND GROWTH DIFFERENTIATION FACTORS AS MODIFIERS OF AGING**

     Leader(s):   **LEBRASSEUR, NATHAN K**

                          MAYO CLINIC

                          NIH R01AG055529 / (2018-2023)

PROJECT SUMMARY/ABSTRACTAging is the primary risk factor for the majority of chronic diseases. Studies in mice have implicated specificgrowth and differentiation factors (GDFs) and proteins secreted by senescent cells as potential modifiers ofaging. The objective of this proposal is to establish the rationale and provi health outcomes and can be altered by physicalactivity. Samples from the Lifestyle Interventions and Independence for Elders (LIFE) Study; the largest andlongest randomized trial of a physical activity intervention in older adults, will be used to test this hypothesis,and samples from the Health, Aging, and Body Composition (CCL11, ICAM1, AA and PAI2 are associated withbaseline measures of physical (i.e., gait speed, Short Physical Performance Battery (SPPB) score),cardiopulmonary (i.e., blood pressure, forced expiratory volume), and cognitive (i.e., processing speed,memory) function, inflammation, and prevalence of multimorbidity (based the number of chronic conditions (asin Aim 1), at 1 and 2 years in LIFE and at 2 and 4 years in HABC will be determined. Finally, Specific Aim 3 willaddress whether a structured physical activity intervention impacts longitudinal changes in GDF8, GDF11,CCL11, ICAM1, AA, and PAI2, compared to a health education contr may be viable targets for innovative therapiesto extend human healthspan.

15. **Project Title:**   **INTERMITTENT PNEUMATIC COMPRESSION FOR DISABILITY REVERSAL IN PAD: THE INTERCEDE TRIAL**

     Leader(s):   **MCDERMOTT, MARY MCGRAE**

                          NORTHWESTERN UNIVERSITY AT CHICAGO

                          NIH R01AG057693 / (2018-2023)

PROJECT SUMMARY Our work and that of others has established that people with lower extremity peripheral artery disease(PAD) have greater functional impairment and faster rates of functional decline than people without PAD.However, few therapies improve functioning or prevent functional decline in people with PAD. suggests that IPC improves lower extremity blood flow and walking endurance in people with PADand that benefits persist for up to 12 months after intervention completion. However, evidence is limited bysmall sample sizes, high loss to follow-up, lack of blinding, and lack of sham controls. Clinical practiceguidelines do not (2 x 2 factorial design) of 230 PAD participants randomized to one of four groups:Group A: IPC + exercise; Group B: IPC + ?no exercise? control; Group C: sham control + exercise; and GroupD: sham control + ?no exercise? control. The IPC and sham interventions will be delivered for six months. Inour primary specific aims delineate mechanisms by which IPC affects walking performance, by measuringchanges in MRI-measured calf muscle perfusion, physical activity (measured with ActiGraph), and calf musclebiopsy measures of angiogenesis, muscle regeneration, mitochondrial biogenesis, mitochondrial activity, andautophagy. Based on precli intervention will have a major impact onpreventing mobility loss and improving quality of life in the large and growing number of people with PAD.

16. **Project Title:**   **MECHANISMS OF OXYTOCINS ANALGESIA IN OLDER ADULTS**

     Leader(s):   **CRUZ-ALMEIDA, YENISEL ; EBNER, NATALIE C ;**

                          UNIVERSITY OF FLORIDA

                          NIH R01AG059809 / (2018-2023)

ABSTRACTOsteoarthritis (OA) represents a significant cause of disability worldwide in individuals aged 65 and older, arapidly growing segment of our population. The knee is the most commonly affected joint with pain being theprimary symptom, negatively impacting physical, cognitive, and emotional functioning. Sympto mechanisticmodel of OT's analgesic effects leveraging pilot data supporting efficacy and safety of self-administeredintranasal OT over 4-weeks in older individuals. Relative to placebo (P), daily administration of intranasal OTdiminished self-reported pain intensity, and increased self-repo effect ofintranasal OT administration on clinical and experimental pain sensitivity in older adults with symptomatic kneeOA and 2) characterize inflammatory mechanisms contributing to the inter-individual variability in analgesicresponses to OT. Older adults with symptomatic knee OA will self-administer intranasal OT or P management in older adults with littlepotential for addiction. Embedded in a biopsychosocial framework, our proposal will help pave the way for futureinvestigations using a mechanism-based treatment optimization strategy for individuals suffering from chronicpain.

17. **Project Title:**   **ACTIVE ROLES OF GLIAL CELLS IN OLFACTION AND AGE-RELATED OLFACTORY DECLINE**

     Leader(s):   **XIAO, RUI**

                          UNIVERSITY OF FLORIDA

                          NIH R01AG063766 / (2019-2024)

Project SummaryAge-dependent olfactory decline (presbyosmia) is widely present in many species, including humans. At leastfifteen million Americans over 55 years old suffer from presbyosmia. By affecting the well-being, quality of life,and overall health, presbyosmia presents a significant challenge to public health. Patient physiology andhealth, the cellular and molecular mechanisms underlying presbyosmia are poorly understood (knowledgegap).As a major cell type in the nervous system, glial cells are typically considered as passive modulators duringneural development and synaptic transmission. Whether glial cells play active roles in sensory process across species.This proposal will bring together in vivo calcium imaging, optogenetics, molecular genetics, and behavioralanalysis to investigate and discover the molecular mechanisms through which the olfactory glial cells playactive roles in odorant detection and age-dependent olfactory decline. Since both olfaction

18. **Project Title:**   **BIOBEHAVIORAL BASIS OF KNEE OSTEOARTHRITIS PAIN**

     Leader(s):   **CRUZ-ALMEIDA, YENISEL**

                          UNIVERSITY OF FLORIDA

                          NIH R01AG067757 / (2020-2025)

Discovery and validation of strong candidate biomarkers and clinical endpoints for pain is urgently needed that can be used to facilitate the development of non-opioid pain therapeutics from discovery through Phase II clinical trials. Emerging research using a combination of biomarkers deliver individualized predictions about b biological changes using a biobehavioral perspective which is needed for predicting future health and to be able to use as clinical endpoints for interventions. The proposed study will prospectively address biobehavioral factors (i.e., cognitive, psychological, social and cultural) affecting the experience and interpretation of knee using a comprehensive biobehavioral multi- methods approach, we will be the first to prospectively determine the trajectory and interactions among pain, biological biomarkers and multiple domains of function within race/ethnic groups in OA pain. Findings will contribute towards increased understanding of pain and its biobeh

19. **Project Title:**   **THE EFFECT OF INTERMITTENT HEMIDIAPHRAGM STIMULATION DURING SURGERY ON MITOCHONDRIAL FUNCTION, SINGLE FIBER CONTRACTILE FORCE AND CATABOLIC PATHWAYS IN HUMANS**

     Leader(s):   **SMITH, BARBARA K ; BEAVER, THOMAS M ;**

                          UNIVERSITY OF FLORIDA

                          NIH R01AR072328 / (2017-2021)

Although mechanical ventilation (MV) is life-sustaining in patients with respiratory failure, it comes with a cost.MV dramatically reduces diaphragm contractility, induces ventilator-induced diaphragm dysfunction (VIDD) andsometimes leads to weaning failure. VIDD includes reduced mitochondrial respiration and increased o prevents/attenuatesVIDD in the active hemidiaphragm.Mitochondrial function is central to energy metabolism and skeletal muscle function in a physically activemuscle, such as the diaphragm. Although abnormal mitochondrial function is thought to precipitate VIDD inanimal models, limited data are available concerning mit a within-subjects experimental design,muscle samples from a stimulated hemidiaphragm will be compared with samples from the unstimulatedhemidiaphragm. We will investigate mitochondrial dysfunction and oxidative stress during prolonged CTS/MV,and the potential of ES to attenuate or prevent VIDD (Aim 1). Next, we mechanisms contributing to human VIDD. Our long-term goal is to test variousintermittent hemidiaphragm ES protocols on a larger population to determine its ability to prevent or attenuateVIDD. Data from this R01 application will advance our understanding of mechanisms giving rise to humanVIDD, and may inspire new th

20. **Project Title:**   **REVIVE - RESVERATROL TO ENHANCE VITALITY AND VIGOR IN ELDERS**

     Leader(s):   **ANTON, STEPHEN D**

                          UNIVERSITY OF FLORIDA

                          NIH R01AT007564 / (2013-2019)

A large and growing number of older adults experience progressive declines in physical function, culminating in physical disability with no clear connection to a single disease. Although the etiology of age-related physical disability is complex and multi-factorial, emerging evidence implicates the mitochondria as pl and specific Sirtuins (i.e., SIRT3) in skeletal muscle, both of which are regulators of mitochondria biogenesis. The natural compound resveratrol appears to oppose the reductions in mitochondrial function associated with aging by affecting the expression of key genes, such as PGC-1α,, which support oxidative phosphorylation of resveratrol supplementation on mitochondrial function in older adults, or whether the hypothesized changes in mitochondrial function translate to improvements in physical functioning. Thus, the proposed randomized, parallel study will determine, in older men and women (> 70 years), whether 90 days of resveratrol supplen resveratrol (n=20), or 1500 mg/day of resveratrol (n=20) for a 90-day period. We will collect muscle specimens from the vastus lateralis and blood at baseline and 90 days for biochemical analyses, as well as monitor blood chemistries and adverse events at monthly clinic visits. If our hypotheses are supported, this study will be

21. **Project Title:**   **THE BENEFITS AND HARMS OF LUNG CANCER SCREENING IN FLORIDA**

     Leader(s):   **BIAN, JIANG ; GUO, YI ;**

                          UNIVERSITY OF FLORIDA

                          NIH R01CA246418 / (2020-2023)

Lung cancer is the leading cause of cancer related death in both men and women in the United States. Currently, approximately 70% of lung cancer patients are diagnosed at advanced stages, and the 5-year survival rate of advanced stage lung cancer is very low, at only 16%. Investigators have been searching for effective scree years making history or former smokes who have quitted within the past 15 years. Since the release of the landmark NLST results, many medical associations published guidelines to recommend LDCT-based screening for individuals at high risk for lung cancer and the Centers for Medicare and Medicaid Services (CMS) also d and policy makers started questioning whether the complication rate and false positives in real-world settings would be even higher than the rates reported in the NLST, which was conducted in a setting with well-established facilities and proficiency in cancer care. Therefore, we propose to understand the contemporary use of l related clinical information from clinical notes such as radiology reports; 2) to determine the appropriate and inappropriate use of LDCT among high-risk and low-risk individuals in Florida and to examine the test results of LDCT, the rates of invasive diagnostic procedures, postprocedural complications, and incidental findings patients and physicians better understand the harm- benefit tradeoff of lung cancer screening and transform such knowledge into practice to prevent avoidable postprocedural complications.

22. **Project Title:**   **COCHLEAR DETOXIFICATION SYSTEM**

     Leader(s):   **SOMEYA, SHINICHI**

                          UNIVERSITY OF FLORIDA

                          NIH R01DC014437 / (2015-2020)

DESCRIPTION (provided by applicant): Living organisms are continuously exposed to and must defend against naturally occurring toxins and non- nutrient foreign chemicals (1-3). Cells possess a wide range of detoxification enzymes capable of removing thousands of toxic and foreign compounds. The glutathione transferase have become attractive drug targets. Epidemiological studies found a significant association between age-related hearing loss and GSTT1 null polymorphisms was found in a Finnish population (5) and a Hispanic population (6). McElwee et al (7) conducted a cross-species comparative analysis to compare gene exp display increased expression of Gsta4, Gstm1, Gstm5, and Gstt1 genes in the cochlea. Collectively, these results suggest that GST detoxification enzymes may play an important role in ototoxicity. Cisplatin, a platinum-containing compound, is one of the most widely used chemotherapeutic agents (8-10). Evidence indicates tha associated with increased cisplatin resistance. Our preliminary study also found that cisplatin treatment up-regulates GSTA and GSTM genes in mouse cochlear organotypic cultures. Yet, how the cochlear detoxification system fights such ototoxic drugs at the molecular level remain poorly understood. The overall goal of our re

23. **Project Title:**   **AUTOPHAGY IN LIVER INJURY**

     Leader(s):   **KIM, JAE-SUNG**

                          WASHINGTON UNIVERSITY

                          NIH R01DK079879 / (2007-2020)

DESCRIPTION (provided by applicant): Mitochondrial dysfunction is the major mechanism precipitating I/R injury which commonly occurs during liver surgery, trauma, hemorrhagic shock and liver transplantation. Sirtuin 1 (SIRT1) is an NAD+-dependent deacetylase that induces longevity, stress resistance and tumor suppre Accordingly, we propose that restoration or enhancement of hepatic SIRT1 will promote mitophagy and consequently ameliorate mitochondrial failure and liver dysfunction after reperfusion. To test our hypothesis, we will use hepatocytes isolated from SIRT1 wild type (WT) and knockout (KO) mice for characterization of cel establish novel therapeutic approaches for improving I/R-mediated liver failure.

24. **Project Title:**   **Evaluation of an Adaptive Intervention for Weight Loss Maintenance**

     Leader(s):   **ROSS, KATHRYN MARIE**

                          UNIVERSITY OF FLORIDA

                          NIH R01DK119244 / (2019-2024)

Obesity remains a substantial public health challenge in the United States. Behavioral weight management programs have demonstrated effectiveness for weight loss, but long-term maintenance of these weight losses after the end of treatment tends to be poor. Evidence has demonstrated that individuals who can maintain their w attendance at intervention sessions). Attendance has been closely tied to weight outcomes, but rates tend to be poor and decline over time. The once-per-month, static treatment schedules of existing programs may contribute to these suboptimal outcomes; a participant experiencing a small lapse in weight-related behaviors may n adherence to program goals, and long-term weight maintenance outcomes. We propose to evaluate an innovative method of providing phone-based extended-care adaptive to participant needs. We have built a smartphone application that can be used by participants to track weight, dietary intake, and physical activity (key self-n propose to conduct a randomized controlled trial evaluating the impact of ADAPTIVE (delivered only when indicated by our algorithm or when initiated by participants via an in-app support request) versus STATIC (the monthly, pre-scheduled format used in existing extended-care programs) treatment provision on weight reg research will fill a critical gap in the weight management literature by building a foundational evidence base of proximal predictors of weight-related behaviors for future adaptive intervention development.

25. **Project Title:**   **HEMATOPOIETIC STEM CELL DYSFUNCTION IN THE ELDERLY AFTER SEVERE INJURY**

     Leader(s):   **EFRON, PHILIP A**

                          UNIVERSITY OF FLORIDA

                          NIH R01GM113945 / (2015-2020)

g of the therapeutic window observed as decreased effectiveness of E2 treatment with advanced age.The goal of the proposed research is to provide an understanding of the mechanisms for E2 effects onmemory and the closing of the therapeutic window. Closing of the therapeutic window is marked by a decreasein E2-responsive transc
novel object recognition tasks. Aim 2 will test the hypothesis that E2 effects on memory andNMDAR function are mediated by reversal of NMDAR hypofunction, mediated by redox regulation ofphosphatase/kinase activity, similar to that previously described in aging males. Thus, it is predicted that priorto closing of the therapeutic wi
tioxidant enzyme activity or reduce oxidative stress, and the NMDAR responseand CaMKII activity will be decreased due to an oxidized redox state. Aim 3 will test the hypothesis that age-related changes in transcriptional responsiveness to E2 are due, at least in part, to epigenetic regulationthrough DNA methylation. It is predicted that
scription, and DNA methylation.

de robust clinical evidence for GDF8,GDF11, and senescence-related proteins eotaxin (CCL11), intracellular adhesion molecule 1 (ICAM1), activinA (AA), and plasminogen activator inhibitor 2 (PAI2), as indicators of biological age and age-related conditionsin humans. The central hypothesis is that circulating concentrations of GDFs
HABC) Study will be used to validate studyfindings. A novel multiplexed liquid chromatography-tandem mass spectrometry assay will be leveraged toaccurately quantify GDFs, and an advanced multiplexing platform will be used to measure senescence-relatedproteins in LIFE and HABC biospecimens. In Specific Aim 1, a multidiscipl
on the ICD-9 codes for 20 chronicconditions). In Specific Aim 2, the degree to which baseline concentrations of GDFs and senescence-relatedproteins predict longitudinal changes in a) gait speed and SPPB score, b) major mobility disability (i.e., theinability to walk 400m), c) combined cardiovascular events (e.g., myocardial infarction,
ol intervention, and the degree to whichchange in the concentrations of these proteins parallel change in the health outcomes described in Aim 2. Thesuccessful completion of the proposed research will fill an important translational gap in our understanding ofhow GDFs and senescence-related proteins predict and, therefore, potentially

Intermittent pneumatic compression (IPC) is a non-invasive intervention, consisting of an air pumpinside inflatable cuffs that are wrapped around the feet, ankles, and calves and worn for two hours daily. Every20 second, the cuffs rapidly inflate, followed by rapid deflation. During deflation, arterial blood return into thearteriovenous pr
mention IPC as a therapeutic option in PAD. A definitive randomized trial is needed. Walking exercise is first-line therapy for PAD. However, many PAD patients are unable or unwilling toexercise. Therefore, in people with PAD, we will determine whether IPC augments the benefits of exercise onwalking endurance and whether IPC a
s, we will determine whether IPC combined with exercise improves the 6-minute walkat 6-month follow-up compared to exercise alone and whether IPC alone improves the 6-minute walk at 6-month follow-up, compared to sham control. In secondary aims, we will determine whether benefits of IPCpersist by re-measuring study outcom
nical evidence that IPC increases nitric oxide abundance and promotesvasodilation in skeletal muscle distant from the lower extremities, we will determine whether IPC improvessystemic endothelial function, by measuring changes in brachial artery flow-mediated dilation. If the IPC intervention with and without exercise improves func

matic knee OAhas been traditionally attributed to peripheral mechanisms, but measures of joint damage only modestly accountfor the presence or severity of OA-related pain. The neuropeptide oxytocin (OT) has been recognized as amediator of endogenous analgesia in animal and human studies. However, little is known about theneuro
rtedphysical and emotional functioning. Of evergreater importance, there are no interventions available to attenuate these defects in humans. Here, we will test the impact of an innovative experimental treatment, intermittent electrical stimulation (ES) of thehemidiaphragm during prolonged surgeries with MV, on mitochondrial fun
over 4 weeksusing a double-blinded, parallel study design. With strong support from the University of Florida and the McKnightBrain Institute, our interdisciplinary project, using a comprehensive multi-methods approach, will be the first todetermine the potential benefit of OT as a novel analgesic therapy for knee OA pain in aging. OT

s with presbyosmiaoften show a decreased interest in food, can withdraw socially, and exhibit higher rates of depression.Furthermore, many age-related neurological diseases, including Parkinson's disease and Alzheimer's disease,are commonly associated with olfactory dysfunction. In fact, olfactory loss often precedes various motorics
transductionand brain aging is not well understood. C. elegans is a well-established model organism for neuroscience andaging research due to its simple nervous system, short lifespan, and powerful genetic tools. Very importantly,genetic studies from multiple model organisms have shown that the evolutionarily conserved genetic prog
and aging areregulated by the evolutionarily conserved genes and signaling pathways, our innovative studies on C. elegansglial cells in olfaction and age-associated olfactory decline will provide mechanistic insights into similarprocesses in other species.

future brain and body health. Our own findings suggest that behavioral chronic pain characteristics are associated with multiple biological biomarkers where a greater pain burden is associated with accelerated detrimental biological processes. However, prospective research is urgently needed to determine pain?s impact on the heterogene
pain and physical function across racial/ethnic groups over time. We will prospectively assess pain along with multiple biomarkers as predictors of cognitive, psychological and physical functional progression among middle-aged and older non- Hispanic Blacks and non-Hispanic Whites with knee pain and controls over a four-year study
aviorial basis, with the potential to reduce race/ethnic group disparities and improve pain-related health and functional outcomes.

oxidativestress, muscle fiber damage and decreased diaphragm force production. In animal models, intermittentdiaphragm contraction during MV support attenuates VIDD. However, there are only limited data addressingthis problem in humans. Here, we propose to directly test the hypothesis that intermittent electrical stimulation(ES) o
ochondrial contributions to VIDD in humans. Of evergreater importance, there are no interventions available to attenuate these defects in humans. Here, we willtest the impact of an innovative experimental treatment, intermittent electrical stimulation (ES) of thehemidiaphragm during prolonged surgeries with MV, on mitochondrial fun
will investigate the effects of ES onsingle fiber contractile properties and Titin integrity (Aim 2). Finally, we will study the effect of ES on proteolyticpathways (caspase, calpain and ubiquitin-proteasome) and ribosomal RNA markers of decreased proteinsynthesis implicated in VIDD (Aim 3).This research will provide evidence concern
erapeutic strategies to maintain human diaphragm function during MV support.

laying a key role in the initial onset and progression of functional decline in many older adults. Additionally, our pilot data strongly suggest functional declines are associated with reductions in mitochondrial respiration, as well as decreases in oxidative mitochondrial enzyme activities and enzyme content. These changes were linked to a
and mitochondrial biogenesis. In another recently completed pilot study, we found resveratrol, at a dose of 1000 mg/day, significantly enhanced resting muscle oxidative metabolism (measured using near infrared spectroscopy), as well as cognitive and physical function, in older adults (age > 65 years). Despite promising findings from o
entation is associated with (i) increases in muscle mitochondrial function (State 3 & 4 respiration), (ii) increases in levels of PGC-1a, AMP-activated protein kinase (AMPK), and Sirtuins (i.e. SIRT1 and SIRT3), and (iii) improvements in functional performance, as well as metabolic risk factors. To achieve these aims, 60 moderate to lo
the first to show that resveratrol improves mitochondrial function in muscle, and that these changes are associated with increased levels of physical function in moderate to low functioning older adults - the population who is at greatest risk of functional decline and physical disability.

ning modalities for the early detection of lung cancer so that patients can receive curative treatments at an early stage. When the National Lung Screening Trial (NLST) demonstrated the effectiveness of using low-dose computed tomography (LDCT) scan for lung cancer screening (LCS), researchers and physicians hope to save lives fro
ecided to cover the LCS for Medicare beneficiaries who are at high risk for lung cancer. While many efforts have been made to accelerate the dissemination the beneficial LCS, the concerns over the high false positive rates (96.4% of the positive results), invasive diagnostic procedures, postprocedural complications and health care costs
lung cancer screening and associated health care outcomes and costs using data from a real-world setting. Our study has three goals: 1) to develop an innovative computable phenotype algorithm to identify high-risk and low-risk individuals for LCS from both structured and unstructured (i.e., clinical notes) electronic health record (EHR)
in real-world settings; and 3) to develop and validate a microsimulation model of the clinical courses of LCS incorporating the real-world data in LCS to estimate the long-term benefits and the cost-effectiveness of LCS. Our proposed study has the potential to reduce lung cancer incidence and mortality by informing policymakers and p

: (GST) detoxification system converts a non-polar toxic compound into a more water-soluble and less toxic form by conjugating the toxic compound to reduced glutathione by a variety of GST enzymes. GSTs are a superfamily of enzymes that are divided into several classes on the basis of their primary structure (1-3). Because of their
ression changes in long-lived worms, flies, and mice, and found that GST and other cellular detoxification gene categories were significantly up- regulated in long-lived members of the three species, suggesting the GST detoxification system plays a major role in longevity or protection against aging in multiple species. Consistent with t
t one-third of all cisplatin-treated patients develop hearing loss. Such hearing impairment is dose-dependent, irreversible, and associated with loss of hair cells. Wheeler et al (11) performed meta-analyses of over 3 million single-nucleotide polymorphisms (SNPs) for cisplatin-induced cytotoxicity in 608 lymphoblastoid cell lines from se
esearch proposal is to provide new basic knowledge of the molecular basis for the cochlear detoxification system and its role in the elimination of foreign chemicals throughout the lifespan.

ession. The role of SIRT1 in ischemia/reperfusion-mediated liver injury is unknown. The goal of this study is to investigate the role of SIRT1 in I/Rinjury to liver and to develop therapeutic strategies to improve liver function after I/R. Our principal hypothesis is that calpain-dependent SIRT1 loss causes a sequential chain of defective mi
lular mechanisms causing SIRT1 depletion, defective mitophagy, and onset of the MPT and cell death after I/R. In addition, we will use anesthetized WT and KO SIRT1 mice to confirm and extend our in vitro findings to an in vivo model of hepatic I/R. Finally, we will extend and translate our findings from mice into human liver biopsi

hanges in eating and activity can successfully maintain their weight loss; thus, attempts to improve weight loss maintenance have often involved provision of continued support through monthly ?extended-care? intervention sessions. While these interventions have demonstrated significant improvements in weight loss maintenance, effe
not receive support for several weeks, by which point they may be experiencing a larger lapse or weight regain. This can lead to feelings of frustration, shame, or embarrassment and disengagement from intervention. In contrast, tailoring intervention delivery such that sessions are provided when individuals are at ?high risk? for weight r
monitoring behaviors in traditional behavioral weight management programs) and can further query participants throughout the week regarding self-report factors (e.g., ratings of hunger and the importance of staying on track with weight management goals) that indicate high risk for weight regain. We have also developed a predictive alg
ain at 24 Months in 258 adults who successfully lose = 5% of initial weight during a gold-standard 16-week behavioral weight management program. Results of this study have clear treatment implications for the timing/frequency of sessions within extended-care weight maintenance programs, and this study will result in an innovative, l

ription and an inability of E2 treatment to enhance N-methyl-D-aspartate
ndow (i.e. in animals in which E2 treatment improves cognition and increasesNMDAR function),
decreased responsiveness of E2-sensitive genes will beassociated with DNA hypermethylation,

and senescence-related proteinsare associated with, and predictive of, clinically important
inary team will first determine theextent to which baseline concentrations of GDF8, GDF11,
heart failure, stroke); d)adjudicated falls and injurious falls, e) cognitive function (as Aim 1), and f)
mediate aging related disabilityand disease in older women and men. Ultimately, these proteins

essure gradient generates shear stress and stimulates nitric oxide production. Preliminaryevidence
alone improves walking endurance compared to sham control. We willconduct a randomized trial
es at twelve-month follow-up, six months after the IPC intervention iscompleted. We will also
tional performance and preventsfunctional decline in PAD, this non-invasive and well tolerated

biological mechanisms underlying OT's pain-relieving properties. This proposal is based on a
flammatory mechanisms contribute to these analgesic responses. We aim to 1) determine the
is currentlyused in obstetrics and may be an inexpensive, effective method for pain

ymptoms in these deadly neurological diseases. Despite the importance of olfaction to human
ramsand signaling pathways play pivotal roles in regulating sensory transduction and aging

city of these biological processes within an individual to elucidate the underlying patterns of
y period. With strong support from the University of Florida, our interdisciplinary project,

f the human hemidiaphragm during prolonged cardiac surgeries with MV support
tion, single fiber contractileproperties and catabolic muscle pathways in human diaphragm. Using
ning the ability to improve mitochondrial function in the stimulatedhemidiaphragm, and identify

large decline in peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a)
ne recent clinical trial involving obese, middle-age men, no study to date has examined the effects
w functioning participants will be randomized to receive a placebo (n=20), 1000 mg/day of

m lung cancer by screening high-risk population who aged 55 to 77 years and have a 30 pack
may hinder the utilization of lung cancer screening. This concern was magnified as researchers
data and to develop advanced natural language processing (NLP) methods to extract LCS
ractitioners on the appropriateness of contemporary use of LCS. This knowledge will help both

cytoprotective role and involvement in the development of resistance to anti-cancer agents, GSTs
hese reports, our preliminary studies found that long-living calorie-restricted C57BL/6 mice
ven HapMap panels. The study found that increased GSTM1 and GSTT1 expression was

itophagy, mitochondrial permeability transition (MPT) onset and hepatocyte death after I/R.
es. These studies provide critical mechanistic insights into lethal I/R injury to the lver, and will

ets have been modest. A key challenge is continued participant engagement (often assessed as
egain offers potential to disrupt this cycle and significantly improve program engagement,
orithm that uses this data to identify when individuals are at ?high risk? of weight regain. We
ow-cost, and easily scalable intervention for weight loss maintenance. Further, the proposed

DESCRIPTION (provided by applicant): People of advanced age (greater than 55 years old) have significantly increased morbidity and mortality after trauma. Since the elderly population is expanding, research into this disease process is increasingly relevant, especially with the escalating economic and health care burdens on aged after severe injury and subsequent infections. Specifically, neutrophils are replaced after inflammation through a process known as 'emergency myelopoiesis.' This occurs after severe injury when bone marrow granulocyte stores are rapidly released, and increased stem cell proliferation and differentiation along myeloid par associated with aging modifies the emergency myelopoietic response to traumatic injury, resulting in inappropriate differentiation and maturation of myeloid cells, leaving the host susceptible to subsequent infection. We further propose that this failure of emergency myelopoiesis is due to age-associated, chronic activation of N properly expand and differentiate along myeloid pathways in the elderly response to trauma, and, if the resultant dysfunctional neutrophil population seen in the elderly after trauma results from these suboptimal ST-HSCs; (2) determine if the defects in aged ST-HSC function after severe injury, as compared to their juvenile cou in aging is due, at least in part, to defects in myelopoiesis that lead to genotypically, phenotypically and functionally deranged PMNs that fail to control infection. The third specific aim will translate our 'bench side' animal work to humans and this innovative approach could identify areas for intervention in cell types that are sti

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26. **Project Title:**   THE ROLE AND MECHANISMS OF LIPID AND LIPOPROTEIN DYSREGULATION IN SEPSIS

    Leader(s):   GUIRGIS, FAHEEM W

                UNIVERSITY OF FLORIDA

                NIH R01GM133815 / (2020-2025)

Sepsis is a dysregulated response to infection that has both fatal and non-fatal morbid consequences. Unfortunately, initial survival does not provide relief from morbidity for most sepsis survivors. Initial clinical trajectories include rapid recovery, early in-hospital death, and progression to chronic critical illness (ICU stay = 14 sepsis via several mechanisms (antioxidant/anti-inflammatory function, bacterial toxin clearance, steroid synthesis), but the exact mechanisms by which HDL and LDL protects against sepsis are not known. Lipid and lipoprotein dysregulation occurs in early sepsis, leading to failure to protect against sepsis. We have shown that sepsis, and the severity of the drop is predictive of death; and 5) low baseline LDL levels are associated with increased long-term community-acquired sepsis risk. Highly biologically active lipid metabolites are also present in the circulation during sepsis that may propagate and promote inflammation resolution and contribute t illness and sepsis recidivism). To test our hypothesis, we will capitalize on an established and experienced sepsis research team and the opportunity provided by an existing bank of samples from a diverse cohort of 80 community-acquired (CA) and 85 hospital-acquired (HA) sepsis patients from two-centers. This approach has s also propose two-site prospective enrollment of a small cohort of sepsis readmission patients to study this novel and important outcome. This project satisfies the NIGMS mission of researching biological mechanisms that underlay the foundation for advances in treatment of diseases such as sepsis.

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27. **Project Title:**   IMPROVE PAD PERFORMANCE WITH METFORMIN. THE PERMET TRIAL

    Leader(s):   MCDERMOTT, MARY MCGRAE

                NORTHWESTERN UNIVERSITY AT CHICAGO

                NIH R01HL131771 / (2016-2021)

PROJECT SUMMARY Improve PAD PERformance with METformin: The PERMET Trial. Our work and that of others has established that people with lower extremity peripheral artery disease(PAD) have greater functional impairment, faster functional decline, and increased rates of mobility losscompared to people without propertiesof metformin in pre-clinical models that may benefit people with PAD include: calf skeletal muscle increases inperoxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a) (a major regulator ofmitochondrial biogenesis), calf skeletal muscle increases in mitochondrial protein expression and activit skeletalmuscle perfusion. No randomized clinical trials have studied whether metformin improves lowerextremity functioning in PAD. A definitive trial is needed. We propose a placebo controlled double-blind randomized clinical trial to establish whether metformin(2,000 mgs daily) improves and/or prevents decline in walkin performance, and quality of life. Calf muscle outcomes consist ofchanges in PGC-1a abundance, mitochondrial quantity, mitochondrial enzyme activity, capillary density,reactive oxygen species (ROS)-induced tissue damage, and autophagy. If metformin improves functional performance and prevents functional decline in PAD

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28. **Project Title:**   TRANSCRIPTIONAL REGULATION OF KCNH2

    Leader(s):   DELISLE, BRIAN P

                UNIVERSITY OF KENTUCKY

                NIH R01HL141343 / (2019-2023)

SummaryCircadian rhythms help to match the optimal function of the cardiovascular system to the daily changes in theenvironment. Normal cardiovascular rhythms provide a physiological advantage to people. Unfortunately,normal circadian signaling can also unmask a time-of-day pattern in adverse events like heart attack, st that helps toentrain endogenous rhythms to the environment. SCN rhythms are synchronized to the environment via light,and its signaling helps to coordinate the molecular rhythms in cells throughout the body. That is new aboutthis application is we determine how repeated changes in light cycle will impact molecular circadia molecular clocksignaling in the mouse heart and its regulation on ion channel function.Aim 1. To identify new mechanisms with which the cardiac molecular clock regulates different ion channels.Aim 2. To determine how repeated changes in light impact molecular clock signaling in the heart and ionchannel regulation.This pr

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29. **Project Title:**   IMPAIRED MITOCHONDRIAL ENERGETICS IS A DRIVER OF HEMODIALYSIS ACCESS RELATED HAND DYSFUNCTION

    Leader(s):   SCALI, SALVATORE T.

                UNIVERSITY OF FLORIDA

                NIH R01HL148597 / (2019-2024)

PROJECT SUMMARYCurrently, in the United States, there are ~425,000 patients receiving hemodialysis (HD) and it is estimated that30-60% of this population have some element of hand dysfunction after hemoaccess surgery. The underlyingpathophysiologic mechanisms responsible for this devastating problem are poorly u AVF surgery causes significanthemodynamic changes in the extremity which presents an adaptive challenge to the skeletal muscle andneuromotor end-plate. Supported by our previous work, as well as preliminary data on RD associated skeletalmuscle mitochondrial phenotypic changes, we propose that RD driven mitochondria undergoing AVF surgery todeveloping skeletal muscle and neuromuscular junction perturbations causing clinically significant handdysfunction. RD mediated mitochondrial impairments are further exacerbated by local hemodynamic changesfollowing AVF creation through maladaptive OS metabolic responses that drives the d mitochondrial-targetedantioxidant therapies delivered prior to- following AVF surgery in mice. Using a novel RD murine AVF model,we will determine whether global (N-acetylcysteine) or mitochondrial-targeted (AAV delivery of mitochondrialtargeted catalase) antioxidant therapy have therapeutic potential for AVF-ind outcomes modulating the spectrum ofhand function will be determined.

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30. **Project Title:**   MOLECULAR MECHANISMS REGULATING PERIPHERAL ARTERIAL DISEASE PATHOBIOLOGY IN CHRONIC KIDNEY DISEASE

    Leader(s):   RYAN, TERENCE E

                UNIVERSITY OF FLORIDA

                NIH R01HL149704 / (2019-2024)

Peripheral artery disease (PAD) is caused by atherosclerosis in the lower extremities which leads to a spectrum of life-altering symptomatology, including claudication, ischemic rest pain, and gangrene requiring limb amputation. Complicating the etiology of PAD, patients typically present with comorbid conditions or risk facto diabetes. We have uncovered a novel molecular pathway that may link CKD and PAD pathobiology. We find that many uremic metabolites, which accumulate in CKD, cause chronic activation of the aryl hydrocarbon receptor (AHR) which leads to disruption of the mitochondrial electron transport system that exacerbates isch pathobiology. This hypothesis will be tested using muscle- and vascular-specific inducible knockout of the AHR as well as adeno- associated virus-mediated expression of the a constitutively active AHR in pre-clinical models of CKD/PAD. Finally, our recent human data indicate elevated AHR signaling in PAD patients with C

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31. **Project Title:**   CIRCADIAN CLOCK REGULATION OF MYOCARDIAL ION CHANNEL EXPRESSION AND FUNCTION

    Leader(s):   ESSER, KARYN A ; DELISLE, BRIAN P ;

                UNIVERSITY OF FLORIDA

                NIH R01HL153042 / (2020-2024)

The overall objectives of this proposal are to 1) define the genomic and transcriptomic mechanisms by which the cardiomyocyte clock regulates ion channels that contribute to cardiac excitability; and 2) disrupt the cardiomyocyte clock to link changes in circadian-ordered gene expression with electrophysiological properties of link time of day with a large-scale transcriptional program to support cellular homeostasis To date, our labs have used an inducible cardiomyocyte specific mouse model to knock out the core clock gene, Bmal1 (iCSBmal1). These studies showed that disruption of the myocardial clock is sufficient to decrease ventricular K+ and approaches with our mouse model system to define the circadian clock dependent control of temporal gene expression in both atrial and ventricular tissues. To address abnormal circadian clock function, our lab has used different models of circadian disruption, such as chronic phase advance or time restricted feeding to test link myocardial clock function with outcomes that include modified ion channel expression, cardiac excitability and arrhythmia vulnerability. The aims of this proposal are designed to test the following hypotheses: 1) The molecular clocks in both atrial and ventricular cardiomyocytes are necessary to direct daily chromatin accessib

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32. **Project Title:**   EMOTIONAL ENGAGEMENT DRIV

    Leader(s):   DING, MINGZHOU ; KEIL, ANDRE

                UNIVERSITY OF FLORIDA

                NIH R01MH112558 / (2017-2022)

Project?Summary??Emotional?dysfunction?is?at?the?core?of?many?psychiatric?disorders,?in?particular?fear,?anxiety,?post-?traumatic,?and?mood? disorders.?Describing?the?neural?mechanisms?associated?with?emotional?processing?is?therefore?a?critical?issue?in?mental?health? care.?Previous?attempts?to?define?the?neu functional? brain? imaging,? which? is? high? in? spatial? precision.? This?approach,?called?steady-?state?potential?frequency-?tagging,?achieves?stimulus?specificity,?temporal,?and?spatial?resolution?across?the?whole?brain.?It?is?unique?in?that?it?allows?researchers?to?identify?distinct?brain?networks?selectively?activa large-?scale? brain?dynamics? mediating? the? emotional? response? to? an? element? that? is? embedded? in? a? complex? visual? array.? (2)?We? determine? how? conflicting? appetitive? and? aversive? information,? visual? and? auditory,? affects? these? brain?dynamics.? (3)? Finally,? we? translate? this? novel? method? avenues? for? objectively? evaluating? pre-?? to? post-?treatment? changes? in? appetitive/aversive?neural? reactivity.? It? also? enables? measuring? neural? circuit? function? to? enable? quantitative? measurements? of?specific?psychopathology?and?for?identifying?treatment?targets?in?a?personalized?medicine?framework

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33. **Project Title:**   BIOBEHAVIORAL MECHANISMS UNDERLYING SYMPTOMS AND HEALING OUTCOMES IN OLDER INDIVIDUALS WITH CVLU

    Leader(s):   STECHMILLER, JOYCE K. ; LYON, DEBRA E ;

                UNIVERSITY OF FLORIDA

                NIH R01NR016986 / (2018-2023)

ABSTRACT Our long-term goal is to elucidate the complex biobehavioral mechanisms responsible for symptoms andhealing outcomes for older adults? with venous leg ulcers (VLUs) for the development of targeted therapies thataddress both the patient-oriented outcomes and healing outcomes in this growing group of affecte both wound-relatedsymptoms and symptoms of pain, depression, anxiety, fatigue and cognitive dysfunction, collectively labeled as?psychoneurologic symptoms (PNS).? Guided by the National Institutes of Health Symptom Science Model(NIH-SSM) framework, the central hypothesis of this application is that there are interrel wound-related); and,(2) Test associations and models over time for: (a) Patient-host factors and systemic inflammation with woundmicroenvironment; (b) Patient-host factors, systemic inflammation, and wound microenvironment with wound he across eight weeks time. We willfully characterize patient-host characteristics (age, comorbidities, sex, race/ethnicity, BMI, nutritional status,lifestyle habits, and wound treatment [pressure therapy, debridement, antibiotics]); systemic inflammatoryactivation (C-reactive protein and cytokines); wound microenvironment factors from a holistic perspective and toprovide a basis for preventing or reversing the adverse health outcomes of CVLUs, a condition thatdifferentially affects older and minority individuals.

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34. **Project Title:**   OPTIMIZING AAV VECTORS FOR CENTRAL NERVOUS SYSTEM TRANSDUCTION

    Leader(s):   HELDERMON, COY D

                UNIVERSITY OF FLORIDA

                NIH R01NS102624 / (2017-2022)

Project SummaryMucopolysaccharidosis (MPS) IIIB is a neurodegenerative lysosomal storage disease (LSD) caused by deficientdegradation of heparan sulfate. Clinically this manifests as cognitive decline, developmental regression, impairedmobility and ultimately premature death. There are currently no effective therapies. D been published for AAV9. However,for translation to human trials, it is essential to identify a highly effective AAV capsid serotype that will deliverto cells in the requisite brain regions. More generally, for any treatment of human neurologic disease in whichthe central nervous system (CNS) is of substantially larger volume genetic bar code that identifies each vector and a second barcode that is incorporated during PCR amplification of each brain region isolated. The bar code system allowsdetermination of distribution and the expression levels of each serotype in anatomical areas of interest. We willuse this novel two-step barcoded AAV vector s provide the best delivery by region, and select by presence of the disease,and are similar between primate and mouse models. The results will inform clinical trial vector selection acrossthe spectrum of central neurologic disorders, including MPS III. Subsequently, our MPS IIIB gene construct willbe packaged into the optimal i two-step bar-coded AAV vector system to allow simultaneous delivery and assessment of 40 serotypes with capsid variants in each animal via injections into the brain or surrounding fluid. Brain distribution for each serotype will be assessed by quantitative next generation RNA sequencing of the various brain regions. The top enzyme assays to determine preclinical benefit in the mouse model.Overall, these studies will determine the effects of species, delivery site and disease state on brain delivery froma multitude of AAV serotypes. Through this study, we will identify the most promising vector(s) for clinical trialdevelopment in MPS IIIB and othe

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35. **Project Title:**   HEAT SHOCK PROTEINS AND DISUSE MUSCLE ATROPHY

    Leader(s):   JUDGE, ANDREW ROBERT

                UNIVERSITY OF FLORIDA

                NIH R03AR056418 / (2009-2013)

DESCRIPTION (provided by applicant): Project summary/Abstract Skeletal muscle disuse atrophy is a widespread physiological phenomenon associated with immobilization, bed rest, denervation, and space flight, or any general reduction in weight bearing activity. However, our understanding of the signaling molecules that r rapidly, induced by a variety of cellular stresses. This induction has been shown to provide a variety of cytoprotective functions. During muscle disuse a member of the heat shock family, Hsp70, is consistently down-regulated and overexpression of Hsp70 during disuse abolishes the increase in NF-:B and Foxo3a transactivatio Aims 1 and 2 if an increase in Hsp70 expression is sufficient to inhibit NF-:B-induced or Foxo3a-induced muscle fiber atrophy, and in Aim 3 if knock down of Hsp70 is sufficient to cause muscle fiber atrophy. To address these specific aims we will inject WT IKK2 plus Hsp70 expression plasmids (Aim 1), WT Foxo3a plus Hs The findings from these experiments will lead to a greater understanding of Hsp70 in the regulation of NF-:B and Foxo3a signaling during skeletal muscle atrophy. PUBLIC HEALTH RELEVANCE: Project Narrative Skeletal muscle wasting due to disuse is associated with immobilization, bed rest, denervation, and space fligh wasting.

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36. **Project Title:**   WEARABLE TECHNOLOGY INFRASTRUCTURE TO ENHANCE CAPACITY FOR REAL-TIME, ONLINE ASSESSMENT AND MOBILITY (ROAMM) OF INTERVENING HEALTH EVENTS IN OLDER ADULTS

    Leader(s):   MANINI, TODD ; RANKA, SANJAY ;

                UNIVERSITY OF FLORIDA

                NIH R21AG059207 / (2019-2021)

ABSTRACTOlder Americans experience approximately 29 million falls and 13 million hospitalizations per year. Theseintervening health events (IHE - episodic falls, injuries, illnesses, and hospitalizations) are strong precipitants ofdisability in older adults. Because of their episodic nature, IHEs are extremely difficult to study. continuousconnectivity, bidirectional interactivity and remote programming. ROAMM will create a detailed narrative aboutmobility (activity patterns, walking speed, life space), patient reported outcomes/symptoms (pain, poor mood,fatigue, disability), cognition (working memory, processing speed, and executive functioning) framework consisting ofthe watch application and accompanying server. We will also assess test-retest reliability, convergent validityand participant usability/acceptability. Each year, an Independent Advisory Panel and External AdvisoryCommittee will evaluate milestone-driving activities and our Go/No-Go checkpoints for t collected by ROAMM areindependent predictors of incident IHE's; 2) IHE's will negatively impact the course of ROAMM measures; and3) Additional value will be gained for explaining the change variability and recovery trajectories. An exploratoryaim will evaluate safety while using ROAMM features and identify predictor become the go-to place formote data capture. These activities will create a sustainable infrastructure to ensure research on older adultsis keeping pace with the state-of-the-art ?smart and connected? health with wearable technology.

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37. **Project Title:**   SYSTEMATIC ANALYSIS OF CLINICAL STUDY GENERALIZABILITY ASSESSMENT METHODS WITH INFORMATICS

    Leader(s):   HE, ZHE ; BIAN, JIANG ;

                FLORIDA STATE UNIVERSITY

                NIH R21AG061431 / (2019-2021)

our society. Despite decades of promising preclinical and clinical investigations in trauma, our understanding of this entity and why its effects are exacerbated in the elderly remains incomplete, with few therapies demonstrating success in any patient population. Recently, several aspects of innate immunity have been determined to be of ...hways results. Proper differentiation of myeloid cells from stem cells is dependent on activation of nuclear factor kappaB (NF- a protein complex that partially controls DNA transcription after stressful stimuli. Anappropriate emergency myelopoietic response to inflammation is essential to host survival but appears to be inadequate in the ...FB-dependent inflammatory pathways, and a failure of hematopoietic stems cells (LSK populations) after trauma to create functional myeloid populations in a NF B-dependent manner. Using a novel murine polytrauma (PT) model of murine hemorrhagic shock and injury that better recapitulates the human condition, we will: (1) determi ...nterparts, are caused by a chronic low-grade NF B-dependent inflammatory state and a subsequent failure to appropriately activate NFB-dependent pathways after trauma; and, (3) determine if the HSC senescence associated with elderly humans after severe trauma is also due to a failure to appropriately activate NFB-dependent pathway ...ll exhibit plasticity.

days with organ dysfunction. Late complications include sepsis readmission and late death, both of which have rates of approximately 40% at 90 days and 6 months, respectively. Circulating lipids play an important role in sepsis and cholesterol levels of both high density lipoproteins (HDL-C) and low density lipoproteins (LDL-C) are ...: 1) HDL becomes dysfunctional (pro-oxidant and pro-inflammatory) in early sepsis (Dys-HDL); 2) elevated Dys-HDL levels positively correlate with and predict organ failure severity and are associated with poor outcomes including 28-day mortality; 3) HDL from older septic patients exhibits impaired cholesterol efflux capacity (requ ...o cholesterol dysfunction. Our data strongly suggest that lipid and lipoprotein dysregulation occurs in sepsis and leads to altered function, oxidation, and reduced levels that may influence clinical outcomes. We hypothesize that specific functional, lipidomic, and genomic changes in lipid and lipoprotein metabolism occur in early sepsis a ...several advantages: 1) cost-savings from use of existing samples with isolated mRNA, 2) a recent cohort of sepsis patients (2016-2018) consistently treated with institutional evidence-based management bundles, 3) availability of serial samples over time (enrollment, 48h, 28d, and 90d), sepsis readmission samples, and mRNA for the C/

PAD. However, few therapies are available that improve functioning or preventfunctional decline in people with PAD. Metformin is an inexpensive, widely available, well tolerated biguanide medication and the mostcommonly prescribed drug for Type 2 diabetes mellitus worldwide. Recent pre-clinical and preliminary humanevidence ...y,increases in capillary density in ischemic tissue, reductions in oxidative stress, increased autophagy (repair ofcellular damage), and improved endothelial function. These therapeutic properties target pathophysiologicconditions present in PAD. Therefore, we hypothesize that metformin will improve lower extremity functioningin peopl ...g performance in people with PAD. Participantswill be 212 people with PAD who do not have diabetes mellitus, since metformin is a first-line therapy for Type2 diabetes. Our primary outcome is change in six-minute walk at 6-month follow-up. Secondary outcomes are6-month changes in treadmill walking performance, brachial artery ...), this widelyavailable, inexpensive, and well tolerated medication will have a major impact on preventing mobility loss andimproving quality of life in the large and growing number of people with PAD.

roke,and sudden death in patients with underlying cardiovascular disease.Emerging data now show that abnormal or unhealthy daily rhythms can create a negative impact on normalhealth too. For example shiftwork, which repeatedly causes shifts in endogenous circadian rhythms, is anindependent risk factor for cardiovascular disease.I ...n signaling inthe heart.Most cells have a molecular clock signaling mechanism that cycles with a periodicity of ~24 hours. We foundgenetic disruptions in the molecular clock mechanism of heart cells (cardiomyocytes) primarily causesabnormal changes in cardiac electrophysiology by disrupting the regulation of ion channel function.T ...oject creates new knowledge at the interface between chronobiology and cardiac electrophysiology.

understood. The renaldysfunction (RD) milieu causes a variety of physiologic derangements in HD patients including increasedoxidative stress (OS) and chronic inflammation that have been implicated as major contributors to accelerateatherosclerosis and elevated mortality. Profound changes in OS contribute to skeletal muscle and neu ...al dysfunction alters skeletalmuscle and neuromuscular junction responses to AVF induced ischemia leading to clinically apparent handysfunction. Further, these pathways can be modified either prior to AVF creation or at first evidence of handysfunction to reverse/prevent the functional impairment. Our hypothesis is that the RD mil ...iversity of clinicallyapparent hand dysfunction. Aim 1 will establish how RD impacts mitochondrial and cellular energetics that areexacerbated by AVF-induced limb ischemia. Using a series of in vitro experiments, we will uncover thebiochemical mechanisms by which RD impacts mitochondrial energetics leading to impaired oxidativ ...uced muscle dysfunction. Aim 3will evaluate the association between mitochondrial health and AVF-induced hand dysfunction in humanpatients. Mitochondrial health will be examined in-situ using permeabilized myofibers prepared from RD patientsbefore and after AVF surgery: mitochondrial phenotypic changes will be evaluated an

ors that accelerate disease evolution and substantially worsen pathology contributing to increased mortality risk. Among these, chronic kidney disease (CKD) accelerates the development of atherosclerosis, decreases functional capacity, and increases risk of amputation or death, however the underlying biologic mechanism(s) are poorly ...emic muscle injury and impairs angiogenesis. Preliminary experiments demonstrate that genetic knockdown of the AHR is protective against uremic toxicity, whereas expression of a constitutively active AHR causes mitochondrial dysfunction. Thus, we propose to test the novel hypothesis that the chronic activation of the AHR pathwa ...CKD. We propose to extend these findings to establish a clinical link between muscle health/function, mitochondrial energetics, and AHR signaling in human PAD patients. Success in these studies will provide mechanistic insight into the impact of CKD on PAD pathobiology, and would provide a novel target for therapeutic developmen

atrial and ventricular cardiomyocytes. The outcomes will address significant gaps in our understanding for how the myocardial circadian clock regulates the expression of key cardiac ion channels and how abnormal cardiac clock function contributes to arrhythmia vulnerability. The mechanism regulating circadian timing, the molecular ...l Na+ channel gene expression, disrupt current levels, disrupt cardiac excitability, and increase arrhythmia susceptibility. These studies establish a critical role for the cardiomyocyte clock, independent of the central clock, in regulating the expression of different families of ion channel genes that impact the ionic balance needed for norm ...s between circadian disruption and arrhythmia vulnerability in mouse models. We have found that disrupting either light or feeding time cues is sufficient to induce pathological changes in cardiac rhythms in normal mice and to accelerate sudden cardiac death in a genetic mouse model of arrhythmia susceptibility. These studies support ...ility and transcriptional output including expression of key ion channel and ion channel regulatory genes. 2) Chronic disruption of the cardiomyocyte clock using altered time of feeding is sufficient to cause dysregulation of the cardiac clock resulting in an imbalance in cardiac ion channel expression and currents leading to altered excita

VEN BY COMPLEX VISUAL STIMULI: NEURAL DYNAMICS REVEALED BY MULTIMODAL IMAGING

AS ;

rophysiology?of?human?emotions?in?the?cognitive? neuroscience? laboratory? have? been? hampered? by? the? unavailability? of? conceptual? and?methodological? frameworks? for? studying? complex? emotional? responses? in? context? and? with? conflicting?information?present.?The?proposed?research?establishes?a?novel?tec ...ted?by?different?elements?of?a?complex?visual?scene?even?when?the?elements?are?spatially?overlapping? and? accompanied? by? stimulation? in? other? sensory? modalities? We? combine? this? innovative?approach?with?a?novel?conceptual?framework?that?considers?changes?in?visual?perception?an?active?part?of?an?observe ...? to? socially? anxious? observers,? testing? mechanistic?hypotheses? regarding? the? interactive? effects? of? trait? anxiety? and? chronic? stress? on? short-?term? reactivity? to?emotional? challenge.? The? long-?term? clinical? implications? of? the? proposed? research? are? manifold:? For?diagnostic?assessment?and?for?monitoring ...?

d individuals.VLUs, which account for 70?90% of ulcers found in the lower leg, affect 2 million persons annually, includingnearly 4% of people over age 65 years. To date, the basic biology underlying the development and persistenceof VLUs and the influence of aging and multiple disease conditions on wound healing are generally n ...lated molecularmechanisms by which the immune activation that contributes to the development and persistence of CVLUalso leads to the development, persistence and severity of PNS. The specific aims of the proposed study areto: (1) Characterize the strength of the associations at baseline among patient-host factors, systemicinflamm ...ling; (d) Patient-hostfactors, systemic inflammation, and wound microenvironment with symptoms (PNS and wound-related) and (e)Patient-host factors, systemic inflammation, wound microenvironment and wound healing with symptoms (PNSand wound-related). To achieve the specific aims, we will longitudinally examine 200 older ...(local inflammation [Matrixmetalloproteinase (MMP) enzymes C-reactive protein, cytokines], biofilm, and micro RNAs); symptoms (PNS[cognitive dysfunction, pain, fatigue, and depressive/anxiety symptoms] and wound-related); and woundcharacteristics and healing trajectory at the five timepoints. This knowledge is critical to provi

due to the neurodegenerativenature of this disease, optimal CNS transduction is necessary for human trials. Several groups havedemonstrated improvement of the mouse model using different adeno-associated viral (AAV) vectors. We haverecently demonstrated that AAV8 has better brain gene delivery in MPS IIIB than wild type mice. ...and is phylogenetically distant compared toour current mouse models, we will need to identify an optimal vector and delivery method for CNS approaches.To this end, we have developed a novel two-step bar code AAV vector system that allows assessment of multipleAAV vector serotypes within the same animal, greatly reducing the n ...ystem to simultaneously identify brain delivery of 40 AAVserotypes and capsid variants in wild type and MPS IIIB mice as well as in non-human primates - the closest tohuman model available to us. We will identify whether injections into the body of the brain or the less invasiveinjection into the fluid around the brain method provides ...vector to assess transduction effect in MPS IIIB mice. We hypothesize that CNStransduction and distribution will differ by serotype and species and that some serotypes will transduce differentlybetween wild type and Sanfilippo Syndrome mice. Our specific aims are therefore:1. We will determine the brain delivery of AAV serotypes in no ...three vectors for brain delivery by this method will be used individually to identify the cell types treated and pattern of gene expression in mice and NHP.2. Assess the effect of the AAV serotype with the best distribution in the thought processing and motor coordination regions of the brain carrying the MPS IIIB gene to treat the MPS II ...r neurodegenerative disorders. If this project is successful, we will be in aposition to quickly move towards such clinical trials.

regulate muscle mass during disuse are ill defined. Therefore the long-range goal of our research program is to understand the regulation of signaling pathways that cause muscle atrophy during disuse. Eventually improved understanding will lead to the identification of targets for specific interventions. Heat shock proteins (Hsps) are a fa ...n, and completely prevents skeletal muscle atrophy. This is important since NF- B and Foxo3a are required for disuse muscle atrophy. However, it is currently unknown whether Hsp70 overexpression is sufficient to specifically inhibit NF- B-induced or Foxo3a-induced muscle atrophy. It is also unknown whether knock down of Hsp70 i ...p70 expression plasmids (Aim 2), or a plasmid producing shRNAs specific for Hsp70 (Aim 3) into the skeletal muscle of rats and measure NF- B or Foxo3a activity, the mRNA expression of specific atrophy genes and muscle fiber cross sectional area. If an increase in Hsp70 expression inhibits NF- B activity and/or Foxo3a activity we ...t, or any general reduction in weight bearing activity. In the proposed work we will genetically overexpress or knock down a protein that is believed to regulate muscle size and is known to be down-regulated during muscle wasting caused by disuse. This will allow us to directly determine the involvement of this protein in the regulatio

Continuous,long-term monitoring with remote capabilities using wearable technology is an ideal solution for capturinginformation surrounding an IHE and in particular, preceding it. This R21/R33 project aims to develop asustainable research infrastructure built on the foundation of a smart watch application and server calledROAMM ...and reports ofhealth events (falls and hospitalizations). The infrastructure is composed of a diverse group of investigatorswith expertise in mobile technology/data science and applied/medical sciences who will serve in the followingcores: Wearable Technology, Phenotyping, Clinical Outcomes, Data Science Management & Quality, an ...transitioning to the R33phase. Work proposed in the R33 phase will showcase the ROAMM infrastructure by conducting aprospective, longitudinal study (range 1.25-2.5 yrs) in 200 community-dwelling persons aged 70+ yrs. Thisphase will test a field deployable version of ROAMM in real world settings to address the following hypoth ...s of ROAMM adherence using bothkey-informant interviews and examine demographic and health histories to create boundaries for usingROAMM and other systems like it for long-term, continuous monitoring in research and practice. We willsustain ROAMM by targeting grant opportunities for the wearable technology surge for remo

vital importance to the young adult immune response, and this response is suboptimal in the
elderly as compared to younger patients. Specifically, we hypothesize that the myelodysplasia
ne if certain hematopoietic stem cells (HSCs), specifically short term-HSCs (ST-HSCs), fail to
s in bone marrow HSCs. This work proposes that increased susceptibility to infection after trauma

dynamically regulated in sepsis. HDL and LDL are both thought to play protective roles in
ired for toxin clearance and steroidogenesis); 4) HDL and LDL levels drop precipitously during
nd relate to relevant clinical trajectories (rapid recovery, early death, and chronic critical
cohort, 4) age/gender matched control samples, 5) available clinical and outcomes data. We

suggest that metformin has previously unrecognized therapeutic properties. Therapeutic
e with PAD, by facilitating favorable changes in calf skeletal muscle and by increasing calf
flow-mediated dilation, calf skeletal musclebiopsy measures, patient-reported walking

n mammals the suprachiasmatic nucleus (SCN) in the brain is the primary circadian pacemaker
he goal of this application is to determine how repeated shifts in the light cycle impact

romuscularjunction dysfunction associated with muscle atrophy and frailty in this population.
ieu disruptsmitochondrial and cellular energetics resulting in elevated OS predisposing patients
ephosphorylation and increased OS. Aim 2 will determine the efficacy of global or
d their association withchanges in serial hemodynamic, neurophysiological and biomechanical

nderstood and vastly understudied compared with other comorbidities (i.e. smoking and
y results in ischemic muscle injury and impaired angiogenesis, thereby linking CKD and PAD
t aimed to treat a patient population that currently has few available options.

clock, exists in virtually all cell types in the body. A critical function of the molecular clock is to
al excitability. One goal of this project is to utilize large scale genomic and transcriptomic
our premise that disruption of day- night rhythms through environmental factors leads to altered
bility and increased arrhythmia vulnerability.

hnique?for?combining?electrophysiological?recordings,? high? in? temporal? precision,? with?
er?s? emotional? response,? to? address? the? following? Aims:? (1)? We? characterize? the?
?treatment?efficacy,?a?quantitative?brain-?based?marker?of?emotional?engagement? opens?

t wellunderstood. Individuals living with chronic VLU (CVLU) have a high symptom burden of
ation, and wound microenvironment with wound area and symptoms (PNS and
adults (age >60)who are receiving state of the art, standardized wound treatment biweekly
e a foundationfor developing targeted interventions to address this critical health problem

A similar findingof altered brain delivery in Sly Syndrome compared to wild type mice has
number of animals needed for statisticalcomparisons of brain delivery. This system has a
a better vector distribution. We will identify which wild-type AAV serotypes or capsid mutants
n-human primates (NHP) and in wild type and MPS IIIB affected mice. We will use a novel
IB mouse. We will use day/night activity, hearing, coordination, lifespan, lysosomal storage and

mily of proteins that are constitutively expressed in cells, but whose expression is further, and
is sufficient to cause skeletal muscle atrophy. The objective of the current proposal is to determine in
will determine the mechanisms of this by determining the proteins in each pathway that Hsp70 binds.
n of skeletal muscle mass, and could identify the protein as a novel therapeutic target for muscle

(Real-time Online Assessment and Mobility Monitor). It will offer long-term and
dRecruitment, Retention & Compliance. In the R21 phase, we will create the ROAMM
eses:1) Pre-event patterns of low mobility, disability, fatigue, pain and depressive mood
te patientinteraction, adopting licensing fees, and aligning our services with larger entities to

Clinical studies are often conducted under idealized and rigorously controlled conditions to improve their internal validity and success rates, but compromise their external validity (i.e., generalizability to the target populations). These idealized conditions are sometimes exaggerated and reflected as overly restrictive eligibility c assess the generalizability of a clinical study, so that stakeholders including pharmaceutical companies, policymakers, providers, and patients would be able to understand and anticipate the possible effects of the interventions in the real world. In the past two decades, a large number of studies have assessed generalizability, but two-fold: (1) the lack of evidence to demonstrate their validity, which also leads to the lack of consensus on the best practice for generalizability assessments; and (2) the lack of readily available, well-vetted statistical and informatics tools. Motivated to fill this gap, we propose to first systematically review the extant methods f documentations and tutorials. The success of this R21 project will (1) fill a knowledge gap on the validity and utility of the different generalizability assessment methods; (2) provide an easy-to-use toolbox ctGATE for assessing study generalizability much-needed by the clinical research community; (3) help the clinical researc

38. Project Title: ADVANCING INTERDISCIPLINARY SCIENCE OF AGING THROUGH IDENTIFICATION OF IATROGENIC COMPLICATIONS: THE UF EHR CLINICAL DATA INFRASTRUCTURE FOR ENHANCED PATIENT SAFETY AMONG THE ELDERLY (UF

Leader(s): INGIBJARGARDOTTIR BJARNADOTTIR, RAGNHILDUR ; LUCERO, ROBERT J ;

UNIVERSITY OF FLORIDA

NIH R21AG062884 / (2019-2021)

Iatrogenic conditions are a continuing public health concern, causing death among an estimated two hundred and fifty thousand older adults annually in United States (US) hospitals. Hospital-acquired falls and hospital- induced delirium are among the most common and costly iatrogenic conditions, and their occurrences are link methods. The development of a research data infrastructure that supports the use of text and structured data is critical for a learning health system aimed at improving care and patient outcomes. In this project, we propose to expand the research infrastructure for electronic data-driven knowledge generation through the developm registered nurses' (RNs) progress notes for prediction of hospital-acquired falls. We will employ a combination of supervised and unsupervised text-mining methods to identify text attributes associated with patient falls. We will then leverage a predictive model of patient fall risk factors developed in previous work to generate a into the existing UF Health Clinical Data Warehouse (CDW) infrastructure and test to assess functionality, durability and scalability. In addition, we propose to develop the human resource infrastructure to support data-driven interdisciplinary aging research. This will be achieved by training graduate students in interdisciplinar every day.

39. Project Title: NICOTINAMIDE RIBOSIDE AS AN ENHANCER OF EXERCISE THERAPY IN HYPERTENSIVE OLDER ADULTS: THE NEET TRIAL

Leader(s): MANKOWSKI, ROBERT

UNIVERSITY OF FLORIDA

NIH R21AG064282 / (2019-2021)

ABSTRACTMore than 80% of older adults have hypertension, with higher prevalence of high systolic blood pressure (SBP)putting them at high risk for cardiovascular (CV) disease and death. Because drug therapy that lowers SBP isassociated with side effects such as hypotension, syncope, and kidney dysfunction, there is a g adeninedinucleotide (NAD+), a cofactor for the deacetylase sirtuin1 (SIRT1), may contribute to age-related vasculardysfunction via oxidative stress and reduced nitric oxide (NO). Exercise-induced overexpression of NAD+-dependent SIRT1 improves the bioavailability of NO. Preclinical evidence suggests that poor vascular-f SBP-lowering effect in hypertensive older adults. Initial human clinical trials demonstrated that nicotinamide ribosidesupplementation (1,000 mg/day) was safe and showed a higher potential to reduce SBP and arterial stiffnessin participants with elevated SBP. As we have preclinical evidence that combining NAD+ replenishm center-basedwalking exercise, or (2) the same exercise program combined with placebo, or (3) 1,000 mg/day ofnicotinamide riboside alone. All participants will undergo daytime continuous SBP and arterial-stiffnessmeasurements by pulse-wave velocity at baseline and at 6 weeks. Elevated SBP will then be determined asdaytim Phase III clinical trial in hypertensive older adults. The ultimate goal of this line of research is to findadjuvant strategies to improve the exercise's SBP-lowering effects in older adults.

40. Project Title: DYSREGULATION OF SARCOMERE STABILIZING PROTEINS CAUSE MUSCLE ATROPHY AND WEAKNESS DURING CANCER CACHEXIA

Leader(s): JUDGE, ANDREW ROBERT

UNIVERSITY OF FLORIDA

NIH R21CA194118 / (2015-2018)

DESCRIPTION (provided by applicant): Cachexia is characterized by progressive skeletal muscle and body weight loss and affects up to 80% of cancer patients. This loss of muscle mass contributes to significant muscle weakness and diminished physical function and is associated with reduced tolerance to chemotherapy and i stimulus, and there is speculation that these disruptions may initiate catabolic processes which lead to the muscle atrophy and weakness. Unpublished and preliminary data from our lab has identified that Kyphoscoliosis peptidase (Ky), which is essential to the structural integrity of the sarcomeric Z-disk, and Myocilin (Myoc), v downregulation of Ky and Myoc are causative to the loss of muscle structure leading to muscle wasting and weakness during the progression of cancer cachexia. Unpublished bioinformatics analyses of the -1kb to +1kb proximal promoters of genes significantly downregulated in skeletal muscle of C26 tumor-bearing mice reve activity in skeletal muscle of tumor-bearing hosts is causative in the downregulation of Ky and Myoc, and initiates disruptions in muscle fiber integrity and muscle wasting. Thus, our two specific aims are: Specific Aim 1: To test the hypothesis that the downregulation of Kyphoscoliosis peptidase (Ky) and Myocilin (Myoc) pla muscle wasting and weakness, opening up new avenues for therapeutic interventions.

41. Project Title: MOLECULAR BIOLOGY IN BURNS AND TRAUMA

Leader(s): MOLDAWER, LYLE L

UNIVERSITY OF FLORIDA

NIH T32GM008721 / (1999-2024)

This Ruth Kirschstein NRSA training Program proposes to take primarily surgeons and other critical caremedicine physicians during the second or third year of their general residency programs, and expose them totwo, three and even four years of mentored research in inflammation biology with highly productive basic science research experience. Select trainees will have the opportunity to complete a Ph.D. program in the GraduateSchool in three to four years. Other trainees can participate in graduate certificate programs which are formalcollections of courses that together form a coherent program of study offered through an academic unit. Thistrai vascular injury,delayed wound healing and the burn wound. The faculty will be drawn from funded basic and clinical scientistsin the Surgery, Medicine, Pathology, Aging and Geriatric Research and Molecular Genetics and MicrobiologyDepartments, who will serve as research mentors to the trainees. Clinical mentors from the Jacksonville). Successfulapplicants with the Executive Committee will identify a research and clinical mentor who will help formulate aformal training program and periodic review of the trainee?s progress. Furthermore, trainees are expected toparticipate in basic science seminars in the Institute on Aging, Emerging Pathogens successfully compete fortransitional funding in inflammation research and become leaders in academic surgery.

42. Project Title: THE ENRGISE STUDY

Leader(s): PAHOR, MARCO ; AMBROSIUS, WALTER T ;

UNIVERSITY OF FLORIDA

NIH U01AG050499 / (2015-2019)

DESCRIPTION (provided by applicant): Growing evidence from our group and others shows that low-grade chronic inflammation, characterized by elevations in plasma C-reactive protein, tumor necrosis factor alpha, and particularly Interleukin-6 (IL-6), is an independent risk facto o disability, impaired mobility, and lower w interventions for preventing major mobility disability by improving or preserving walking ability. We have maximized the public health impact of our proposed interventions by selecting interventions that are safe, tolerable, acceptable, and affordable for vulnerable older persons. Based on an extensive literature review, we prop impairment, as measured by slow gait speed and self-reported mobility difficulty, and who have elevated levels of IL-6, the marker most consistently associated with mobility limitations. Preliminary data regarding feasibility need to be gathered before such a tria can be effectively designed and implemented. We propose to con needed for the ENRGISE pilot and main trials, including the biorepository, and we will develop the materials needed for implementing the trials, including the protocol, manual of operations, data and safety monitoring plan, forms, quality control and quality assurance plan, and recruitment and retention materials.

43. Project Title: UF PASS: REGULATION OF EXERCISE TRANSDUCERS

Leader(s): ESSER, KARYN A

UNIVERSITY OF FLORIDA

NIH U01AG055137 / (2016-2022)

Abstract Exercise is a powerful and pleiotropic physiological stimulus that helps prevent many chronicdiseases and is used as a therapeutic for disease. While the beneficial effects of exercise are extensivelyacknowledged there is still very little understood about the molecular transducers of the systems-wide effects.The goal of support screening of novel transducers to quickly move the field forward.In Phase 1, UF PASS proposes to collect biospecimens for the Chemical Analysis sites following endurance(run-training) or resistance exercise protocols on male and female Fischer 344xBrown Norway rats (F344-BN)at three different ages. To better cap transducersthat function throughout the system to improve the well-established stress tolerance. The goal of these studieswill be to employ high throughput screening technologies to test up to 1500 myokines. We will then usesecondary screening techniques to test 100 candidates from which we will select up to 3 candidates for at 3-4, 16-18, and 27-29 mo.Specific Aim 3: Phase 2 Studies. The goal in Aim 3 is to test myokines as the exercise transducers forimproved stress tolerance.

44. Project Title: MULTIMODAL IMAGING OF BRAIN ACTIVITY TO INVESTIGATE WALKING AND MOBILITY DECLINE IN OLDER ADULTS

Leader(s): MANINI, TODD ; CLARK, DAVID J. ; SEIDLER, RACHAEL D ;

UNIVERSITY OF FLORIDA

NIH U01AG061389 / (2018-2023)

Project Description: Mobility impairments in older adults decrease quality of life and are associated with highsocietal and economic burden. NIH RFA-AG-18-019 solicits applications ??to investigate the central neuralcontrol of mobility in older adults?using innovative and cutting-edge methods.? Current approaches to studyth Wewill achieve this by using innovative mobile brain imaging with high-density electroencephalography (EEG).This approach relies upon innovative hardware and software to deliver three-dimensional localization of activecortical and subcortical brain regions with high spatial and temporal resolution during walking. The resu walking explainsmobility decline. In both cross sectional and longitudinal designs, we will determine whether poorer walkingperformance and steeper trajectories of decline are associated with the Compensation Related Utilization ofNeural Circuits Hypothesis (CRUNCH). CRUNCH is a well-supported model of brain activity tasks of increasingcomplexity. When the ceiling is reached, performance suffers. The RFA also calls for proposals to?Operationalize and harmonize imaging protocols and techniques for quantifying dynamic gait and motorfunctions?. In accordance with this call, our second aim is to characterize and harmonize high-density EE amajority of the objectives in NIH RFA-AG-18-019 and will identify the neural correlates of walking in olderadults, leading to unprecedented insight into mobility declines and dysfunction.

45. Project Title: MOTRPAC CONSORTIUM COORDINATING CENTER

Leader(s): PAHOR, MARCO ; MILLER, MICHAEL E. ; REJESKI, WALTER JOHN ; TRACY, RUSSELL P ;

UNIVERSITY OF FLORIDA

NIH U24AR071113 / (2016-2022)

SummaryPhysical inactivity is a major public health challenge underlying a broad range of health problems at all ages.While physical activity (PA) has shown to produce relevant health benefits, the underlying molecularmechanisms are poorly known. The coordinated effort of clinical and animal studies supported bybioinform pivotal role in ensuring the cohesion of the MoTrPAC by enhancing communication and integration across allstudy components, including the Clinical Sites, the Preclinical Animal Study Sites, the Bioinformatics Center,the Chemical Analysis Sites, and the various study committees. The CCC will develop strategies and strateg goals andmaximize the progress and productivity of the MoTrPAC, the CCC will promote team science, team leadership,and innovative leadership approaches across all study components. Strategic planning that follows theprinciples of the dynamic theory of strategy will be fostered to evaluate alternative approaches, maintain the DataManagement, Analysis, and Quality Control Center (PI Dr. Miller), the Biospecimens Repository (PI Dr. Tracy),and the Exercise Intervention Core (PI Dr. Rejeski). The CCC will employ innovative project management toolsand web-based tracking of exercise adherence and diet, and will capitalize on the outstanding t multidisciplinary teams.The CCC will ensure and promote the continued success of the MoTrPAC in advancing knowledge about themolecular changes that occur in response to PA, and relating these changes to the health benefits of PA.

46. Project Title: 1/2 + PROMOTE WEIGHT LOSS IN OBESE PAD PATIENTS TO PREVENT MOBILITY LOSS: THE PROVE TRIAL

Leader(s): MCDERMOTT, MARY MCGRAE

NORTHWESTERN UNIVERSITY AT CHICAGO

NIH UG3HL141729 / (2019-2020)

PROJECT SUMMARY for the PROVE Trial More than 65% of people with lower extremity peripheral artery disease (PAD) are overweight or obese.People with PAD who are overweight or obese have greater functional impairment and faster functional declinethan normal weight people with PAD. Walking exercise is first li will improve walking ability more than EX alone. However, effects of intentional weight loss in overweight/obese people with PAD are unknown and maynot be beneficial if weight loss exacerbates PAD-related sarcopenia. Behavior change that achieves sustainedWL is challenging in older obese people with chronic disease. T achieved mean weight loss of 5.6 pounds andimproved the 6-minute walk by 64.1 meters in eight PAD participants with BMI> 28 kg/m2. Preclinical evidence shows that obesity is associated with impaired limb perfusion. Human evidenceshows that obesity is associated with reduced skeletal muscle mitochondrial biogenesis a University, andthe U. of Minnesota. Our primary outcome is change in six-minute walk distance at 12-month follow-up.Secondary outcomes are change in 6-minute walk distance at 6-month follow-up and change in exerciseadherence, physical activity, patient-reported walking ability (measured by the Walking ImpairmentQue arecorrect, the PROVE Trial will have a major public health impact by preventing functional decline and mobilityloss in the large and growing number of people with PAD who are overweight or obese.

riteria. Certain population subgroups are often excluded with unjustified criteria and are subsequently underrepresented. Older adults have been especially underrepresented in cancer studies. The underrepresentation of these population subgroups reduces the treatment effects and increases the likelihood of adverse outcomes in diverse pc mostly were after the fact, ad hoc, not systematic, and focused on specific diseases and sets of trials without a formalized approach. So far, there is a significant knowledge gap between the available methods for generalizability assessment and their adoption in research practice. Most generalizability assessments have been conducted as r generalizability assessments, and then use a data-driven strategy to reproduce, evaluate, and compare these methods with our unique data resource, the OneFlorida Data, one of the 13 PCORI-funded Clinical Data Research Networks that contains linked EHRs, claims, and cancer registry data for ~15 million Floridians. We will develop hers choose the most appropriate generalizability assessment methods with readily available implementations; and (4) build a body of evidence to support the development of an eligibility criteria design tool for optimizing study generalizability at the study design phase.

-ECLIPSE)

ked to each other. Advances in computing technology and availability of electronic data presents opportunities to more accurately identify identifying patients at risk of suffering a hospital-acquired fall or hospital-induced delirium. Clinical data is now being captured electronically for about 80% of the US population. Approximately 75- ent of the University of Florida (UF) EHR Data Infrastructure for Patient Safety among the Elderly (UF-ECLIPSE). The long-term goal of our research program is to enhance the safety of hospitalized older adults by reducing iatrogenic conditions through an effective learning health system. We plan to carry out the following aims: Spec composite model of text and structured data to predict the odds of a patient falling. Specific Aim 2 (R33 Phase): Determine and evaluate the structural and human resources of an expanded research-data infrastructure to support sustained interdisciplinary aging studies. We will develop and pilot test text-mining pipelines to generate a pr y data science for aging research. The UF-ECLIPSE research team will be among the first to implement and test an integrated data repository that utilizes nurse-generated structured and text data to support a learning health system. This study will create important new research data infrastructure, and will be a model for health care organ

reat need foreffective lifestyle SBP-lowering interventions for the older population that can replace drug therapy. Whileaerobic exercise is a recommended lifestyle intervention for controlling SBP and preventing CV diseasenaturally, in older adults it has been shown to be less effective in vascular-tissue remodeling because ofarterial sti unctionimprovement in response to exercise in older mice is caused by insufficient NAD+ levels to stimulate SIRT1activity. Importantly, replenishment of NAD+ levels induced vascular remodeling, improved vascularfunction, and reduced SBP in mice. An objective of this study, therefore, is to test a combination of aerobicexercise and ent withexercise is an ideal strategy for improving vascular function, our central hypothesis is that the intervention ofaerobic-exercise training combined with nicotinamide riboside supplementation will reduce SBP inhypertensive older adults more effectively than will exercise alone. We will enroll 45 participants 65 years andolder into me average above 130 mmHg, measured by the 24-hour blood-pressure device. To our knowledge, thisstudy will be the first attempt to enhance exercise therapy with nicotinamide riboside in hypertensive olderadults. We believe that nicotinamide riboside is ?the missing piece of the puzzle? in improving vascularremodeling and SBP ma

ncreased complications from surgical/radiotherapeutic treatments. Consequently, cachexia decreases both quality of life and survival time in cancer patients and cachexia itself is responsible for up to 30% of all cancer-related deaths. Interestingly muscles from preclinical models of cancer cachexia as well as cachectic human cancer pati which is important to the sarcolemmal dystrophin associated protein complex (DAPC), are highly downregulated at the mRNA and protein level at time points which precede and parallel muscle atrophy and weakness during tumor progression. Moreover, preliminary data show that overexpression of Ky in the muscles of tumor bearing m aled a conserved consensus binding motif for myocyte enhancing factor-2 (MEF2) among the top two most commonly shared motifs. Moreover, both the Ky and Myoc gene promoters contain conserved MEF2 binding motifs. This observation, coupled with the findings that MEF2 protein c (MEF2c) is decreased at the mRNA and protein lev y causative roles in the cancer-induced loss of muscle fiber integrity and the initiation of muscle wasting. Specific Aim 2: To test the hypothesis that loss of MEF2c transcriptional activity is causative in the cancer-induced downregulation of Ky and Myoc and initiates muscle wasting. The results of these studies will provide new insight

mentors focused on inflammation-related topics. Four training positions are requested. The overall researchprogram will focus on mastery of molecular biology, functional genomics and gene regulation, as it appliesbroadly to inflammation research. Although the bulk of the training program will be in the laboratory of anexperienced res ning program takes advantage of the unique strengths of the College of Medicine in the expanding field offunctional genomics and molecular biology, as well as the existing collaborations between basic scientists andclinicians committed to the training of future clinical academicians. The interface between molecular biology andinflamm Surgery, Medicineand Pathology Departments will interact with the trainees and the research faculty to assure that the traineesare being exposed to clinically-important issues in inflammation research. Overall direction of the program willrest with the Program Director and an Executive Committee. Candidates for the fellowship are rec Institute and GeneticsInstitute, and in their own basic science departments, as well as laboratory research meetings. They will also beexpected to attend clinical seminars, including Surgery and Critical Care Medicine Grand Rounds and theDepartment of Surgery Academic Research Conference. Based on our past experiences, it is antici

/alking speed. Low-grade chronic inflammation is a modifiable risk factor. However, it is unknown whether interventions that reduce the levels of inflammatory markers per se improve mobility, or avert decline in mobility in older persons. To address this gap in evidence we propose the randomized clinical trial ENRGISE (ENabling Re pose to test the efficacy vs. placebo of the angiotensin receptor blocker losartan and omega-3 polyunsaturated fatty acids in the form of fish oil, alone and in combination. Both angiotensin receptor blockers and omega-3 polyunsaturated fatty acids have shown to reduce IL-6 in clinical trials and preliminary data suggest that they may imp duct a feasibility phase that includes performing meta-analyses of existing trials and cohorts, and conducting a pilot trial to assess the effects of the interventions on several inflammatory markers and walking speed. This will allow us to refine the design, recruitment yields, target population, adherence, retention, tolerability, sample-size,

this University of Florida Molecular Transducers of Physical Activity Preclinical Animal StudySites application (UF PASS) is to conduct experiments in animals that will provide tissues/blood (i.e.biospecimens) to the Chemical Analysis Sites for identification of molecular transducers induced by definedmodels of physical activity from ture the dynamics of the exercise/adaptation responses we propose to:1) Collect biospecimens at 5 selected timepoints following an acute bout of exercise on na?ve and trained rats;2) Collect biospecimens following short duration training (after 5 bouts) and 3) Collect biospecimens followinglong-term (8 weeks) training.For Phase 2, ou in vivotesting. The results of the experiments in Aim 3 will provide molecular evidence identifying a set of transducers,released from muscle, that are necessary for exercise induced systemic health. The goals of the UF PASS willbe pursued by the following Specific Aims:Specific Aim 1: Center Coordination Phase.Specific Aim 2: Pha

e neural control of walking are limited by either the inability to measure people during walking (functionalmagnetic resonance imaging, fMRI) or the inability to measure activity below the cortex (functional near-infrared spectroscopy, fNIRS). We assert that a full and accurate understanding of the neural control of walkingin older adult It isunprecedented insight into the neural control of walking. Here, our overarching objective is to determine thecentral neural control of mobility in older adults by collecting EEG during walking and correlating these findingswith a comprehensive set of diverse mobility outcomes (clinic-based walking, complex walking and community patterns that areseen when older individuals perform tasks of increasing complexity. CRUNCH describes the over-recruitmentof frontoparietal brain networks that older adults exhibit in comparison to young adults, even at low levels oftask complexity. CRUNCH also describes the limited reserve resources available in the older brain. T Gduring walking with fNIRS (during actual and imaged walking) and fMRI (during imagined walking). This willallow us to identify the most robust CRUNCH-related hallmarks of brain activity across neuroimagingmodalities, which will strengthen our conclusions and allow for widespread application of our findings. Ourthird aim is to

atics and chemical analyses will achieve the Molecular Transducers of Physical Activity Consortium(MoTrPAC) goals of assessing the molecular changes that occur in response to PA. The ConsortiumCoordinating Center (CCC) for the MoTrPAC will provide support for the organization, administration, planning,standardization, documen jcplanning processes by integrating activities of the MoTrPAC investigators with the input provided by the DataSafety Monitoring Board, the External Scientific Advisors, outside experts, and the NIH. The CCC will facilitateinteractions and communications with junior and senior investigators outside the consortium to maximize theuse thecutting-edge scientific focus, leverage state-of-the-art coordination technologies, anticipate challenges, andmaximize future opportunities to ensure the success of the consortium. The CCC will comprise four integratedcomponents led by four highly qualified PIs who have a long-lasting track record of successfully working insynergy. rack record andexpertise of its investigators in: (a) working together; (b) successfully coordinating, managing, and leadinglarge long-term multicenter clinical trials involving PA and other interventions; (c) implementing rigor andtransparency in research, (d) acquiring, managing, storing and analyzing biological samples; (e) conducting

ne therapy to improve functional performancein PAD. However, our observational longitudinal data show that overweight and obese PAD participants whocombined weight loss with walking exercise had less functional decline than those who walked for exercise butdid not lose weight. Therefore, we hypothesize that among people with herefore, among people with PAD and BMI>28kg/m2, we will test the hypothesis that WL+EX achieves greater improvement in functional performance thanEX alone. Our innovative weight loss intervention uses a group mediated cognitive behavioral framework,connective mobile technology, remote monitoring by a coach, and a calo sd activity. Theseobesity related changes exacerbate the pathophysiology of PAD. Therefore, we hypothesize that weight losswill improve walking ability in part by improving calf perfusion, and increasing calf mitochondrial activity. Wewill randomize 212 participants with PAD and BMI > 28 kg/m2 to one of two groups for 12 month; stionnaire), and quality of life (measured by the SF12 Physical Component Score) at 12-month follow-up.Tertiary outcomes include MRI measured calf perfusion, MRI-measured calf muscle quantity and fatabundance, and diet quality. We will perform calf muscle biopsies in 50 participants to measure mitochondrialbiogenesis and activ

pulations when the interventions were moved into clinical practice. It is imperative to rigorously
an ad hoc auditing effort by a third party after the fact. We believe the key barriers are
 an open-source generalizability assessment software toolbox and its accompanying

80% of clinical data is text data which cannot be analyzed using traditional statistical
cific Aim 1 (R21 Phase): Identify and test the feasibility of text-mining pipelines to process
 ediction model of hospital-induced delirium. We will then integrate the developed pipelines
 izations to increase safe effective care for the millions of older adult Americans hospitalized

ffness, resulting in less efficient SBP control. Reduced bioavailability of nicotinamide
 nicotinamide riboside, a compound that replenishes NAD+ levels, to optimize exercise's
 either: (1) 1,000 mg/day of nicotinamide riboside plus 3 days/week of supervised,
 nagement in older adults. Preliminary evidence from this pilot study may support a full-scale

ents show disruptions in sarcomere and myofiber membrane integrity despite the lack of an injury
 nce inhibits muscle fiber atrophy. These observations support our first hypothesis that the
 el in tumor bearing mice, supports our second hypothesis that loss of MEF2c transcriptional
 into transcriptional mechanisms involving protein downregulation which initiate cancer-induced

earch mentor, trainees will be expected to participate in didactic experiences that complementtheir
 ation research will be targeted to trauma, sepsis syndromes, ischemia/reperfusion injury,
 uitednationally and from the University of Florida College of Medicine (Gainesville,
 ated thatsuccessful graduates of this training program will possess sufficient research skills to

duction of low-Grade Inflammation in SEniors) to test the ability of anti-inflammatory
 rove physical function. We plan to recruit older persons who are at risk for, or with, mobility
 , and cost for the main ENRGISE trial. We will assemble the multicenter research infrastructure

 tissues that cannot be obtained from humans as well as to conductmechanistic studies that can
 r hypothesis is that factors released from muscle (i.e. myokines) are the molecular
 se 1 Studies. To perform endurance and resistance exercise using male and femaleF344BN rats

 s requires real time measurement of active regions throughout the brain during actual walking.
 mobility measures). Our first aim is to evaluate the extent to which brain activity during actual
 hesefactors cause older adults to quickly reach a ceiling in brain resources when performing
 study the mechanisms related to CRUNCH during walking. Thus, our project will address

 entation, monitoring and reporting activities relating to the MoTrPAC. The CCC will playa
 of the MoTrPAC resources toward achieving the overall research goals. To accomplish these
 . The four CCC components comprise the Administrative Coordinating Center (PI Dr. Pahor),
 animal exercise studies; (f) sharing resources; (g) publishing results; and (h) leading

 PAD who are overweight or obese, aweight loss intervention combined with exercise (WL+EX)
 rie restricted DASH-derivedOMNIHeart diet. In a seven week pilot study, our intervention
 s:WL+ EX vs. EX alone. Participants will be randomized from Northwestern University, Tulane
 rity, capillary density, inflammation, and senescent cell abundance. If our hypotheses

UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO
Claude D. Pepper Older Americans Independence Center

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Principal Investigator

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Co-PI

Marisa Lopez-Cruzan   210 363 3066   lopezcruzan@uthscsa.edu
Program Administrator

CENTER DESCRIPTION

A core tenet of the geroscience concept is that multiple human diseases arise from aging itself. Thus, the central theme of the San Antonio (SA) Claude D. Pepper Older Americans Independence Center (OAIC) is translational geroscience – moving research on the basic biology of aging from the laboratory bench to the clinic, with the overarching goal of promoting healthy aging and developing desperately needed treatments, mainly pharmacological, for aging-related diseases. This goal is achieved through the following Aims:

1) Expand the knowledge base in translational geroscience by catalyzing transformative research;

2) Create a cadre of multidisciplinary early-stage investigators with customized expertise in translational geroscience;

3) Serve as a resource and partner to investigators from other OAICs and institutions;

4) Provide intellectual leadership, disseminate knowledge, and stimulate discussion on translational geroscience-related themes.

CORES

Leadership and Administrative Core (LAC)

Leader 1: Elena Volpi, MD, PhD   volpi@uthscsa.edu

Leader 2: Randy Strong, PhD   strong@uthscsa.edu

The Leadership and Administrative Core (LAC) fosters integration of aging-related basic and clinical sciences, catalyzes scientific discoveries, promotes education and mentorship, and partners with other scientists and the community at large to develop novel interventions to improve the health, quality of life, and independence of older Americans. The LAC monitors, stimulates, sustains, evaluates, and reports progress toward our OAIC's goal through the following Specific Aims:

1. Provide logistical support and promote operational cohesiveness to the SA OAIC.
2. Promote research protocol adherence and maintain regulatory compliance with university and governmental policies for the responsible and ethical conduct of OAIC-supported research.
3. Disseminate the scientific innovation accomplished by OAIC investigators, inside and outside our institution, regarding the latest knowledge on geroscience and promotion of healthy life extension.
4. Stimulate and facilitate interdisciplinary collaboration among OAIC investigators, cores, committees, and projects, to advance basic science in aging biology from the bench to the clinic.
5. Select and monitor pilot and exploratory studies and progress of Scholars aligned with the OAIC theme.
6. Monitor and evaluate OAIC progress, foster institutional collaborations, and leverage resources.
7. Provide programmatic and scientific guidance to training programs, pilot studies, and resource cores (RCs).
8. Participate actively in the national OAIC network to help advance its mission of promoting independence in older Americans.

Research Education Component (REC)

Leader 1: Robert Clark   clarkra@uthscsa.edu

Leader 2: Peter Hornsby, PhD   hornsby@uthscsa.edu

Leader 3: Blake Rasmussen, PhD   rasmussenb@uthscsa.edu

The REC promotes the Aims of the San Antonio Older Americans Independence Center (OAIC) by supporting career development, mentoring, and research training for early-stage investigators to transition to independent research careers. The Aims of our REC are:

Aim1: Oversee the recruitment, selection, monitoring, and evaluation of a highly qualified, dedicated and diverse group of early-career REC Scholars; assisting with their development into clinical and translational scientists in geroscience who can effectively lead and contribute to interdisciplinary research teams.

Aim 2: Provide active multidisciplinary supervising (mentoring) teams that regularly monitor, evaluate, and guide the progress of each REC Scholar through their research and career development programs; Scholars and their mentors will develop individualized structured research education plans with clearly defined responsibilities and milestones based on their investigative needs and focused on cross-training in translational sciences.

Aim 3: Recruit and advance the careers of a diverse cadre of Scholars across multiple dimensions, including women, underrepresented minorities and active-duty military and veterans representative of our patient population to build a geroscience workforce with expertise in medicine, nursing, psychology, pharmacy and other health care disciplines necessary for advancing geriatric care in a team science environment.

Aim 4: Promote cross-fertilization and assure integration of the REC participants' career development and activities with a) all San Antonio OAIC programs and b) the national OAIC network.

Pilot and Exploratory Studies Core (PESC)

Leader 1:   Kelly Reveles, PharmD, PhD, BCPS   revelesk@uthscsa.edu

Leader 2:   Randy Strong, PhD   strong@uthscsa.edu

The PESC plays a key role in the San Antonio OAIC's central theme of translational geroscience by supporting projects that move research on the basic biology of aging from the laboratory bench to the bedside, in order to extend healthy life expectancy. The PESC will provide merit-based support for rigorously designed pilot studies that test both the efficacy and side effect profiles of promising pharmacologic, as well as nonpharmacologic cell-based and behavioral interventions, in pre-clinical marmoset models and early human clinical studies. The PESC will strive to achieve its objectives through the following specific aims:

Aim 1: To promote innovative, collaborative, multidisciplinary research to test interventions designed to extend healthy life expectancy, both in early human trials and in non-human primate marmoset models.
Aim 2: To work closely with the Resource Cores and Research Education Component to provide infrastructure, scientific support, and funding for innovative pilot proposals from mentored junior faculty investigators, as well as established researchers.
Aim 3: To encourage pilot studies that will develop and apply novel methods and technologies.
Aim 4: To sustain effective processes to solicit, review, and fund pilot projects, as well as ensure study completion, robust tracking of downstream impact, and optimal dissemination and implementation.

Preclinical Research Core (RC1)

Leader 1:   Adam Salmon, PhD   salmona@uthscsa.edu

Leader 2:   Cory Ross, PhD   cross@txbiomed.org

RC1 plays a central role in the SA OAIC by providing the knowledge, skills, and technical support to assist OAIC investigators in using the common marmoset (Callithrix jacchus) as a pre-clinical model for aging interventions (mainly pharmacological). RC1 achieves its mission through the following Specific Aims:

1) To provide OAIC investigators access to a unique colony of aging marmosets.

2) To provide resources required for studying effects of aging interventions on marmoset healthspan.

3) To provide and maintain a bank of tissues from marmosets across the age range.

4) To provide services to assess analytical pharmacology in marmosets.

5) To support the research training and dissemination missions of the OAIC.

Clinical Research Core (RC2)

 Leader 1:   Elena Volpi, MD, PhD   volpi@uthscsa.edu

The overarching goal of RC2 is to offer comprehensive, centralized, clinical trial support for study design, regulatory compliance, recruitment, retention, assessment, procedures, pharmacology, and data management. RC2 achieves its mission through the following Aims:

1) Provide expertise and advice for investigators to plan and design innovative clinical studies to rigorously
test interventions to improve healthspan;
2) Enhance the SA OAIC support infrastructure to ensure successful subject recruitment and safe and ethical conduct of all OAIC-supported clinical studies;
3) Catalyze translational human studies and trials through provision of comprehensive core services;
4) Provide analytical and clinical pharmacology expertise supporting drug pharmacokinetic, and pharmacodynamic analyses as well as toxicity and safety assessment;
5) Disseminate to the lay public and scientific community the latest research on geroscience-related health promotion and the importance/relevance of translational geroscience research; and
6) Support training in translational geroscience for early-stage faculty and those new to clinical research.

Trial Design and Integrative Informatics Core (RC3)
Leader 1:   Jonathan A. L. Gelfond, MD, PhD   gelfondjal@uthscsa.edu
Leader 2:   Meredith Zozus, PhD   zozus@uthscsa.edu

The goals of RC3 are to provide biostatistical collaboration and expertise, as well as centralized research information services to ensure ready access to superior data quality for SA OAIC members. The Core will greatly facilitate data sharing and integrated analyses within the OAIC. Importantly, RC3 develops and implements unique services within UTHSCSA, capitalizing on its members' biostatistical and informatics expertise in aging-related research. RC3 brings these substantial resources to support the SA OAIC through these Specific Aims:

Aim 1: Trial design: Provide biostatistics and informatics support and expertise for the OAIC, including: study design, power analysis, and planning; protocol development; and EHR-based feasibility analysis.

Aim 2: Trial conduct, reporting, and integrated analysis: Provide OAIC clinical trials with advanced research informatics tools to support the conduct, analysis, and reporting of clinical studies.

Aim 3: Training and education: Provide expertise, education and hands-on training in the collection, management, and analysis of data in translational geroscience, and analytics mentoring for OAIC trainees.

Aim 4: Developmental projects (DPs) and novel informatics methodology: 4A. Create a database of geroscience-focused clinical trials to identify promising therapeutics and sensitive/specific aging-related biomarkers (DP4). 4B. Develop and validate predictive algorithms to identify cohorts within large databases that both meet trial criteria and are likely to enroll efficiently (DP5).

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications
Jamie Walker, MD Assistant Professor of Pathology / UTHSCSA <u>Establishing a San Antonio Longevity and Successful Aging Cohort</u> The goal is to establish a successful aging cohort where we will recruit these resistant and resilient individuals and learn their secrets of healthy aging. We will be studying both the physical and cognitive aspects of aging and how these interact.	2021-2023 / 34 (total) 12 (1st/Sr)
Juan Pablo Palavicini, PhD Assistant Professor of Medicine, Diabetes Division / UTHSCSA <u>Effects of mTOR inhibition on central and peripheral ceramide metabolism in old marmosets and cognitively impaired human subjects</u>	2021-2023 / 32 (total) 10 (1st/Sr)
Tiffany Cortes, MD Assistant Professor of Medicine, Division of Endocrinology / UTHSCSA <u>The Effect of GLP1 Receptor Agonists on Physical Function, Body Composition, and Biomarkers of Aging in Older Overweight/Obese Adults with Insulin Resistance</u>	2021-2023 / 11 (total) 2 (1st/Sr)

Past Scholars

Mitzi Gonzales, Biggs Institute, UT Health Science Center San Antonio (2019-2021)
Jia Nie, Barshop Institute, UT Health Science Center San Antonio (2019-2021)
Rozmin Jiwani, School of Nursing, UT Health Science Center San Antonio (2019-2021)
Gustavo Almeida, UT Health San Antonio (2020-2022)
Christopher Shannon, Department of Medicine, UT Health San Antonio (2020-2022)

PILOT/EXPLORATORY PROJECTS (12 Pilot Projects Listed)

1. Project Title: **Effect of aging on hepatic steatosis in marmosets: A model of non-alcoholic fatty liver disease (NAFLD)**

Leader: **Amrita Kamat, PhD**

The objective of the proposed study is to investigate for the first time whether there are age-related changes in hepatic fat accumulation, a hallmark of NAFLD, in marmosets. We hypothesize an age-associated increase in hepatic steatosis and alterations in serum lipid profile in the marmoset model. To test our hypothesis, we propose the following Aims.

Aim 1) To investigate whether hepatic fat accumulation increases with age in marmosets. In this aim, we will measure liver and abdominal fat in young and old male and female marmosets using magnetic resonance imaging (MRI) and spectroscopy (MRS). We will also utilize diffusion-weighted imaging (DWI) which is an emerging tool to evaluate liver fibrosis.

Aim 2) To elucidate whether there are changes in serum lipid profile with age in marmosets. A serum lipidomic profile will be determined and evaluated to look for significant changes in the lipids with aging. To investigate associations between hepatic fat accumulation and cardiovascular health, blood pressure measurements will also be conducted.

2. Project Title: **Effect of SGLT2 inhibition on aging-related biomarkers in older obese adults with pre-diabetes**

Leader: **Carolina Solis-Herrera, MD; Curtis Triplitt, PharmD.**

Inhibitors of the sodium-glucose co-transporter (SGLT2) are FDA-approved for the treatment of type 2 diabetes (T2DM). Their mechanism of action involves lowering of blood glucose concentration secondary to increased glucose excretion of glucose by the kidney. These drugs also cause significant improvements in body weight, blood pressure and cardiac function. Based on these pleiotropic effects, including its calorie restriction-mimetic properties, we hypothesize that SGLT2 drugs will impact several markers related to aging, including reductions in oxidative damage to DNA and proteins, DNA methylation, advanced glycation end products-receptor for AGE (AGE-RAGE), cellular senescence, and improvements in mitochondrial function.

Aim 1: To determine whether SGLT2 inhibitors improve biomarkers of aging in older obese adults with pre-diabetes
Aim 2: To determine whether changes in aging-related biomarkers are linked to changes in glucose metabolism and healthspan.

3. Project Title: **Differential effect of glucose regulating drugs on the onset and progression of frailty: healthcare analytics meets aging research**

Leader: **Tiffany Cortes, MD; Alex Bokov, PhD**

The purpose of this proposal for the 2021 San Antonio Calude D. Pepper Older American Independence Center Pilot and Exploratory Studies Core Pilot application is to understand the factors that lead and the effect of anti-hyperglycemics on frailty progression and incidence in older adults with diabetes. Briefly, our specific aims are: (1) Examine predictors of frailty progression in older adults with Type 2 diabetes from our UT Health San Antonio/University

Hospital patient population. (2) Determine the effect of timing of metformin initiation and different classes of diabetes medication on frailty in older adults with Type 2 diabetes. Analyses will be conducted in older adults with well controlled diabetes who are either prescribed metformin alone or no drug treatment (Aim 2a) and in patients who have been prescribed at least one additional antihyperglycemic agent to manage their diabetes (Aim 2b). a. Compare the trajectories of frailty in older adults with well-controlled type 2 diabetes (HbA1c ?7.5%) on metformin monotherapy versus no anti-hyperglycemic agents in the UT Health San Antonio/University Hospital population over four years. b. Compare the trajectories of frailty among older adults with type 2 diabetes who are prescribed metformin monotherapy compared to those prescribed metformin plus a second line antihyperglycemic agent. We hypothesize that hyperglycemia, adiposity and increased inflammation will accelerate frailty progression in older adults with diabetes (Aim 1).

4. Project Title: **Development of marmoset age-dependent iPSC line resources to determine single cell transcriptome and regulome atlas**

Leader: **Marcel Daadi, PhD**

With a significant gap between preclinical success and clinical failure and the stagnant development of effective treatments for age-associated diseases, it is essential to develop relevant and reliable biological materials with information resources to guide the development of novel groundbreaking therapies. We propose to generate high quality validated induced pluripotent stem cell (iPSC) from marmosets at two ages, young adult and aged, to be used to conduct comprehensive characterization of the effect of donor age on these cells, at the single cell level. We will generate a single-cell transcriptome and regulome atlas of gene regulatory networks in marmosets that's age-specific. These studies will determine for the first time whether age of donor significantly affects outcomes, which will be invaluable for developing models of age-associated biological variations towards understanding age-associated disease pathogenesis and development of novel interventions. IPSCs offer powerful model systems, including standardized organ and cell-specific assays to understand organ-specific responses to aging and for screening drugs or vaccines. Looking forward, iPSCs have the potential to be powerful translational interventions to improve or reverse numerous age-related pathologies and diseases. This proposal will be the initial step in understanding what role age may play in development of potential iPSC-derived treatment options. In Aim 1 we will generate, in vitro characterize and authenticate iPSC lines from young adult marmosets 4-6 year old (3 males, 3 females) versus aged marmosets >10 year old (3 males, 3 females). We will compare age-related changes in the mitochondrial functions and cellular resilience in a fluorescent-based high throughput-screening assay. The iPSC lines will be generated from skin biopsies or blood from live animals and thus will require no animal euthanasia. In Aim 2 we will use high-resolution single-cell RNA sequencing and single-cell ATAC sequencing on the iPSC lines and iPSC-derived brain organoids to generate a single-cell transcriptome and regulome atlas of age-associated gene regulatory networks that will serve as a blueprint for novel discoveries and interventions relevant to human aging. When complete, these resources will for the first time uncover whether age of donor significantly alters iPSC in marmosets. As potential project extensions, these data will be used, in collaboration between Daadi's and Salmon's lab in high throughput screening assays for anti-aging small molecules. The proposed project will develop into broadly applicable and invaluable resources stimulating new collaborations to expedite translational research and discoveries of novel insights into the human aging, health and diseases.

5. Project Title: **Direct measurement of high?energy phosphate compounds in breast cancer survivors in response to exercise ± creatine supplementation**

Leader: **Darpan Patel, PhD; Geoffrey Clarke, PhD**

Individuals with breast cancer are at high risk for skeletal muscle wasting that may be exacerbated by chemotherapy or tumor-related factors. Given the implications of treatment toxicities in relation to muscle mass, identifying strategies to enhance muscle post treatment are required. Exercise after treatment has been found to be beneficial in rehabilitating breast cancer survivors post chemotherapy, helping improve muscle strength, physical function and quality of life. However, fatigue can impair adaptations to exercise. Fatigue in breast cancer survivors is hypothesized to be associated with reductions high energy phosphates leading to reduced intramuscular adenosine triphosphate. Creatine is one of the most widely studied supplements with research demonstrating its efficacy in augmenting training adaptations such as improved strength and physical function in a variety of healthy populations. In cancer-related physical impairments, supplementing creatine phosphate may promote muscle hypertrophy, strength and endurance; reversing the deleterious effects of chemotherapy observed in this population. No studies to date have been conducted in breast cancer patients. The primary objective of this proposal is to is to test the hypothesis that creatine phosphate supplementation will increase high energy phosphates in vivo and accelerate adaptations associated with exercise in breast cancer survivors that have recently completed chemotherapy. The secondary objectives are to (1) compare in vivo high energy phosphate concentrations in breast cancer survivors compared to age-matched controls; (2) determine if high energy phosphate concentrations are associated with muscle cross-sectional area, body composition or physical function; and (3) determine the effects of creatine phosphate supplements in modulating strength and physical function in cancer survivors. To test the primary objective's hypothesis, we will conduct an open-label, randomized controlled trial of exercise ± creatine phosphate supplementation, enrolling 15 breast cancer survivors into each arm of the study (30 breast cancer survivors in all). All participants will complete 12 weeks of exercise, 3 times per week, administered virtually via Zoom. Creatine phosphate supplementation will be administered at 20 grams per day for 7 days (loading phase), later reduced to 5 grams per day for the subsequent 11 weeks (maintenance phase). To complete the secondary objectives of this study, we will conduct a cross-sectional study comparing in vivo high energy phosphate concentrations, body composition and physical function in the 30 breast cancer survivors recruited for the clinical trial to 30 age-matched controls.

6. Project Title: **Mechanisms to Reduce Mental and Physical Fatigue Following Diet and Exercise Training in Older Adults**

Leader: **Monica Serra, PhD; Jason O'Connor, PhD**

Fatigue is a strong predictor of negative health outcomes in older adults. Tryptophan, an essential amino acid, may play an integral role in fatigue progression. The accumulation of oxidative metabolites of tryptophan metabolism (i.e., kynurenines) is strongly associated with fatigue. Reductions in fatigue observed with exercise training appear to be mediated by skeletal muscle peroxisome proliferator-activated receptor-? co-activator-1? (PGC-1?), inducing a shift of kynurenine to kynurenic acid. This is catalyzed by kynurenine aminotransferase (KAT) enzymes, which precludes oxidative kynurenine metabolism and its. However, we find that subjects participating in exercise training often continue to report fatigue after the intervention,

suggesting a need to identify additional methods to maximize the fatigue response to exercise. In the past two decades, numerous studies have shown the advantageous effects of branched-chain amino acids (BCAAs) on exercise performance. Further, studies in animal models suggest that BCAAs decrease the transport of tryptophan and its metabolites into the CNS because BCAAs and tryptophan compete for the same carrier system. Thus, combining BCAA with exercise may synergize to divert metabolism away from formation of neurotoxic tryptophan metabolites with known deleterious effects on mental and physical fatigue. This randomized pilot examines the influence of systemic and skeletal muscle tryptophan metabolism on mental and physical fatigue following exercise training with and without BCAA supplementation in fatigued older adults. Our central hypothesis is that eight weeks of BCAA added to exercise will increase expression of KATs shifting kynurenine metabolism towards enhanced synthesis of kynurenic acid, thereby reducing fatigue. Aim 1) Evaluate the impact of EX+PLA vs. EX+BCAA on changes in mental fatigue, in association with changes in systemic and skeletal muscle tryptophan metabolism. We hypothesize that EX+BCAA will result in greater increases in PGC-1?, KATs, and kynurenic acid and decreases in kynurenine in plasma and skeletal muscle, leading to declines in mental fatigue measured by Brief Fatigue Inventory. Aim 2) Determine the effects of EX+PLA vs. EX+BCAA on changes in physical fatigue, in association with changes in systemic and skeletal muscle tryptophan metabolism. We hypothesize that EX+BCAA will result in greater changes in tryptophan metabolism (as outlined in Aim 1), leading to improvements in physical fatigue measured by aerobic capacity and strength. The discovery that kynurenine concentrations are associated with fatigue and are responsive to BCAA supplementation during exercise training could have important implications for the development of future interventions, both lifestyle and pharmacologic, to treat fatigue in older adults.

7. Project Title: **Improvement in vestibular function using mitochondrial antioxidant therapy**

Leader: **Brian Perry, MD**

This project proposes to determine if daily supplementation with alpha lipoic acid (ALA) and Co- Q 10 can improve or stabilize vestibular function in an elderly population as determined by rotational chair testing. Our hypothesis is that the use of dietary supplementation with alpha lipoic acid and Coenzyme Q10 (CoQ-10) will improve vestibular function in older adults. To test our hypothesis, we propose the following Aims. Aim 1. To determine if supplementation with known mitochondrial antioxidants (alpha lipoic acid and CoQ-10) will stabilize or improve vestibular function in older adults. Aim 2. To demonstrate that those individuals who are not provided supplementation with alpha lipoic acid and CoQ-10 will have a decline in vestibular function. Aim 3. To demonstrate a reduction in falls in the group provided with mitochondrial antioxidant therapy compared to the control group.

8. Project Title: **Nutritional optimization and bone health management for older adults undergoing hip fracture: a pilot study.**

Leader: **Boris Zelle, MD**

The overall objective of this pilot study is to examine the feasibility of a best practice protocol for optimization of nutrition and bone health in these patients. The rationale for our proposal is that implementing a feasible perioperative nutritional and bone health intervention will inform future clinical trials and request for extramural funding. We will pursue the following two specific aims: Aim 1. Test the feasibility of a perioperative nutritional and bone health intervention in aging patients undergoing hip fracture surgery. We hypothesize that a nutritional intervention is feasible within this patient population. Aim 2. Determine the primary efficacy of the perioperative intervention to improve surgical outcomes in aging patients undergoing hip fracture surgery. We will use the pilot data to calculate the estimated magnitude of potential impact on select surgical outcomes to be used for future clinical trials.

9. Project Title: **Exploring the effects of blood flow restriction training on neuroplasticity in older adults.**

Leader: **Gustavo Almeida, PhD, PT**

A comprehensive examination of the primary motor cortex-mediated neural mechanisms underlying BFRT is crucial for optimizing therapeutic exercises to maximize CME and gains in neuromuscular performance. Yet, it is still unclear whether BFRT can improve neuromuscular performance by means of eliciting CME in older adults. Thus, the specific aims of our study are Aim 1: To determine the effects of BFRT on CME and neuromuscular performance in older adults. We hypothesize that older adults in the BFRT program (n=10) will show improved CME, gait speed, balance and quadriceps muscle power compared to the low resistance group (n=10). Aim 2: To explore associations between CME and neuromuscular performance in older adults. We hypothesize that change in CME parameters will be positively associated with change in gait speed, balance, and quadriceps muscle power only in the BFRT group.

10. Project Title: **Brain rejuvenation by replacement and enhancement of aged microglia in marmoset models.**

Leader: **Senlin Li, MD**

We hypothesize that the aged marmoset brain can be effectively rejuvenated/restored by replacement and enhancement of the aged microglia population. In this pilot project, we will use a pharmacological approach to test the hypothesis. Signaling through CSF1R is essential for microglia survival. Rapid depletion of microglia can be achieved in adult mice through oral administration of CSF1R inhibitors, without inducing notable compensatory mechanisms or overt phenotypic health abnormalities. A small molecular CSF1R inhibitor PLX3397 (pexidartinib) has been granted US FDA approval as treatment for tenosynovial giant cell tumors, making it advantageous to study translation of CSF1R inhibition toward broader clinical applications. Furthermore, a newer generation CSF1R inhibitor, PLX5622, exhibits both a higher specificity for CSF1R and improved brain penetrance. It is thus conceivable that eliminating age-associated primed microglia and resetting/repopulating the system through CSF1R inhibition could ameliorate age-related cognitive decline. Mouse studies using PLX5622 support this idea. To translate these exciting findings in rodents toward human trials, we propose this pilot study in marmosets with two specific aims. Aim 1: Find an effective dose of PLX5622 in marmosets through pharmacokinetic (PK) study. PK data of PLX5622 in preclinical species (mouse, rat, dog, and monkey) have been well documented in the literature. However, the conversion charts for larger primates (old world monkeys) are not particularly applicable to marmosets (new world monkeys) likely because of their anatomical differences.

Therefore, we propose to obtain the marmoset specific data through a simplified PK study.
Aim 2: Evaluate the effects of PLX5622 therapy on the cognitive abilities of aged marmosets.

11. Project Title: **mTOR inhibition: A novel therapy for reducing age-associated endothelial dysfunction in older subjects**

Leader: **Ellen Kraig, PhD; Dean Kellogg, MD**

With aging, systemic inflammation increases and likely contributes to the development of age-associated pathologies including cardiovascular diseases (CVDs). CVDs are not only cardiac diseases, but also the arterial system and are associated with reduced large artery compliance and reduced endothelial function. Recent work in old (30mo) mice showed that both large vessel compliance and nitric oxide (NO) dependent endothelial function improved with 6-8 weeks of RAPA treatment (3). This application requests funds to determine whether RAPA is similarly able to reverse age-associated endothelial dysfunction in humans. Aim I. Test whether RAPA treatment improves endothelial function in elderly subjects. Plasma from the human RAPA clinical trial (17 RAPA-treated subjects and 14 placebo subjects) will be tested in Dr. Doug Seals' ex vivo assay for endothelial function. The pre-treatment values will be compared to values obtained for the 6-8 week treatment time point in order to detect any change in endothelial function associated with mTOR inhibition. Aim II. Correlate changes in endothelial function with the other general, immune, physical, epigenetic, and cognitive measures already available. To gain insight into the underlying mechanisms regulating RAPA's pleiotropic effects, we will perform a correlation analysis to assess which of the parameters previously measured are coordinately regulated and associated with any detected RAPA-induced change in endothelial function.

12. Project Title: **Aging Biology of Salivary Glands in a Non-human Primate Model**

Leader: **Chih-Ko Yeh, BDS, PhD**

In addition to clinical observations showing that human salivary flow rates decrease with advancing age, histological studies have shown that the secretory units (i.e., acini) in the SG are replaced by non-functional fibrotic and fatty tissues during human aging. Our study of the histomorphological, cellular, and transcriptomic changes that occur in the marmoset SG during aging is critical to our understanding of this NHP's oral gerontology. We hypothesize that the marmoset SG is similar to that of humans and thus represents an appropriate NHP model for studying human SG aging biology. To test our hypothesis, we have developed two Specific Aims: Aim 1. To determine aging-related histological changes in major SGs of the marmoset. Rationale: To establish the relevance of marmosets as a NHP model of human oral gerontology, it is critical to determine if histological changes and loss of acinar cells in the marmoset SG parallel that of humans. Aim 2. To determine how the transcriptome of key SG structures change during marmoset aging. Rationale: Both clinical studies and pre-clinical rodent models indicate that SG progenitors, involved in homeostasis and the injury response, are dysregulated during aging9,10. However, changes in the cell composition and microenvironment of SG tissues during aging have scarcely been investigated. To address this gap, our first aim will identify histomorphological changes occurring in the acinar compartment and within SG regions responsible for maintaining homeostasis or response to injury. The second aim will utilize state-of-the-art single-cell spatial transcriptomics to map and quantify age-related changes in the genome-wide transcriptional profiles of SG

structures[11,12] identified by histology in the first aim.

DEVELOPMENT PROJECTS (5 Development Projects Listed)

1. Project Title: **Comparative assessment of the role of mTOR in cardiac aging**

Leader: **Marc Feldman, MD and Yuji Ikeno, MD, PhD**

Core(s):   Preclinical Research Core (RC1)
         Clinical Research Core (RC2)
         Trial Design and Integrative Informatics Core (RC3)

Study Question: Does rapamycin improve age-related changes in cardiac compliance and reduce fibrosis/collagen?

Preliminary RC2-supported studies using cardiovascular magnetic resonance imaging (CMR) suggest that rapamycin treatment improves diastolic function in healthy older adults (see RC2). Now, this DP will use CMR with late gadolinium enhancement (LGE) to evaluate the effects of 2 months of rapamycin (vs. placebo) on parameters related to cardiovascular aging in 20 healthy adults over 70 years old. CMR data will include measurements of global and regional ventricular systolic and diastolic function, and LGE measurements of myocardial extracellular volume to assess fibrosis. RC1 will conduct parallel studies in marmosets; from an ongoing study, Dr. Ikeno will quantify collagen and elastin in banked aorta and heart samples from young (

2. Project Title: **Comparative lipidomics of aging**

Leader: **Xianlin Han, PhD,**

Core(s):   Preclinical Research Core (RC1)
         Clinical Research Core (RC2)
         Trial Design and Integrative Informatics Core (RC3)

Study Question: Can changes in the circulating lipidome be developed as a cross-species biomarker of aging, age-related disease, and functional decline?

Diverse lipid signaling pathways can modulate the aging process and systematic analyses of the total lipid structure – the lipidome – in clinically relevant samples can reveal novel mechanisms in aging biology, biomarkers for diagnosis, and targets for therapeutics. As an initial step, using samples provided from generally healthy marmosets (RC1) and humans (RC2) across the normal age range for both species, this DP will assess the effects of age on the plasma lipidome. RC1 will provide plasma from ~20 each young (2-5 yrs.), middle-aged (6-9 yrs.) and old (10+ yrs.) naturally aging marmosets. All animals will be phenotyped by our common battery and resilience assessment. RC3 will assist with statistical comparisons of effects of age on changes and test the extent to which the lipidome reflects health and functional status. Identification of similarities in the aging lipidome across species may elucidate important biomarker targets for geroscience. Reflecting the growing interest in this topic, NIA recently released RFA-AG-20-039, "Lipid Signaling in Healthspan and Longevity Regulation".

3. Project Title: **Development of senescence biomarkers for clinical trials**

Leader: **Paul Hasty, PhD**

Core(s):   Clinical Research Core (RC2)
         Trial Design and Integrative Informatics Core (RC3)

Senolytic/senomorphic drugs hold promise for aging and aging-related diseases. However, clinical trials to evaluate these drugs will require sensitive and specific senescence biomarkers. The goal of this project is to lay the foundation for the development and evaluation of non-invasive measures of cellular senescence. The ongoing repository (STARR) will be leveraged to (i) link known markers of senescence [p16 in CD3+ cells, senescence associated secretory phenotype (SASP) gene expression, and b-gal staining] obtained from tissues (blood, skin, fat) with healthspan outcomes; and to (ii) identify novel senescence biomarkers. This DP will also leverage ongoing and future trials on drugs/interventions with senolytic/senomorphic activity (e.g. dasatinib, polyphenols, metformin, mTOR inhibitors, exercise, weight loss) to determine which biomarkers change with the intervention and can predict functional outcome measures. In the future, this DP will conduct earlyphase precision medicine research on senolytics. For example, it will evaluate whether transcriptomic profiling (by RC3) of adipose tissue obtained in vivo can be used to determine which senolytics are most effective in clearing senescent cells and reducing SASP using in vitro cell functional assays. We could then test if molecular profiling predicts in vitro and in vivo clearance of senescent cells and whether their clearance is linked with changes in putative peripheral (non-invasive) senescence biomarkers and healthspan-related outcomes.

4. Project Title:		**Aging trial meta-analytic database (ATMDb)**
Leader:		**Joel Michalek, PhD**
Core(s):		Clinical Research Core (RC2)
		Trial Design and Integrative Informatics Core (RC3)

RC3 is focused on designing aging-related trials that are rigorous, efficient, feasible, and based on solid preliminary data. This can be challenging because 1) trials with multimorbidity endpoints are novel; 2) biomarkers related to these endpoints are in development; and 3) treatment effect sizes are unknown.

Goal: Through this DP, we will create a database of aging-related clinical trials involving drug classes related to aging, multimorbidity endpoints, and aging-specific biomarkers. The database and research publication will include trials' primary clinical endpoints, anticipated/realized effect sizes, sample sizes, inclusion/exclusion criteria, durations of treatments, classes of compounds, secondary endpoints and related effect sizes.

Methods: RC3 will formally examine translational geroscience-focused trials (completed and in-progress) through a systematic review of the literature and clinicaltrials.gov. This online database of multimorbidity and disease-agnostic healthspan-extending trials will be freely available to all OAICs. The initial trial searches will focus on SA OAIC priority agents such as rapamycin, metformin, senolytics, and other compounds under study by OAIC investigators. This database will also include a meta-analytic perspective on the sensitivity to intervention of the assessed aging biomarkers so that investigators will be informed by empirical evidence in selecting cost-effective assays to measure treatment effects. Initial biomarker searches will focus on SA OAIC priority outcomes, namely frailty, epigenomic aging assays, and senescence markers. Article search criteria will be aided by a research librarian (funded by RC3). Abstraction will be done by Dr. Michalek (Project Lead) and Dr. Gelfond, with quality control and abstraction done in coordination with RC2 lead Dr. Espinoza. RC3 will record trial design consultations and note those consultations that use the meta-analytic database. The web-accessible database will allow for crowdsourcing feedback to evaluate accuracy and adapt

search criteria. Reporting will comply with Preferred Reporting Items for Systemic Reviews and Meta-Analyses guidelines. This systematic review and meta-analysis will inform power calculations and primary/secondary outcome selection in future studies supported by RC3 of the SA OAIC as well as other scientists in the field.

5. Project Title: **Adaptive cohort identification (ACI)**
Leader: **Meredith Zozus, PhD**
Core(s):   Trial Design and Integrative Informatics Core (RC3)

Rationale: To help with recruitment of OAIC studies during the current grant cycle, RC3 investigator Dr. Alex Bokov used the i2b2 application and data warehouse containing de-identified electronic medical record (EMR) data for 1.7 million patients to pull data from diverse sources (Epic Clarity, Sunrise, IDX, etc.), seeking potential participants who meet trial inclusion/exclusion criteria. While this uncovered participants who met highly specific criteria, subjects were not always efficiently enrolled. Goal: This DP will use machine-learning methods to leverage information within the EMR and clinical trial operational databases to more efficiently identify eligible participants who are more likely to enroll in the trial. Methods: Dr. Zozus (Project Lead) and Dr. Gelfond will use machine learning to adaptively model the full i2b2 patient profiles to match participant characteristics with those associated with successful trial enrollment. Using machine-learning tools (KNN, SVM, LASSO, etc.), subjects more similar to enrolled participants will be prioritized for screening. The effectiveness of this algorithm will be measured by a changepoint analysis that compares the enrollment rate (proportion who successfully enroll) before and after project implementation and examines the accrual rates in specific randomization strata to minimize sampling bias. Efficiency will also be measured by in-person screenings per enrolled subjects. We hypothesize that adaptive cohort identification will enhance accrual rates. If our hypothesis is supported, this algorithm will be made available to other scientists in the OAIC network and broad scientific community.

RESEARCH (4 Projects Listed)

1. Project Title: **BINGE EATING SPECTRUM TREATMENT IN OLDER WOMEN (BESTOW): AN INVESTIGATION AND INTERVENTION-TAILORING PROJECT**

Leader(s): **KILPELA, LISA**

UNIVERSITY OF TEXAS HLTH SCI CTR SAN ANT

NIH K76AG060003 / (2019 - 2023)

Core(s):

PROJECT ABSTRACTThis Beeson Emerging Leaders in Aging Career Development Award (K76) seeks to equip Dr. Lisa Kilpela withthe expertise and professional skill set needed to become a leading gerontological expert in disordered eatingand nutrition pathology, and to advance this emerging and important field. As women age, biological,psychological, and lifestyle changes can contribute to nutritional disorders and associated health problems.Among older women, an increasingly recognized factor that can exacerbate these concerns is eating disorderpathology, which constitutes a group of complex psychiatric disorders characterized by dysregulated andabnormal eating behaviors. When left untreated, eating disorders can cause significant morbidity and mortality.Historically conceptualized as disorders of youth, a rapidly evolving body of research suggests that eatingdisorder symptoms are surprisingly prevalent in older women. Dr. Kilpela s preliminary research as a PepperCenter RL5 Scholar found that the most common form of disordered eating in older women is binge eating(BE; defined as eating an unusually large amount of food while feeling a loss of control), with 26.5% of womenaged 60+ reporting at least weekly BE episodes. BE is closely linked to obesity and depression and, evenindependent of these comorbidities, is associated with metabolic dysfunction, sleep problems, disability, andpoorer quality of life. Therefore, BE appears to represent a significant health problem for older women withgreater prevalence than once thought. Although evidence-based treatments for BE exist for younger women,these treatments need to be tailored for older women in order to address aging-related factors not present inyounger women that have implications for treatment (e.g., cognitive decline, menopausal symptoms). As such,the proposed research aims to: (1) identify factors that uniquely impact older women in relation to BE, (2)utilize information gathered in Aim 1 to guide development of a theory-driven, behavioral intervention tailoredfor older women with BE and pilot implementation to determine its feasibility, and (3) integrate work completedin Aims 1 and 2 within a career development program to advance the Dr. Kilpela s knowledge and expertise in(a) clinical gerontology, (b) women s health in aging, and (c) their integration in the context of BE, to support anR01 application for a full-scale trial. Complementary to the proposed research, Dr. Kilpela will complete aprogram of career development to gain the scientific and professional development skills to transition to anindependent investigator. This proposal is supported by a mentorship team of renowned scientists in agingresearch (Drs. Musi and Espinoza), women s health (Dr. LaCroix), and eating disorders (Dr. Keel), andadvisors in geriatric medicine education (Dr. Sanchez-Reilly) and biostatistics (Dr. Gelfond). This team, alongwith resources available through the San Antonio Pepper Center and Barshop Institute for Longevity and AgingStudies, comprise an ideal environment for Dr. Kilpela to successfully reach her goal to promote healthy agingin older women by addressing disordered eating and nutrition pathology.

2. Project Title: **NOVEL APPROACHES TO IDENTIFYING AND ENGAGING DISADVANTAGED PATIENTS WITH ALZHEIMER?S DISEASE (AD) IN CLINICAL RESEARCH**

Leader(s): **GILMORE-BYKOVSKYI, ANDREA L**

UNIVERSITY OF WISCONSIN MADISON

NIH K76AG060005 / (2018 - 2023)

Core(s):

Despite well-documented disparities in Alzheimer s disease (AD) prevalence, incidence, diagnosis, treatment, and mortality, individuals from disadvantaged backgrounds (e.g. racial/ethnic minorities) are disproportionately under-represented in clinical AD research. Current recruitment methods for AD research predominantly identify patients from outpatient clinics and community settings, or with pre-existing diagnoses. Reliance on these recruitment approaches may create barriers to participation for disadvantaged individuals as they are more likely to lack information about AD services, be undiagnosed and have limited access to outpatient care. Yet, greater enrollment of disadvantaged individuals into AD studies is critically needed to achieve national goals for AD research. Targeted AD screening and tailored recruitment within acute care settings has strong potential to address these gaps, as disadvantaged individuals often rely on these settings to meet their health

needs. This K76 proposal is designed to provide Dr. Gilmore-Bykovskyi, PhD, a geriatric trained nurse and expert in AD symptom management with the training required for success as an independent clinician-scientist focused on improving AD identification to promote greater participation in research and access to effective care and therapies, specifically targeting high-risk disadvantaged populations. The overarching objective of the proposed research is to design screening and recruitment approaches for identifying and engaging disadvantaged AD patients/caregivers and their biological children in research from acute care settings. The proposal consists of validation of an electronic health record (EHR) Phenotype Model for AD using EHR clinical data identified in preliminary studies (Aim 1), and specification of this Model for performance among disadvantaged individuals (Aim 1a). To address recruitment from acute care environments, mixed methods strategies will inform the design of tailored recruitment approaches appropriate to acute care (Aim 2) which will be piloted with 30 AD patients/caregivers to determine their feasibility, acceptability and preliminary impact on willingness to enroll in a Trial Registry (Aim 2a). As a junior faculty member at an institution with extensive support for early stage investigators and significant infrastructure in AD disparities and EHR Phenotyping, Dr. Gilmore-Bykovskyi is in an ideal environment to complete the proposed research and pursue advanced training relevant to her career goals. Dr. Gilmore-Bykovskyi s career development plan integrates didactic and practical training, individual mentoring and mentored research activities in the areas of 1) clinical trial design, 2) advanced statistical and machine learning techniques, 3) acute care research, 4) AD health disparities, 5) recruitment and retention of vulnerable populations and 6) leadership. This proposed award addresses fundamental gaps and barriers to improve inclusion of disadvantaged individuals in AD research while affording training and mentored research critical for Dr. Gilmore-Bykovskyi to lead an independent research program in clinical AD research.

3. Project Title: MEMBRANE LIPID PEROXIDATION IN PATHOGENESIS OF ALZHEIMER?S DISEASE

Leader(s):   **RAN, QITAO**

UNIVERSITY OF TEXAS HLTH SCI CTR SAN ANT

NIH R01AG064078 / (2019 - 2024)

Core(s):

ABSTRACT Alzheimer's disease (AD) is the most common neurodegenerative disease affecting millions of Americans.Neurons have a large amount of polyunsaturated fatty acids in membrane phospholipids that are vulnerable toattack by reactive oxygen species to result in lipid peroxidation. Lipid peroxidation is increased in AD brains andis believed to play a key role in driving neurodegeneration of AD. However, supplementation of lipid solubleantioxidants yields only mixed results in clinical trials. So the importance of lipid peroxidation in AD remainsunproven. Glutathione peroxidase 4 (Gpx4) is a glutathione peroxidase that can suppress lipid peroxidation bydirectly reducing phospholipid hydroperoxides in membranes. Therefore, Gpx4 suppresses lipid peroxidationthrough a mechanism distinct from that of lipid antioxidants. Gpx4's role in reducing phospholipid hydroperoxidesin cells such as neurons is critical and indispensable. Gpx4 also serves as the master regulator of ferroptosis.We have demonstrated that Gpx4 plays a critical role in ensuring heath and survival of neurons in adult animals,such as forebrain neurons that are severely afflicted in AD. In preliminary studies, we obtained data indicatingthat there is a Gpx4 dysfunction in AD brains that could lead to exacerbated pathogenesis and that enhancedGpx4 function retards cognitive impairment of AD mouse models. In this project, we will determine whetherincreased membrane lipid peroxidation induced by Gpx4 deficiency aggravates disease pathogenesis such asneurodegeneration, and determine the efficacy of Gpx4 overexpression in retarding cognitive impairment andneurodegeneration in AD mice. The overall hypothesis tested in this project is: Membrane lipid peroxidationaggravates A neurotoxicity in vivo, and augmentation of Gpx4 function to suppress membrane lipid peroxidationwill retard AD pathogenesis. The hypothesis will be tested by three specific aims. Aim 1 is to determine the effectof membrane lipid peroxidation induced by Gpx4 deficiency on AD pathogenesis. Aim 2 is to determine whetheroverexpression of Gpx4 can suppress neurodegeneration and improve cognition in AD mice. Aim 3 is todetermine whether Gpx4 overexpression via transduction with viral vector can retard progression of disease inAD mice at different disease stages. Our study will establish the importance of membrane lipid peroxidation inneurodegeneration of AD and provide proof-of-concept evidence for the efficacy of Gpx4 as a target ofintervention to retard progression of AD.

4. Project Title: MARMOSETS AS A MODEL FOR UNDERSTANDING SOCIAL, NEUROENDOCRINE, AND VASCULAR CONTRIBUTIONS TO COGNITIVE AGING

Leader(s):   **PHILLIPS, KIMBERLEY ANN**

TRINITY UNIVERSITY

NIH R01AG064091 / (2019 - 2024)

Core(s):

Project SummaryThe number of U.S. residents over age 65 is projected to be 98.2 million by 2060, comprisingapproximately 1 in 4 U.S. residents. According to the Pew Research Center, approximately 26%of older adults live alone. While loneliness does not necessarily correlate with living alone, morethan 40% of seniors regularly experience loneliness. Loneliness is thought to acceleratecognitive decline in older adults, possibly mediated through rising glucocorticoid levels andincreasing inflammation. There is a great unmet therapeutic need for the development ofcognitive therapeutics for the treatment of neurocognitive disorders associated with agingincluding dementias and Alzheimer s disease. Identifying characteristics of animal models thatmay contribute to the development of such a cognitive therapeutic would have significantimpact. Common marmosets are poised to become an important nonhuman primate model inthe study of age-related disease. The focus of this research is healthy brain aging, and thesocial, neuroendocrine, and vascular contributions associated with normal aging rather thandisease states. The population will be characterized using standardized cognitive assessmentsto define those that have good vs poor cognitive aging. The likelihood of the following variablesas determinants of cognitive aging outcomes will be modeled: sex, social history, currenthousing condition, cerebral blood flow (imaging assessments), and myelination. Aim 1 will focuson assessing whether social support buffers the effects of stress on cognitive andneuroendocrine function during aging. An experimental manipulation of a period of separation ofa long-term pair, then reunion, will allow us to investigate the role of social buffering on cognitionand examine how quality of the social support affects cognition and regulation of the HPA axis.Aim 2 will focus on identifying vascular contributions to aging. We will assess cognitiveperformance and cerebral blood flow (CBF) by arterial spin labeling in aged and geriatricmarmosets. We expect cognitive outcomes will be positively correlated with CBF and brainvascular density. Aim 3 will determine whether changes in white matter integrity are associatedwith cognitive dysfunction. The results of this study will contribute novel insights and deeperunderstanding of the role of social stress and neuroendocrine disruption in age-associatedcognitive dysfunction. We anticipate that identifying these links will fundamentally advanceresearch in the study of aging, and may advance the establishment of the marmoset as a highlytranslational model of these conditions.

PUBLICATIONS

2023

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   Geroscience, 2023 Jan 13
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   Citations: | AltScore: 64.38

2. **Regulation of astrocyte lipid metabolism and ApoE?secretionby the microglial oxysterol, 25-hydroxycholesterol.**
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   Citations: 67 | AltScore: 18.7

3. **Drugs Targeting Mechanisms of Aging to Delay Age-Related Disease and Promote Healthspan: Proceedings of a National Institute on Aging Workshop.**
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   Citations: 68 | AltScore: 8.45

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5. **Cost of Failure to Achieve Textbook Outcomes: Association of Insurance Type with Outcomes and Cumulative Cost for Inpatient Surgery.**
   Jacobs MA, Kim J, Tetley JC, Schmidt S, Brimhall BB, Mika V, Wang CP, Manuel LS, Damien P, Shireman PK
   J Am Coll Surg, 2023 Feb 1, 236(2): 352-364
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6. **Differentiating Urgent from Elective Cases Matters in Minority Populations: Developing an Ordinal \Desirability of Outcome Ranking\ to Increase Granularity and Sensitivity of Surgical Outcomes Assessment.**
   Jacobs MA, Schmidt S, Hall DE, Stitzenberg KB, Kao LS, Wang CP, Manuel LS, Shireman PK
   J Am Coll Surg, 2023 Jun 8
   https://doi.org/10.1097/XCS.0000000000000776 | PMID: 37288840
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7. **Association of Cumulative Colorectal Surgery Hospital Costs, Readmissions, and Emergency Department/Observation Stays with Insurance Type.**

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https://doi.org/10.1007/s11605-022-05576-7 | PMID: 36690878 | PMCID: PMC10133377
Citations: 66 | AltScore: NA

8. **Hepatocyte Adenosine Kinase Promotes Excessive Fat Deposition and Liver Inflammation.**
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Citations: 35 | AltScore: 76.93

9. **Senolytics dasatinib and quercetin in idiopathic pulmonary fibrosis: results of a phase I, single-blind, single-center, randomized, placebo-controlled pilot trial on feasibility and?tolerability.**
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Citations: 37 | AltScore: 46.75

10. **Gender-based heterogeneity of FAHFAs in trained runners.**
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Citations: | AltScore: 33.65

15. **Sex-Related Differences in Acuity and Postoperative Complications, Mortality and Failure to Rescue.**
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Ar?valo-Flechas LC, Flores BP, Wang H, Liang H, Li Y, Gelfond J, Espinoza S, Lewis SL, Musi N, Yeh CK
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Citations: | AltScore: 8

2. **Modulation of autophagy: a Phase II study of vorinostat plus hydroxychloroquine versus regorafenib in chemotherapy-refractory metastatic colorectal cancer (mCRC).**
Arora SP, Tenner L, Sarantopoulos J, Morris J, Liu Q, Mendez JA, Curiel T, Michalek J, Mahalingam D
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Citations: 32 | AltScore: 0.75

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Citations: 80 | AltScore: 19

4. **The Effect of Low-Dose Aspirin on Frailty Phenotype and Frailty Index in Community-Dwelling Older Adults in the ASPirin in Reducing Events in the Elderly Study.**
Espinoza SE, Woods RL, Ekram ARMS, Ernst ME, Polekhina G, Wolfe R, Shah RC, Ward SA, Storey E, Nelson MR, Reid CM, Lockery JE, Orchard SG, Trevaks R, Fitzgerald SM, Stocks NP, Chan A, McNeil JJ, Murray AM, Newman AB, Ryan J
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Citations: 7 | AltScore: 32.208

6. **The emerging role of lipidomics in prediction of diseases.**
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Jiwani R, Dennis B, Neri AL, Bess C, Espinoza S, Wang J, Serra MC
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Citations: 93 | AltScore: 112.95

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Palavicini JP, Ding L, Pan M, Qiu S, Wang H, Shen Q, Dupree JL, Han X
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Citations: 64 | AltScore: 10.25

12. **Exercise and Creatine Supplementation to Augment the Adaptation of Exercise Training Among Breast Cancer Survivors Completing Chemotherapy: Protocol for an Open-label Randomized Controlled Trial (the THRIVE Study).**
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Citations: 61 | AltScore: 2.5

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Citations: 100 | AltScore: 182.098

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RECOGNITION AND AWARDS (2022-2023)

<u>Mitzi Gonzalez</u> (2022)

- Article of the Year (Revisiting apathy in Alzheimer's disease: From conceptualization to therapeutic approaches) Behavioral Neurology

MINORITY RESEARCH

General Brief Description of Minority Activities:
Not defined.

Minority Trainee(s):

- Nothing to report, Nothing to report
  Nothing to report

No minority grant information specified.

UNIVERSITY OF TEXAS MEDICAL BRANCH (UTMB)
Claude D. Pepper Older Americans Independence Center

Elena Volpi, M.D.   409-747-1987   evolpi@utmb.edu
Principal Investigator

Stephanie Burt   409-266-9675   stburt@UTMB.EDU
Program Administrator

CENTER DESCRIPTION

The UTMB Claude D. Pepper Older Americans Independence Center (OAIC) has been continuously funded since 2000. From the very beginning, we have nurtured a multidisciplinary translational research culture to fulfill our mission, which is to improve physical function and independence in older adults. Central to this mission has been the career development and training of the next generation of leaders in geriatric research. Our scientific focus has evolved over the years from a narrow interest in the mechanisms of sarcopenia to the translation of our findings in much needed patient-centered interventions to improve physical function and independence. This evolution derives not only from the natural progression of our research from basic discoveries to healthy humans and from healthy humans to patients, but also from a deliberate effort of the OAIC leadership to promote and support collaborations between scientists in muscle aging and investigators in population health and outcomes research on aging and rehabilitation. This second line of research has always been present from the beginning of our OAIC, but was conducted in parallel with muscle research. The intersection of these two lines has accelerated the development of new research foci. An example is the rapid development of patient-centered outcomes research in the elderly, which culminated with the funding of a large infrastructure grant and, more recently, with our participation in the trans-Pepper patient-centered multicenter clinical trials on fall prevention, the STRIDE Study, and the D-CARE.

Our current theme is to "Identify pathways of physical function loss and gain and develop targeted interventions to improve functional recovery from illness in older adults".

Our general hypothesis is that aging induces mild but significant biological and metabolic changes that - in combination with patient factors – progressively lead to functional loss and predispose to potentially catastrophic declines in physical function during bouts of acute illness and hospitalization. Once hospitalized, variations in hospital and post-hospital care will significantly determine whether geriatric patients will recover physical function after their illnesses. Thus, we hypothesize that interventions involving rehabilitation, nutritional supplementation, pharmacologic anabolic treatments, as well as changes in decision making and healthcare delivery can prevent the age- and disease-induced functional loss and improve functional recovery from illness in older adults.

The specific aims of the UTMB OAIC are as follows:

1. Stimulate the growth of multidisciplinary translational research to improve physical function and functional recovery from illness in older adults by:
   □ Funding pilot project research to generate preliminary data in promising new areas of investigation
   □ Funding developmental projects to develop innovative technologies
2. Train future leaders in geriatric research on the mechanisms, prevention and treatment of

functional loss and recovery in older adults

3. Recruit established investigators with expertise relevant to muscle function and functional recovery in older adults into interdisciplinary translational research related to the OAIC focus.
4. Provide core support and add value to funded translational research on functional loss and recovery in older adults.
5. Foster collaborations between UTMB investigators and investigators at other OAICs and other institutions on studies of physical function and functional recovery in older adults.

These specific aims will be accomplished through the Leadership/Administrative Core (LAC), as well as the activities of our Research Education Component (REC), the Pilot/Exploratory Studies Core (PESC) and the three highly productive Resource Cores (RC) that encompass the major areas of our multidisciplinary translational research model: Clinical Research RC1, Metabolism and Biology RC2, and Biostatistics and Data Management RC3.

CORES

Leadership and Administrative Core (LAC)

Leader 1:   Elena Volpi, MD, PhD   evolpi@utmb.edu

Leader 2:   Rebeca Wong, PhD   rewong@utmb.edu

Leader 3:   Stephanie Burt, MS   stburt@utmb.edu

The overall goal of the Leadership/Administrative Core (LAC) is to provide the administrative infrastructure and leadership to support the activities and growth of the entire UTMB OAIC, and fulfill our mission, which is to stimulate translation of the research findings to improve physical function and independence in older adults. The LAC specific aims are: 1. Provide overall leadership and direction for all activities of the UTMB OAIC. We will: a. Evaluate new opportunities for research and collaborations at the local, national and international level with support from our Internal Advisory Committee (IAC) and External Advisory Committee (EAC); b. Attract new investigators by providing training opportunities, as well as pilot and developmental projects; c. Coordinate and integrate Core functions, promoting scientific coherence, access to Core resources and expertise, and new utilization of Core resources; d. Coordinate and leverage OAIC Cores with other institutional resources; e. Foster collaborations between UTMB OAIC investigators and Cores with other OAICs and institutions.

Research Education Component (REC)

Leader 1:   James S. Goodwin, MD jsgoodwi@utmb.edu

Leader 2:   Blake Rasmussen, PhD blrasmus@utmb.edu

Leader 3:   Rebeca Wong, PhD   rewong@utmb.edu

The goal of the REC is to increase the number of rigorously trained, extramurally competitive, and scientifically competent scholars who will conduct translational investigations in aging, lead multidisciplinary research teams, and eventually mentor the next generation of investigators in aging research. To achieve this goal, the REC will address the following objectives: Objective 1: Identify, recruit and select qualified scholars who are beginning their academic/scientific careers in aging and demonstrate the potential for multidisciplinary translational research. Objective 2: Create Individualized Career Development Plans for each scholar that identify a lead mentor and a mentoring team with defined roles, and document expected milestones of research progress including publications, presentations, and submission of grant proposals, and training in the scientific integrity and the responsible conduct of aging related research. Objective 3: Develop and implement a high-quality program of education and training activities integrated with mentoring experiences that provide REC scholars with the skills necessary to establish productive scientific careers.

Pilot and Exploratory Studies Core (PESC)

Leader 1:   Kyriakos Markides, PhD   kmarkide@utmb.edu

Leader 2:   Brian Downer, PhD   brdowner@utmb.edu

Leader 3:   Monique Pappadis, PhD, MEd mrpappad@utmb.edu

The goal of the Pilot/Exploratory Studies Core is to stimulate new research addressing the issues of functional loss and gain and promoting functional recovery from serious illness in the elderly. We target early stage investigators, and also investigators well established in other areas who can turn their expertise to studies consistent with the OAIC theme. We employ our assets and partner with other institutional resources to accomplish the following specific aims: 1. Solicit and select the most meritorious research proposals for PESC funding. 2. Identify opportunities for co-sponsorship of PESC studies. 3. Provide PESC investigators with access to resources from other OAIC cores and institutional research facilities/centers. 4. Monitor the progress of PESC studies. 5. Ensure regulatory compliance, safety and protection of human subjects enrolled in PESC studies. 6. Provide assistance and mentorship to develop PESC studies into independently funded grant applications.

Clinical Research Resource Core (CRRC)

Leader 1:	Elena Volpi, MD, PhD	evolpi@utmb.edu
Leader 2:	Elizabeth Lyons, PhD	ellyons@utmb.edu
Leader 3:	Meredith Masel, PhD	mcmasel@utmb.edu
Leader 4:	Roxana Hirst, MS	rmhirst@utmb.edu

The **Clinical Research Resource Core** is the primary resource for subject recruitment, tracking and retention activities, and for training Scholars in clinical research. This core has been instrumental in developing the infrastructure to support translation of basic discoveries in geriatric populations, developing the ACE Unit Research Laboratory, and participating in large clinical trials, such as ASPREE, STRIDE, D-CARE, MoTrPAC, and STEP-HI. The core supports research studies on the mechanisms underlying function loss and recovery; development and testing of novel treatments; trajectories of physical function and disability in community-dwelling and hospitalized older adults; and pragmatic, patient-centered studies on recovery from illness.

Metabolism & Biology Resource Core (MBRC)

Leader 1:	Blake Rasmussen, PhD	blrasmus@utmb.edu
Leader 2:	Stanley J. Watowich, PhD	sjwatowi@utmb.edu
Leader 3:	Andrew Murton, PhD	ajmurton@utmb.edu

The **Metabolism & Biology Resource Core** promotes and supports basic science and translational research. The MBRC1 significantly contributes to the Center theme and goals by providing fundamental and innovative analytical services, biorepository facilities, training and expertise to explore the biological (molecular and cellular) and metabolic (protein, fat, glucose, and energy) pathways involved in muscle loss and functional recovery in older adults. It also develops and tests novel therapeutics in preclinical models. MBRC1 support has led to several new NIH grants.

Biostatistics & Data Management Resource Core (BDMRC)

Leader 1:	Yong-Fang Kuo, PhD	yokuo@utmb.edu

<u>Leader 2:</u>   Heidi Spratt, PhD   hespratt@utmb.edu

<u>Leader 3:</u>   Xiaoying Yu, PhD   xiyu@utmb.edu

The goal of the **Biostatistics and Data Management Resource Core** is to provide biostatistical collaboration and training, and develop biostatistics methodology and data management tools for research relevant to the Center theme. Core personnel are highly qualified faculty and staff with expertise in study design, computer science, data management, and statistical analysis from a wide range of research applications.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications

Yunfeng Chen, PhD (Phase I)
Assistant Professor / Department of Biochemistry and Molecular Biology
<u>Molecular biology and mechanobiology approaches to study how aging and diabetes affect the glycosylation of proteins in the vascular system</u>

Dr. Chen's current research uses molecular biology and mechanobiology approaches to study how aging and diabetes affect the glycosylation of proteins in the vascular system, and how that contributes to the increased risk of arterial thrombosis in the elderly population. He will also explore a new strategy for preventing arterial thrombosis abiding by the emerging concept of 'mechano-medicine'.

2023-2025 /
32 (total)
9 (1st/Sr)

Huiwen Xu, PhD, MHA (Phase I)
Assistant Professor / Population Health & Health Dispariites
<u>Aging; cancer rehabilitation; long-term care</u>

Dr. Xu is a health services researcher with strong interest in aging, cancer rehabilitation, and long-term care. His past research has examined the hospitalization and emergency department (ED) visits of nursing home residents using national Medicare claims and Minimum Data Set data. His long-term career goal is to become a policy-relevant cancer rehabilitation researcher using large observational data. Dr. Xu's Pepper Center appointment focuses on improving physical function among older patients with cancer admitting to nursing homes. Functional impairments affect over 40% of hospitalized patients with cancer. After hospital discharge, about 20% of patients received rehabilitation in nursing homes to maintain functional independence. But existing literature did not examine the patterns, predictors, and potential disparities in the rehabilitation therapy received by patients with cancer admitted to nursing homes. More importantly, the benefits of excess rehabilitation on patient-oriented outcomes including physical function remains unknown. As an RL5 scholar, Dr. Xu will evaluate the effects of rehabilitation therapy on physical function, symptoms, survival, community discharge, and healthcare utilization among older patients with cancer admitted to nursing homes. He will leverage multiple data sources including the Surveillance, Epidemiology, and End Results (SEER), Medicare claims (inpatient, outpatient, SNF, carrier), Minimum Data Set 3.0, etc. Prior to joining UTMB, Dr. Xu worked as a Research Assistant Professor for two years at the University of Rochester NCI Community Oncology Research Program (NCORP) Research Base to design and analyze nationwide Phase III clinical trials in cancer survivorship and geriatric oncology. Dr. Xu has published extensively in leading medical journals including Lancet, JAMA Oncology, JAMDA, and Medical Care. He currently serves on the Executive Committee of the AcademyHealth Methods and Data Council and Analytics Core of the Cancer and Aging Research Group.

2021-2024 /
47 (total)
12 (1st/Sr)

Andrew Murton, PhD (Phase I)
Assistant Professor / Department of Surgery
<u>The mechanisms of sarcopenic obesity and the causative role of intramuscular lipid accumulation</u>

His REC research will involve studying the mechanisms of sarcopenic obesity and the causative role of intramuscular lipid accumulation, building on Dr. Murton's previous observations that muscle anabolic resistance is worsened by obesity in older adults. The purpose of Dr. Murton's REC research will be to identify novel molecular mechanisms driving obesity-induced anabolic resistance in aging muscle.

2000-2023 /
46 (total)
13 (1st/Sr)

Neil Mehta, PhD (Phase I)
Associate Professor / Epidemiology
<u>Identifying the Causes of the Stagnation in National U.S. Cardiovascular Disease Mortality</u>
Chronic disease epidemiology, socioeconomic and racial/ethnic health disparities, and the modelling of complex population health dynamics.

2021-2023 /
74 (total)
22 (1st/Sr)

Erin Hommel, MD (Phase I)
Associate Professor / Division of Geriatrics
<u>Implementation science; Hip Fracture; Osteoporosis; Malnutrition; eHealth</u>
Stemming from a background as a geriatrician and quality improvement director/educator, Dr. Hommel's aim as a clinical scholar is to develop a foundation in implementation science to guide improvement in care for geriatric syndromes. Specifically, she desires to utilize dataset analysis alongside patient encounters to identify care gaps in geriatric syndromes and to design electronic health resources to close those care gaps. Her first clinical research project is entitled "Usability and Feasibility Testing of the My-Hip Fracture Web Application". The My-Hip Fracture web application is designed to assist clinicians with providing personalized prognostic information to patients and their surrogates after hip fracture. Under the direction of mentors Dr. Peter Cram and Dr. Monique Pappadis, she will be analyzing, through mixed-methods techniques, the ability of the web application to improve shared decision making with these vulnerable patients.

2020-2023 /
7 (total)
3 (1st/Sr)

Past Scholars
Monique Pappadis, PhD, MEd (Phase II), Division of Rehabilitation Sciences (2016-2020)
Rafael Samper-Ternent, MD, PhD (Phase II), Division of Geriatrics (2017-2020)
Rachel Deer, PhD (Phase II), Division of Rehabilitation Sciences (2017-2020)
Kimberly Hreha, EdD, OTR/L (Phase I), Division of Rehabilitation Sciences (2018-2020)
Sadaf Milani, PhD (Phase I), Division of Geriatrics (2021-2021)

PILOT/EXPLORATORY PROJECTS (6 Pilot Projects Listed)

1. Project Title: **Strength Training Treadmill Exercise to Reduce Compensatory Walking Patterns in Post-Stroke Hemiparesis**

Leader: **Mansoo Ko, PhD**

Significance: Stroke is the leading cause of chronic neurological disability in older adults. Our focus is to optimize the delivery of a combined strength and aerobic training regimen to older adults with post stroke hemiparesis and reduce inefficiencies associated with compensation by the nonparetic leg during walking. Approach: We will optimize our combined neuromechanical and biobehavioral approach to enhance bilateral symmetry of limb propulsion using a newly acquired split-belt, force-plate instrumented treadmill that generates backward directed resistance forces. We will also determine feasibility and collect preliminary data for a larger study. With neuromechanics we will measure EMG muscle activity patterns, joint torque output, and trailing limb angle at different levels of resistance, while subjects walk under normal treadmill belt conditions versus the split-belt conditions. In addition, we will assess the maintenance of improved paretic limb propulsion immediately after the split-belt environment is restored to a single belt condition (i.e. aftereffects), and the ability to consciously reduce compensatory walking patterns when they are not engaged with the specialized treadmill setup. Muscle biopsies will be taken to measure differences in fiber type, gene expression and cell signaling in paretic and nonparetic leg. Innovation: This information will provide important feasibility and preliminary data to support an R21 or R01 proposal seeking to validate of the efficacy of a strength and aerobic training regimen to reduce compensatory gait patterns and improve post-stroke mobility.

2. Project Title: **Evaluating the Usability of a Novel Hip Fracture Web-app, My Hip-Fracture (My-HF)**

Leader: **Peter Cram, MD**

Mortality and morbidity are high for older adults after hip fracture (HF), particularly those with multi-morbidity and frailty. While mortality and morbidity after hip fracture is generally well understood by healthcare professionals, recent data suggest that both patients and surrogate decision makers (SDMs) are unaware of the seriousness of hip fracture. In response to this gap, our multi-disciplinary team developed, iteratively refined, and pilot tested the usability of a paper-based educational tool (My-HF) providing personalized estimates of post-HF prognosis among patients and SDM. Based on this initial testing, we have revised My-HF and converted it to a web-enabled mobile application. The aims of this pilot project are two-fold: (1) Assess the usability of My-HF among a sample of healthcare 20 healthcare providers including physicians (orthopaedic surgeons, geriatricians, hospitalists, and palliative care physicians), nurses, and social workers. (2) Evaluate the efficacy of My-HF in a pilot randomized trial enrolling 50 patients hospitalized with low-impact HF and their SDMs (25 randomized to My-HF and 25 randomized to a control group). Aim 1: Usability of the My-HF web-app in healthcare professionals. We will use a mixed-methods approach to solicit feedback from healthcare professionals at UTMB (total sample size 20) on issues of usability, touch, and interactivity. Participants will be provided with an Android Tablet and asked to open and navigate the My-HF, this will be supplemented by a structured survey and structured interview with open ended questions. Aim 2: Pilot randomized trial of My-HF. We will conduct a pilot randomized trial to evaluate the efficacy of My-HF among patients hospitalized with

low-impact HF and their SDMs (total sample size 50, 25 My-HF, 25 control). For participants randomized to receive My-HF, clinical teams will complete the My-HF report and a study RA will review the report with the patient and/or SDM. We will use and "attention control" whereby control group will receive augmented usual care with a RA visit reviewing general topics of ageing and fall prevention strategies. We will evaluate 4 co-primary outcomes: 1) HF knowledge and understanding of prognosis; 2) satisfaction with HF care; 3) anxiety and regret; and 4) readiness to engage in advanced care planning (ACP) using pre-identified questions from validated instruments. Outcomes will be evaluated at 10-14 days after intervention and 26-28 days after intervention. We hypothesize that providing HF education using My-HF will improve knowledge and understanding of HF prognosis, thereby improving satisfaction with HF care, reducing anxiety and regret, and improving readiness to engage in advanced care planning. We anticipate that the pilot data collected will generate 1-2 peer-reviewed publications, and more importantly but used to support an application for a multi-centre randomized controlled trial to definitively evaluate the impact of My-HF on each of the 4 outcomes described above.

3. **Project Title:**   **Inflammaging: Role of HMGB1 mediated chronic inflammation in aging-associated cognitive dysfunctions and decreased lifespan**

   Leader: **Sagar Gaikwad, PhD**

Advanced age is the main risk factor for most chronic diseases, functional and cognitive deficits, and decreased health- and lifespan in humans. Recent studies suggest that senescent cells accumulate with aging in various tissues and play a key role in the pathophysiology of aging-related disorders. Senescent cells are defined by an apoptosis resistant, arrested cell cycle with a distinct "inflammatory" phenotype known as senescence-associated secretory phenotype (SASP). Importantly, human aging is characterized by a chronic, low-grade inflammation known as inflammaging, which can exacerbate naturally occurring age-related tissue deterioration through paracrine mechanisms, and contribute to several diseases associated with aging, including atherosclerosis, osteoarthritis, cardiovascular disease, and Alzheimer's disease (AD). Although, SASP is a common pathogenic inflammatory process in the aforementioned pathologies, the precise etiology of inflammaging and its potential causal role in contributing to cellular senescence and decreased healthy lifespan remain largely unknown, impeding the development of interventions that might delay or prevent age-related disorders and maximize healthy lifespan. Modulation of inflammaging/SASP thus offers opportunities to develop novel therapeutics. HMGB1- a key component of inflammaging: Evidence suggests that release of high mobility group box protein 1 (HMGB1) is an early and central mediator of senescent phenotypes both in humans and mice tissues. It coordinates SASP related chromatin folding and RNA homeostasis and contributes to senescence progression. We recently demonstrated that HMGB1-the major component of SASP is actively secreted by senescent cells in the brain in both humans and mice. HMGB1 is a highly conserved, nuclear protein present in all cell types, and it facilitates DNA replication and repair. The extracellular HMGB1 is a key initiator of inflammation, which slows or stops tissue regeneration and homeostasis, and ultimately causes tissue deterioration. Our studies have shown that inhibition of HMGB1 release effectively prevents paracrine senescence, neuroinflammation, inflammaging and improves cognitive functions in aged human tau expressing (hTau) transgenic tauopathy mice. A very recent study demonstrated that particularly oxidized HMGB1 cause chronic inflammation and subsequent tissue damage and functional decline. In contrast, non-oxidizable HMGB1 (3S-HMGB1) or fully reduced HMGB1 facilitates resolution of inflammation, promote regeneration in multiple tissues and enhances functional recovery. However, the impact of HMGB1 release and

oxidation on accumulation of senescent cells, chronic inflammation, and cognitive and physical dysfunction, healthy lifespan has not been investigated. The central hypothesis is that "HMGB1 release and oxidation promotes paracrine senescence, and inflammaging, which cause cognitive and physical dysfunction and decreases healthy lifespan in animals". Recent studies from our laboratory and others provided evidence that modulation of HMGB1 release reduces inflammation and promotes tissue regeneration, which subsequently improve survival, health span, functional performance. HMGB1 has been shown to trigger hyperinflammation, and HMGB1 levels in blood or tissue are substantially elevated in many chronic inflammatory diseases including AD. Therefore, we wish to investigate the role of HMGB1 release and oxidation in inflammaging using an experimental mouse model of tauopathy as well as tissues and cells, and cerebrospinal fluid (CSF) from AD patients and age-matched control subjects. Our broad research goal is to understand how HMGB1 release and oxidation mechanisms influence inflammaging, cellular senescence, and tissue pathologies, and how de-regulation of these mechanisms contributes to aging and disease. This pilot study will generate preliminary data and provide proof-of concept to support this novel hypothesis. Aging and high-fat diet (HFD) are known to exacerbate effects of senescent cells. So, for subsequent funding applications, we will use genetic and pharmacological approaches to evaluate whether targeting HMGB1 release and oxidation prevents/delay inflammaging and restore cognitive and physical functions and improve lifespan in tauopathy mice subjected to normal diet or HFD. We will examine aging hallmarks such as cellular senescence, and inflammaging in mice and human cells as described earlier. Cognitive function, tau pathology, inflammation, neuron loss in mice will be investigated by methods described earlier9. Physical function and lifespan in old age mice will be examined as previously reported.

4. Project Title: **Neighborhood Structural Inequalities and Opioid Use Disorder among Older Adults: Before and During the COVID19 Pandemic Comparisons**

Leader: **Tse-Chuan Yang, PhD**

Despite a new interest in investigating the impact of the novel coronavirus disease 2019 (COVID-19) pandemic on populations with opioid use disorder (OUD), little attention has focused on how existing neighborhood inequalities, such as neighborhood social isolation, have shaped risk of OUD before and during the pandemic, particularly among older adults. Since the opioid crisis emerged in the 1990s it has become clear that individuals with OUD are at a higher risk of death, morbidity, and other undesirable health outcomes than those without. The COVID-19 pandemic has further complicated the opioid crisis because the fear for infection, uncertain prognoses, and potential shortage of medical resources are associated with various mental health issues, which are likely to increase the demand for opioids. Importantly, older adults have been disproportionately affected by COVID-19, and the recommended precautions to contain the pandemic (e.g., physical distancing and shelter-in-place orders) have severely interrupted older adults' daily routines. In particular, the pandemic has prohibited older adults from receiving regular social support or quality health care, and the time spent in their own residential neighborhood has been prolonged during the pandemic. Under these conditions, older adults' need for opioids, both prescription and illicit, may have increased. Moreover, older adults with extended exposure to poor neighborhood conditions may be at a particularly increased risk of OUD. Using the 2017-2021 Medicare Fee-for-Service Part A and Part B claims data and the American Community Survey 5-year estimates, this project will construct a before and during the pandemic cohort, with both OUD and non-OUD observations;

beneficiaries will then be linked to their neighborhood conditions. Utilizing these hierarchical data, this project has three aims: (1) Investigate whether individual-level characteristics among older adults with OUD have changed during the COVID-19 pandemic. We hypothesize that compared with the observations in the before pandemic cohort, OUD has become more prevalent during the pandemic among older adults with low socioeconomic status, from racial/ethnic minority backgrounds, and having mental and/or physical chronic health issues. (2) Investigate whether the associations between neighborhood-level factors and the risk of OUD have been enhanced during the COVID-19 pandemic. We hypothesize that neighborhood social isolation, concentrated disadvantage, and rurality have stronger associations with the risk of OUD during the pandemic. (3) Investigate whether neighborhood-level factors moderate the association between OUD and individual characteristics before and during the pandemic. We hypothesize that living in neighborhoods with high concentrated disadvantage and isolation aggravates the associations between OUD and individual low socioeconomic status and mental or physical chronic conditions only during the pandemic. The findings of this project will offer evidence for that the pandemic exacerbates the risk of OUD at both the individual and neighborhood levels.

5. Project Title: **Functional Recovery of Asian Older Adults in Skilled Nursing Facilities**

Leader: **Hoang T. Nguyen, PhD**

The Asian and Pacific Islander population aged 65 years and older in the United States is expected to grow to over 7 million by 2060. This study provides a profile of Asian Americans older adults residing in skilled nursing facilities and their functional recovery status. The study four aims are (1) to compare racial/ethnic differences in hospital referral patterns to SNFs and home/self-care for older adults (> 65 years) from 2013- 2019, (2) to compare differences in admission source to skilled nursing facilities between racial/ethnic groups for older adult residents in 2018 or 2019, (3) to compare demographic and clinical characteristics between Asian and other racial/ethnic older adults associated with first SNF stay in 2018-2019, and (4) to examine factors contributing to differences in functional recovery between Asian and non-Hispanic White older adults in SNF after a hospital stay. No comparison in functional recovery will be made between Asian and other minority groups. The study uses Medicare data, specifically the Master Beneficiary Summary File, the Medicare Provider and Analysis Review (MedPAR) file and the Minimum Data Set for Nursing Homes and Swing Bed Provider to address the aims.

6. Project Title: **Rejuvenation of Senescent Cells In vitro and In vivo**

Leader: **Michael Sheetz, PhD**

The UTMB Pepper Center supported our work this past year with a small developmental project. Those studies have indicated that low level ultrasound can rejuvenate senescent cells in vitro and in vivo. Because the treatments have not been optimized and we don't know the molecular mechanism, we would like to have further evidence for an NIH program project grant and this grant is to help us obtain that evidence. This grant is in collaboration with Drs. Rasmussen and Murton to optimize the ultrasound parameters for improving aged mouse performance and wound healing, respectively. The results of these experiments are important for designing clinical trials to improve aged human performance and healing with ultrasound. The background for this grant comes from our studies of senescent cell rejuvenation, which

include massive expansion of fibroblasts and mesenchymal stem cells, without apparent alteration of cell phenotype. Thus, we expect that rejuvenation of cells in tissues will not alter their phenotype either. Our preliminary mouse studies over the last year have shown that ultrasound treatment can significantly improve aged mouse performance on the treadmill and inverted cling assays. The parameters used were not optimized but were the same parameters that produced optimal rejuvenation of cells in vitro. We hope to be able to improve the rejuvenation of the old mice further with more frequent treatments, optimized power level, frequency and duty cycle plus an optimized ultrasound chamber. Because there is preliminary evidence that ultrasound treatment increased the lifespan of the mice, we will undertake an expanded longevity study to determine if ultrasound treatment can significantly increase lifespan. In parallel, we will treat the wounds of aged mice with ultrasound to improve healing. Optimization of the healing effect of ultrasound may require optimizing the timing of delivery of the ultrasound, since it is not expected that ultrasound will be beneficial at all stages of the healing process. Of particular interest, is the effect of ultrasound on the proliferative phase of healing. In the case of senescent cells, we will focus on the molecular basis of the rejuvenation by ultrasound, since it may provide clues to ways to improve the rejuvenation of senescent cells in vivo. From the literature, it is clear that senescence involves mitochondrial fusion and the inhibition of sirtuin 1 activity. Our results show that reversal of senescence with ultrasound causes mitochondrial fission in a Drp1 independent process and requires Sirtuin 1 activity. In addition, inhibition of the Rho kinase is synergistic with ultrasound. Finally, we will fractionate the supernatant from ultrasound-treated normal cells that activates senescent cell growth to identify the critical growth factors. These results are all consistent with hypotheses that senescence involves protein aggregation with decreased autophagy, and ultrasound causes increased protein degradation leading to reversal of senescence. Based upon the outcome of these mice studies, we hope to develop plans with our collaborators for the use of ultrasound in treating aspects of human aging. Since the ultrasound power levels are well within the limits set for humans, we are moving to preliminary trials of the ultrasound effects on diabetic foot ulcers in the next several months. Thus, there are no apparent barriers to developing ultrasound treatments for aging.

DEVELOPMENT PROJECTS (3 Development Projects Listed)

1. Project Title: **Reversal of Senescence Phenotypes by Low Level Ultrasound Treatment**

Leader: **Michael Sheetz, PhD**

Core(s):

In preliminary studies of senescent cells that have a low growth rate and senescence associated secretory phenotype (SASP), we found that mechanical stimulation by structured bursts of low frequency ultrasound will stimulate growth and block SASP without heating. Further, such ultrasound treatment (US) also caused normal cells to secrete growth-activating factors, which further increased growth of senescent cells. This appeared related to mechanical effects on intracellular organelles particularly mitochondria following US treatments. To determine if these findings might be relevant to human aging, we have started collaborations with Dr. Blake Rasmussen, an aging expert and Dr. Andrew Murton, whose lab is studying wound healing. These collaborative studies will test if ultrasound therapy improves the performance of aged mice (Graber et al., 2020) and their healing (Bhattarai et al., 2020). Performance in mice will be measured with the new comprehensive functional assessment battery (CFAB), which was recently developed with support from a UTMB Pepper Pilot Award. The CFAB is similar to the SPPB (Short Physical Performance Battery) assessment tool developed by the NIA to evaluate physical function in older adults. In collaboration with the Murton lab, we will test the effect of ultrasound treatment on healing of mature and aged mice with 5 mm diameter skin excision wounds (an assay that has been working in their lab). In parallel studies, we are treating tumors in mice with structured bursts of ultrasound to cause mechanically-induced tumor cell death (Tijore et al., 2020) under the same conditions used in our preliminary senescence studies. Only minor modifications of the mouse restraining device in the treatment chambers are envisioned for the studies of effects on aging and wound healing. Based upon the outcome of these mice studies, we hope to develop plans with our collaborators for the use of ultrasound in treating aspects of human aging. Since the ultrasound power levels are well within the limits set for humans and we are moving to clinical trials of the ultrasound effects on human tumors in the next several months, there are no apparent barriers to developing ultrasound treatments for aging.

2. Project Title: **A non-parametric approach to predict the recruitment for a randomized clinical trial in an elderly inpatient setting**

Leader: **Alejandro Villasante-Tezanos, PhD & Xiaoying Yu, PhD**

Core(s):

Successfully recruiting the prespecified number of trial participants is critical and remains challenging to the success of clinical trials. The COVID19 pandemic changed inpatient hospitalization and outpatient visit patterns, thus significantly impacted recruitment for a substantial number of clinical trials. An important question to the clinical trial stakeholders is: Given the recruitment data we have so far, how long will it take to recruit the target number of patients now, and do we have to adjust our initial estimates and plans?1 Although various types of prediction models for recruitment have been developed in the past, they either relied on assumptions of parametric distributions or prior information on the recruitment rate. Also, these models did not consider sequential steps, such as, % eligible, % approached and % consented that may provide valuable information to model final recruitment. Furthermore, many of these

models were not tested with real trial enrollment data.2 The objective for this project is to develop and test the recruitment model using simulation-based non-parametric approach for clinical trials based on inpatient settings such as those taking place in acute care for the elderly (ACE) units at UTMB by leveraging the resources of the recruitment data from completed and ongoing trials and real-world data (TriNetX data) at UTMB.

3. Project Title: **Is the 3D position of aging-related genes a biomarker for aging?**
Leader: **Guy Nir, PhD**
Core(s):

Cellular senescence is one of the hallmarks of aging. A major phenomenon in senescing is the rewiring of gene expression programs, likely since the regulation of many genes goes awry. One major regulator of gene expression is genome organization. Indeed, several papers have shown that genomes are reorganized during senescence. However, it remains unknown whether the position of aging-related genes changes as cells age and whether that impacts gene expression. There are two main reasons for this knowledge gap. The need to map the 3D position of several (aging-associated) genes and compare their folding signatures between proliferating and (early and deep) senescing cells. The high degree of cell-to-cell structural and transcriptional variability, especially in senescent cells. My lab has the tools and desire to overcome these two hurdles. We employ multiplexed imaging approaches to describe how the restructuring of genomes, including senescent genomes, impacts gene expression and cell fate decisions at the single-cell level. Here, we propose to compare the position and structure of Senescent-Associated Secretory Phenotype (SASP) genes in proliferating and early and late senescing cells. Our goal is to determine whether the position and structure of these genes change during senescence and whether these structural changes correlate with transcriptional changes. In the long-term, we plan to transition from cells to tissues, taking biopsies from mice and then humans at different ages to look for structural, positional, and transcriptional rewiring that may occur during aging. We also plan to expand our scope to other forms of senescence. And we intend to study whether fully reversible biomolecular condensates carrying transcriptional machinery and encompassing chromatin domains turn into irreversible aggregates that impair genome functions.

RESEARCH (10 Projects Listed)

1. Project Title: **IMPROVEMENT IN PATIENTS' COGNITION AND RELATIONSHIP WITH SNF QUALITY MEASURES**

Leader(s): **DOWNER, BRIAN GREGORY**
UNIVERSITY OF TEXAS MEDICAL BR GALVESTON
NIH K01AG058789 / (2019 - 2023)

Core(s):

PROJECT SUMMARY/ABSTRACTI am an assistant professor in the Division of Rehabilitation Sciences at the University of Texas Medical Branchin Galveston, Texas. The purpose of this K01 proposal is to provide me with the knowledge, analytical skill,and experience necessary to become a successful investigator. To me, this means I will develop a fundedresearch program that advances the quality of post-acute care for older adults, in particular for those withcognitive impairment, Alzheimer's disease and related dementias. My K01 application is focused on skillednursing facilities (SNFs) because they are the most frequent post-acute care site for older adults. My training ingerontology has focused on analyzing cognitive data and using large data sets to identify potentially modifiablerisk factors for cognitive impairment and dementia. During the K01 period, I will receive training in four areasthat build upon my prior training in gerontology and expertise on the epidemiology of dementia: (1) Healthcharacteristics, assessment process, quality outcomes and follow-up needs associated with older adultsreceiving SNF care; (2) Operational standards and regulatory (decision making) policies of SNFs; (3) Statisticalskills for studying post-acute care outcomes using claims data; and (4) Career advancement and leadershipdevelopment. Training in these areas will include coursework, shadowing interdisciplinary teams in clinicalsettings, and experiences accessing, managing, and analyzing Medicare files. This training will make me aresearcher with a highly-informed view of healthcare policy and clinical context. My training activities havebeen integrated with a research project in which I will use national Medicare data files (2012-2014) to completethe following specific aims: (A) Evaluate the change in cognitive status during a SNF stay for older adults withimpaired cognition on admission; (B) Examine the variation across SNFs in the percentage of patients withimpaired cognition on admission whose cognitive status improves during a SNF stay; and (C) Assess therelationship between cognitive status on admission, improvement in cognitive status during a SNF stay, andperformance on SNF quality measures. The expected findings of this research can inform clinical interventionsthat target patient- and facility-level characteristics associated with improved cognitive status. The findings canalso inform healthcare policies meant to incentivize nursing homes to provide high-quality post-acute care.Completion of the K01 mentored training and research plans will provide me with the knowledge and skillsnecessary to develop a program of research that will advance the quality of post-acute care for older adults, inparticular for older adults with cognitive impairment, Alzheimer's disease and related dementias.

2. Project Title: **EPITHELIAL INNATE SIGNALING IN AIRWAY INFLAMMATION AND REMODELING**

Leader(s): **GAROFALO, ROBERTO P**
UNIVERSITY OF TEXAS MEDICAL BR GALVESTON
NIH P01AI062885 / (2004 - 2023)

Core(s):

Respiratory Syncytial Virus (RSV) is a leading cause of childhood respiratory disease, responsible for 75,000 125,000 hospitalizations annually and producing significant morbidity and economic impact. No vaccine iscurrently licensed to prevent RSV infections. Children hospitalized for RSV lower respiratory tract infections(LRTIs) have reduced pulmonary function, a significant predictor of adult chronic lung disease. This is acompeting renewal for our P01, originally funded as AADCRC AI46004 and subsequently through two P01cycles (9/1/2005-present). Work in our P01 has elucidated mechanisms by which RSV infection produces arapid epithelial oxidative stress response, triggering innate signaling and resulting in cytokine secretion thattriggers and shapes adaptive immunity. More recently, we have developed additional compelling evidencesupporting the central theme of this P01 that innate inflammation produced by infection with the ubiquitousviral pathogen RSV impairs antioxidant capacity, producing disease and triggering long-term airwayremodeling. Our projects are developed from original discoveries by our internationally recognized projectleaders (PLs) expert in innate inflammation, oxidative stress, and the DNA damage response. Our renewalincludes three major research projects (RPs): 1) RP1 (Epigenetic regulation of innate inflammation-drivenairway remodeling) will focus on the role of the
NF B-coactivator, a chromatin remodeling complex (CRC)nucleated by bromodomain-containing protein 4 (BRD4) in

RSV-induced remodeling via epithelial-mesenchymal transition and myofibroblast expansion; 2) RP2 (The role of innate immunity indownregulation of the airway antioxidant response during paramyxovirus infection) will focus on howRSV causes disease mediated by unbalanced ROS production via a progressive decrease in NF-E2-relatedfactor 2 (NRF2); and 3) RP3 (Linkage of the oxidant induced OGG1-DNA complex to airwayinflammation and remodeling) will test the hypothesis that RSV-induced epigenetic modification viaoxidation of guanine to oxoG in gene regulatory regions controls acute/chronic inflammation and airwayremodeling via the NfB pathway. This P01 is guided by regular and sustained interactions with our Internaland External Advisory Committees and is nurtured by significant institutional support from UTMB Centers,Departments, and Institutes. All our inter-related and synergistic RPs are supported by an Administrative Core,and human subjects and viral preparations from the Infant Bronchiolitis and Viral Core (IBVC). Translationaladvances include applications of BRD4 inhibitors, NRF2 agonists, and OGG1 inhibitors that in preclinicalstudies show promise to interfere with RSV-induced inflammation and remodeling. Upon completion, this P01will have identified mechanisms of innate signaling-induced remodeling and developed strategies for reversingremodeling and restoring defective innate immunity in allergic airway diseases.

3. Project Title: **LONGITUDINAL STUDY OF MEXICAN AMERICAN ELDERLY HEALTH**

Leader(s):   **MARKIDES, KYRIAKOS S**
UNIVERSITY OF TEXAS MEDICAL BR GALVESTON
NIH R01AG010939 / (1992 - 2023)

Core(s):

ABSTRACTThis application seeks funds to conduct one more in-person follow-up (wave 10) of the Hispanic EPESE(Established Population for the Epidemiological Study of the Elderly) surviving subjects (AGED 90+) and theircaregivers, many of whom were interviewed in 2016 (Wave 9) and/or in 2010-11 (Wave 7). We propose the newfield work for 2019-20. The baseline was conducted during 1993-94 when a representative sample of 3,050Mexican Americans aged >65 residing in Texas, New Mexico, Colorado, Arizona, and California wereinterviewed. At Wave 5 (2004-05), a new cohort of 902 subjects aged >75 was added. The proposed contact willbe our tenth for the original subjects plus the third contact for most of the caregivers whom we interviewed in2010-11 and 2016. At our last contact in 2016 we interviewed 480 subjects that were aged >88 plus 460informants, most of whom were family caregivers. Our specific aims below are based on our key findings fromthe previous nine waves, and the limited information on the health and health care needs of the oldest old Mexican Americans. This is a long living population with a current life expectancy at birth of approximately 2.5years higher than that of non-Hispanic Whites (Arias, 2014) despite their generally lower socioeconomic status(Markides and Eschbach, 2005; 2011). We expect to re-interview at least 300 survivors aged >90. We also planto interview their caregivers (N=300) most of whom were interviewed in 2016 and some of them also interviewedin 2010-11. The Hispanic EPESE has been a multipurpose study with contributions to numerous aspects of agingin the Mexican American population. The proposed application will also have multiple aims mostly centered onthe health and health care needs of the oldest old Mexican Americans with special attention to their caregivingneeds and caregiving arrangements. Also of interest are factors that contribute to survival to such advancedages. Our primary aims are: Aim 1. Assess the dynamics of caregiving and living arrangements of very oldMexican Americans over a nine-year period (2010-2011 to 2016 and to 2019-2020) by obtaining informationfrom both elderly subjects and their caregivers. Aim 2. Examine the association of changes in the subjects physical, cognitive, and mental health on the mental and physical well-being and quality of life of caregivers. Alsoexamined are factors influencing changes in caregiving arrangements, as well as changes in living arrangementsincluding institutionalization. Aim 3. Identify predictors of survival, change in disability, change in cognitivefunction, and level of psychiatric disturbance in the oldest old subjects from Wave 7 (2010-11) to Wave 9 (2016)and Wave 10 (2019-20). Aim 4. Conduct a more extensive assessment of cognitive function of the 300 oldestold subjects and examine their association with caregiver arrangements, caregiver burden and quality of life oftheir caregivers (N=300). Aim 5. Archive proposed Wave 10 data with NACDA (the National Archive ofComputerized Data in Aging). Waves 1 to 8 have been archived with NACDA and Wave 9 collected in 2016 willbe archived this year.

4. Project Title: **PRAGMATIC TRIAL OF THE EFFECTIVENESS AND COST-EFFECTIVENESS OF DEMENTIA CARE**

Leader(s):   **REUBEN, DAVID B.**
UNIVERSITY OF CALIFORNIA LOS ANGELES
NIH R01AG061078 / (2018 - 2023)

Core(s):

PROJECT SUMMARYIn the United States, an estimated 5.5 million persons are affected by Alzheimer's disease, the most commontype of dementia. The clinical manifestations of dementia are devastating and often lead to caregiver stress,burnout, and medical illnesses. Dementia is a prototype of a disorder with complex needs that span both thepatient and caregiver, medical and social domains, and health system and community-based organizations.In response, several dementia care programs have been developed to more comprehensively meet the needsof patients and their caregivers, including those based within health care systems and those based in thecommunity. These programs have been implemented at either single sites or on a relatively small scale; nonehas been replicated widely because of unanswered questions about effectiveness and cost-effectiveness.In November 2017, the Patient Centered Outcomes Research Institute (PCORI) approved a 4-site pragmaticclinical trial to compare the effectiveness of health-systems-based care (based on the UCLA Alzheimer's andDementia Care program) with community-based care (based on the Benjamin Rose Institute Care Consultationprogram) on patient- and caregiver-reported outcome measures, including behavioral symptoms and caregiverdistress (co-primary outcomes), and secondary outcomes of caregiver strain, unmet needs, and depressionover 18-months. Because of PCORI's mandate, neither intervention will be compared to usual care (thus, onlyrelative effectiveness can be determined). Nor will cost-effectiveness of either intervention be evaluated.The proposed research will add a third usual care (UC) arm and expand outcomes to include costs and healthcare utilization. This expansion will permit comparison of each of the intervention arms to current usual care,thereby providing multisite pragmatic randomized clinical trial evidence for effectiveness of the two activetreatment arms. It will also allow evaluation of whether paying for such care will offset the costs anddetermination of which intervention is more cost effective. The study will also conduct exploratory analyses oftertiary outcomes of both interventions versus usual care including mortality, time spent at home, long-termnursing home placement, physician and patient/caregiver satisfaction and comparing all three groups onseveral types of utilization and out-of-pocket expenses.The study's questions are fundamental to planning for the clinical care of persons with dementia. Theyaddress both clinical effectiveness and cost-effectiveness. By answering these questions, clinicians, healthsystems, and insurers can make decisions about which programs to promote, scale and disseminate.

5. Project Title: **A SOCIAL MEDIA GAME TO INCREASE PHYSICAL ACTIVITY AMONG OLDER ADULT WOMEN**

Leader(s):   **LYONS, ELIZABETH J.**
UNIVERSITY OF TEXAS MEDICAL BR GALVESTON
NIH R01AG064092 / (2019 - 2024)

Core(s):

PROJECT SUMMARYOlder adult women are at unique risk for negative outcomes of insufficient physical activity (PA). Mobile healthinterventions using wearable activity monitors have shown promise for increasing walking for PA, butadherence to PA recommendations declines sharply over time. To improve adherence in this at-riskpopulation, we propose to test an innovative method of framing mobile health devices and apps. As opposed tothe more typical corrective frame, a celebratory frame focuses on positive aspects of the target behavior. Thisapproach is rooted in Self-Determination Theory, which posits that autonomous regulations (motivationsrelated to enjoyment, identity, and values) are more powerful predictors of behavior than controlled regulations.We propose to use a socially networked active game to emphasize aspects of walking PA that are enjoyableand related to older womens' identity and values, thus increasing their autonomous regulation for PA and inturn PA adherence. The CHALLENGE study (Challenges for Healthy Aging: Leveraging Limits for EngagingNetworked Game-based Exercise) will consist of an initial sub-study followed by a large randomized controlledintervention trial. During the sub-study, we will conduct cognitive interviews among 20 older women to ensurethat refinements to the game after our pilot trials are acceptable. Then, we will randomize 300 women (aged 65 85,

6. Project Title: **SEX-SPECIFIC DETERMINANTS OF EARLY-PHASE RECOVERY FROM SKELETAL MUSCLE DISUSE**

Leader(s):   **PADDON-JONES, DOUGLAS**
UNIVERSITY OF TEXAS MEDICAL BR GALVESTON
NIH R01AG064386 / (2019 - 2023)

Core(s):

PROJECT SUMMARY .Despite the well-characterized consequences of disuse, we have a limited understanding of the early changesin the molecular environment that influence rehabilitation efforts in men and women. We propose a 2-phase,randomized, clinical trial that includes 7-days of unilateral leg disuse (Phase 1), immediately followed by 14-days of bilateral leg rehabilitation (Phase 2). We will recruit middle-aged men and women; a historicallyneglected research demographic who present with a largely youthful phenotype, but are at risk of accelerateddisuse atrophy.! In Phase 1, we will explore the sex-specific effects of skeletal muscle disuse and characterize subjects most-and least-susceptible to disuse atrophy. In male and female volunteers, single-leg muscle atrophy will be induced using an established knee-brace/disuse protocol. We will obtain skeletal muscle biopsies to characterize the sex-specific, molecular signature of skeletal muscle disuse, while highlighting differences in traditional morphologic and functional outcomes.! In Phase 2, we will map the early molecular time-course of rehabilitation in men and women and determine if disused and healthy muscle respond similarly to an exercise / rehabilitation intervention. Sex-specific volunteer cohorts will complete: i) a structured bilateral, resistance-exercise rehabilitation protocol, or ii) a passive, ambulatory recovery (Control). We will obtain muscle biopsies after 0, 48, 96 h of rehabilitation to characterize the early time course of recovery of molecular transducers of disuse. These early, pre-clinical molecular changes will be supported by traditional morphologic, body composition and muscle functionoutcomes.This project will address critical knowledge gaps that limit the efficacy of current strategies to restore musclehealth following periods of disuse. Current strategies, while well intentioned, are largely inconsistent with thepractice of evidence-based medicine and place a financial and human resource burden on our health caredelivery system. By characterizing changes in the molecular, morphologic and functional landscape of skeletalmuscle during disuse and rehabilitation and reposing our RNASeq data within the Gene Expression Omnibus(GEO) website, this study may serve as the foundation for future, targeted studies of skeletal muscle disuse inclinical populations with comorbid conditions.

7. Project Title: **The impact of sharing audio recorded clinic visits on self-management in older adults: a multisite trial**

Leader(s): **BARR, PAUL JAMES; CAVANAUGH, KERRI ; MASEL, MEREDITH C;**
DARTMOUTH COLLEGE
NIH R56AG061522 / (2019 - 2023)

Core(s):

PROJECT SUMMARY Up to eighty percent of clinic visit information is forgotten by patients immediately post visit. This is a significant barrier to self-management, especially in older adults with multimorbidity leading to poor health outcomes. After visit summaries (AVS) can improve recall, yet concerns exist about their layout, accuracy and low patient uptake. Patients and clinicians have begun audio recording clinic visits. When patients receive an audio recording of the visit, 71% listen and 68% share it with a caregiver, resulting in greater recall. Despite its growing use, to date there is no research on the impact of recording and sharing clinic visits of patient self- management ability, health outcomes or healthcare utilization. The objective of this proposal is to conduct a multi-site trial evaluating the impact of adding an audio recording of clinic visits (AUDIO) to usual care in older adults with multimorbidity, compared to AVS alone (Usual Care; UC). The specific aims are: Aim 1 Conduct a three-site trial in primary care where older patients with multimorbidity (n=540) will be randomized to receive an AVS plus audio recording (AUDIO) versus AVS alone (UC) for all scheduled clinic visits over 12 months; patients will be assessed at baseline, 1 week, 6 months and 12 months; Aim 2 Investigate and describe barriers and facilitators of the implementation of audio recordings among patients, caregivers, clinicians and clinic staff. Applicants hypothesize: (1a) Compared to those receiving the AVS alone (UC), patients randomized to also receive audio recordings (AUDIO) of clinic visits will report a greater self-management ability (measured by the Patient Activation Measure Short Form) at 12 months. Applicants will also explore the impact of AUDIO on the clinic visit, health outcomes, healthcare utilization and whether these impacts are mediated by PAM-SF; (1b) The effect of AUDIO on self-management compared to UC will be greater for patients with low health literacy than for those with high health literacy. Applicants will explore whether the impact of audio recordings is greater for individuals with caregiver support or at highest risk of poor self-management, e.g., high disease burden, moderate to severe depression. In Aim 2, applicants will investigate factors related to the implementation of audio recording and develop recommendations for an implementation toolkit to guide future dissemination of recording. The research is innovative because: i) it seeks to shift current clinical practice where visit information is provided via AVS, by adding audio recording; ii) the routine provision of visit recordings over time moves beyond prior studies that focus on single recordings of specialty visits; and iii) a trial in real-world settings of patients with multimorbidity, regularly excluded from trials, is novel and has greater external validity. The results are expected to have a major positive impact as they will increase clinical understanding of the impact and implementation of audio recording on the significant challenge of improving patient self-management especially in the face of the public health burden of multimorbidity.

8. Project Title: **UTMB HEALTH SERVICES RESEARCH TRAINING PROGRAM**

Leader(s): **KUO, YONG-FANG; OTTENBACHER, KENNETH J. ;**
UNIVERSITY OF TEXAS MEDICAL BR GALVESTON
AHRQ T32HS026133 / (2018 - 2023)

Core(s):

PROJECT ABSTRACT/SUMMARYThis new T32 program for Heath Service Research at the University of Texas Medical Branch (UTMB) seeksfunds for 5 years to support 3 predoctoral trainees per year. The program aims to increase and improve thepool of health service researchers with clinical background to help address complex issues in health caredelivery in the US. Given our strengths in the areas of health service research, we focus on using cutting edgemethodology to study the patterns and trends of health care delivery, to assess the impact of health policy, andto examine the effectiveness of various care models. The trainees are PhD or MD-PhD students in thePopulation Health Science program, Clinical Science program, or Rehabilitation Science program of theDepartment of Preventive Medicine and Community Health.UTMB has an excellent record in conducting health service research. We were funded by an R24 on HealthService Research in Underserved Population between 2001 and 2006 from the Agency for HealthcareResearch and Quality (AHRQ). Since then, we have continuously developed health service research with twoR01s and an R24 on Patient Centered Outcomes Research in the Elderly, currently funded by AHRQ. Besidesfunding from AHRQ and several additional health service research R01s from the NIH, we also have a P2Cgrant for the Center for Large Data Research and Data Sharing in Rehabilitation funded by the NationalInstitute of Child Health & Human Development and another Multi-Investigator Research Award onComparative Effectiveness Research on Cancer in Texas funded by the Cancer Prevention & ResearchInstitute of Texas. The current faculty in the affiliated departments have strengths in biostatistics, epidemiology,economics, computer science, sociology, medicine, health policy, and rehabilitation. We plan to build on ourstrengths and train health care professionals in health service research in different populations. As is the casein our other programs, special efforts will be made to recruit students from diverse clinical backgrounds, and allour trainees will focus their health service research in their clinical field. The Graduate School of BiomedicalSciences and Provost's Office have made significant commitments in the past 5 years to enhance theexcellence of graduate education at UTMB. These commitments include the President's Scholars Program torecruit outstanding graduate students and the establishment of an Office of Postdoctoral Affairs that includesorganized training and opportunities in career development and mentoring. We have developed a formalstructure and related activities to enhance recruitment and facilitate the placement of our trainees regionallyand nationally. We believe that our health care profession trainees will be competitive for leadership positionsamong the next generation of health service researchers in their clinical area.

9. Project Title: **Study in Parkinson Disease of Exercise Phase 3 Clinical Trial: SPARX3**

Leader(s): **CORCOS, DANIEL M.**
NORTHWESTERN UNIVERSITY AT CHICAGO
NIH U01NS113851 / (2019 - 2025)

Core(s):

The study objective is to establish the efficacy of high-intensity endurance exercise as first-line therapy for recently diagnosed people with Parkinson's disease (PD). No medications are yet proven to slow the progression of the signs of PD and dopaminergic medications do not benefit all the signs of PD. As such, people with PD have no adequate treatment to slow down the progression of the motor or non-motor signs of the disease. The key question is whether there is an additional benefit of exercising at high-intensity, in terms of slowing the progression of the signs of the disease, beyond the well documented benefit of treadmill training on general parameters of fitness, gait and functional mobility. Preclinical data, experimental data on humans, and epidemiological data all have demonstrated benefits of endurance exercise on the motor and nonmotor signs and symptoms of the disease, although the best dose for slowing down their progression has not been identified. We recently completed a multicenter Phase II clinical trial, the SPARX study, using a futility design. We studied the feasibility of participants with PD performing moderate intensity (60-65% of their maximal heart rate (HRmax)) and high intensity endurance exercise (80-85% HRmax). Participants had not yet started dopaminergic medication. We demonstrated that: 1) participants will exercise at between 80-85% of HRmax for at least 6 months, 2) they will exercise for at least 3 days per week, 3) adverse events are low, and 4) exercising at 80- 85% HRmax slowed progression by 2.9 points on the motor section of the UPDRS when compared to the wait list usual care group and was not deemed futile. These 4 findings were deemed a priori to be the necessary results to proceed to a Phase III efficacy trial. We now propose to conduct a 12-month

multi-center, randomized (two doses of intensity), evaluator-masked study of high intensity endurance exercise. The 2 doses of treadmill exercise are moderate intensity (4 days/wk for 30 minutes per session at 60- 65% HRmax) and high intensity (4 days/wk for 30 minutes per session at 80-85% HRmax). The study is designed to test 3 specific aims. First, to establish the efficacy of high-intensity endurance exercise to slow the progression of the signs of PD as measured by the change in the MDS-Unified Parkinson Disease Rating Scale (MDS-UPDRS Part III) score over 6 and 12 months. Second, to ascertain the effect of high dose endurance versus moderate dose endurance exercise on the progression of the signs of PD over 6 and 12 months as measured by: 1) distance covered in 6 minute walk, 2) an increased number of daily steps, 3) improved cognitive function, 4) increased VO2max, 5) improved quality of life, and 6) time to initiate dopaminergic medication and the quantity of medication. Third, to test the effects of high intensity endurance exercise on PD over 12 months on biomarkers of dopaminergic neuronal integrity and blood-derived biomarkers of inflammation, and neurotrophic factors. The study design will facilitate the translation of the study results into a meaningful clinical application of clear therapeutic value.

10. Project Title: Preclinical Development of a Novel Therapeutic to Rejuvenate Aging Muscle Stem Cells and Enhance Muscle Strength and Function Post Hip Fracture

Leader(s): **NEELAKANTAN, HARSHINI**

RIDGELINE THERAPEUTICS, LLC

NIH U44AG074107 / (2021 - 2024)

Core(s):

Muscle-aging is defined by progressive declines in mass and strength that poses a high risk for falls, fatal injury, and trauma-related fractures among older Americans (age 60+). Each year, >30% of older adults suffer a fall, resulting in ~2.8 million traumatic fractures that significantly reduce mobility, independence, overall health, and quality of life for the elderly. Among fall-related injuries, hip fractures are the most prevalent and serious; the 300,000 elderly Americans hospitalized each year with hip fracture repairs face long-term post-surgery rehabilitation with a low probability of returning to independent living and a 1-year mortality rate that staggers around 10-30%. Dampened muscle strength predisposes to and predicts poor recovery among the elderly following hip fracture. Standard-of-care including resistance exercise and protein-rich diets only marginally improve muscle strength and functional outcomes post hip fracture. Attempts to improve muscle strength in elderly individuals using pharmacotherapies have not succeeded to date. To address this challenge, Ridgeline Therapeutics has developed first-in-class small molecule nicotinamide N-methyltransferase inhibitors (NNMTis) that reactivate aged muscle stem cells (muSCs). As skeletal muscle and muSCs age, they increasingly express NNMT that interferes with NAD biosynthesis and the downstream events that control muSC regenerative function and cellular energy metabolism. Thus, NNMT is a vital contributing factor to aging muSC dysfunction and associated declines in muscle strength. Since muSCs are fundamental to regeneration and repair, rejuvenation of aged muSCs (including using NNMTi) has proven useful to boost muscle regenerative capacity and improve muscle strength and function in aged mice. Ridgeline s therapeutic development efforts have swiftly progressed from discovery, to lead optimization, mechanistic and preclinical proof-of-concept validations in clinically relevant aged muscle injury models. Treatment of aged, injured mice with the lead NNMTi RT-001 showed 2-fold increase in muSC activity and myofiber fusion index, 35-80% increase in muscle growth, and 70% increase in muscle strength. Robust efficacy and early safety index demonstration for RT-001 have de-risked and positioned it for late-stage preclinical and IND-enabling studies. Ridgeline is advancing RT-001 as a safe and effective small molecule therapeutic for clinical use in improving muscle strength and function among older adults following hip fracture surgical repairs. The objectives of this project directly aligns with this goal and focuses on completing necessary in vivo PK/PD studies to optimize oral dosing regimens, scale up synthesis of a 2 kilogram batch of RT-001, and non-GLP and GLP toxicity studies; accessory metabolism and clinically relevant biomarker assessments will be completed to complement and support IND filing and first-in-human clinical trials.

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Ebert SM, Rasmussen BB, Judge AR, Judge SM, Larsson L, Wek RC, Anthony TG, Marcotte GR, Miller MJ, Yorek MA, Vella A, Volpi E, Stern JI, Strub MD, Ryan Z, Talley JJ, Adams CM
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https://doi.org/10.1093/jn/nxab440 | PMID: 34958390 | PMCID: PMC8970988
Citations: 114 | AltScore: 6.6

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Ebert SM, Rasmussen BB, Judge AR, Judge SM, Larsson L, Wek RC, Anthony TG, Marcotte GR, Miller MJ, Yorek MA, Vella A, Volpi E, Stern JI, Strub MD, Ryan Z, Talley JJ, Adams CM
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Villarreal Rizzo AF, Downer B
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Citations: 51 | AltScore: 17.05

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RECOGNITION AND AWARDS (2022-2023)

<u>Blake Rasmussen, PhD</u> (2023)

- Appointed to Editorial Board for Aging Cell Journal

<u>Guy Nir, PhD</u> (2023)

- Selected to participate in the 2023 Butler-Williams Scholars Program

<u>Huiwen Xu, PhD</u> (2023)

- Selected as RCCN Scholar in Multidisciplinary Research

<u>Monique Pappadis, PhD, MEd</u> (2022)

- Elite Reviewer – Archives of Physical Medicine and Rehabilitation (2021)

<u>Rafael Samper-Ternent, MD, PhD</u> (2022)

- Maribel Sanchez Ayala Award from the Latin American Academy of Geriatric Medicine

<u>Rafael Samper-Ternent, MD, PhD</u> (2022)

- MCC Scholar - HCSRN-OAICs Aging Initiative

<u>Sadaf Milani, PhD</u> (2022)

- Early Career Investigator Award from the Diversity and Disparities Professional Interest Area - International Society to Advance Alzheimer's Research and Treatment

<u>Sadaf Milani, PhD</u> (2023)

- Invited to join the 2023 Research Centers for Minority Aging Research Scientist Advisory Board.

MINORITY RESEARCH

General Brief Description of Minority Activities:

UTMB Pepper Center Hispanic Council on Aging

For Administrative Core/LAC

The Pepper OAIC recognizes the need to formalize and extend its many connections to the UTMB strength in the study of older Hispanics. To do this, we have formalized our relationship with the longstanding UTMB Hispanic Center of Excellence by forming the Hispanic Council on Aging. The Hispanic Council on Aging serves as a focus for outreach in research and minority junior faculty development that will extend our strengths to make us a national focus for best practices in such research and a magnet for future scholars. The Hispanic Council on Aging does the following:

1) Identify Pepper scholars that will benefit from RCMAR funding, and making sure they have appropriate mentoring to develop their projects (REC activities);

2) Innovate approaches to increase recruitment of Hispanic populations as research participants (CRC project);

3) Serve as a portal for attracting and promoting Hispanic faculty, particularly those studying the health of older Hispanics.

The Hispanic Council on Aging consists of the Hispanic Center of Excellence Board: <u>Norma A. Pérez, Kyriakos Markides, Rebeca Wong, Alfredo Torres, Soham Al-Snih, Maria Belelcazar, Monique Pappadis, and Myrna Serna</u>. These senior faculty researchers represent the scope of scholarly activities throughout the university as well as leaders in recruitment and mentorship of minority faculty and students.

The Hispanic Council on Aging meets monthly or as needed to plan activities and report progress. A representative of the Council will attend all monthly Pepper meetings. The Council prepares an annual report as a part of the Pepper report provided to its <u>External Review Panel</u>. Results from their analysis will inform future activities.

For Clinical Research Core CRC

Developmental project: Best Practices in Recruiting Hispanic Research Participants

Recruiting participants into research is always a challenge. Older adults and minority populations each represent an additional challenge; recruiting older Hispanics is therefore doubly difficult. Recruitment strategies which work in other populations do not necessarily translate to Hispanic participants; also, the Hispanic population is widely diverse and different groups also may call for varying strategies. We therefore propose to develop best practices in recruiting Hispanic research participants. The aims of this pilot project are:

1) Review the existing literature to identify strategies used in the past;

2) Conduct qualitative studies within our local community to identify what Hispanics want and do not want in terms of their willingness to serve as research participants.

3) Develop recruitment materials and strategies that are culturally and linguistically appropriate for the target Hispanic population, particularly the aging population under the guidance of the Hispanic Council on Aging members. Develop best practices to increase the number of older Hispanics participating in research.

From these studies, we will be able to develop tailored strategies we think will be successful. We can then pilot them in our ACE unit and other local studies. We will disseminate results nationally to develop an understanding of what represents "best practices" in recruiting Hispanics as research participants.

For Education Core REC

The Hispanic Council on Aging will assist the Pepper OAIC to connect with junior investigators, institutionally and nationwide. Members of the Council will be assigned as advisors to incoming junior Hispanic faculty and help them to find appropriate mentors, development opportunities and career growth. Hispanic junior faculty will be encouraged to mentor underrepresented minority medical students and residents to encourage them early into research and expose them to aging research and geriatric medicine by participating in programs such as MSTAR and Summer Research Programs.

Hispanic Council on Aging/Hispanic Center of Excellence faculty aim to:

1) Attract and train scholars, providing contacts both institutionally and outside UTMB;

2) Develop protocols to attract Hispanics into research;

3) Disseminate best practices.

Publications on Racial Disparities (2022-2023):

Downer, B., Li, C. Y., & Al Snih, S. (2023). Hospitalizations and Emergency Room Admissions by Mexican American Older Adults with and without Dementia and Caregiver Mental Health. *J Alzheimers Dis*, *91*(3), 1185-1195. PMC9946698

Gutierrez, S., Wong, R., & Milani, S. A. (2022). The pain and depressive symptoms cascade: A bidirectional analysis of the Mexican Health and Aging Study 2012-2015. *Int J Geriatr Psychiatry*, *37*(10). PMC9725745

Lopez, D. S., Malagaris, I., Polychronopoulou, E., Tsilidis, K. K., Milani, S. A., Kristen Peek, M., Villasante-Tezanos, A., Alzweri, L., Baillargeon, J., Kuo, Y. F., & Canfield, S.

(2022). Metformin and testosterone replacement therapy inversely associated with hormone-associated cancers (prostate, colorectal and male breast cancers) among older White and Black men. *Clin Endocrinol (Oxf)*, *97*(6), 792-803. PMC9637746

Nicot-Cartsonis, M. S., Digbeu, B. D. E., Raji, M. A., & Kuo, Y. F. (2022). Disparities in Late-Stage Breast and Colorectal Cancer Diagnosis Among Hispanic, Non-Hispanic White, and Non-Hispanic Black Patients: a Retrospective Cohort Study of Texas Medicare Beneficiaries. *J Racial Ethn Health Disparities*, 1-10. PMC9794104

Pappadis, M. R., Chou, L. N., Howrey, B., & Al Snih, S. (2023). Life-space mobility and post-hospitalization outcomes among older Mexican American Medicare beneficiaries. *J Am Geriatr Soc*, *71*(5), 1617-1626. PMC10175172

Shepard, V., Al Snih, S., Burke, R., Downer, B., Kuo, Y. F., Malagaris, I., & Raji, M. (2023). Characteristics Associated With Mexican-American Hospice Use: Retrospective Cohort Study Using the Hispanic Established Population for the Epidemiologic Study of the Elderly (H-EPESE). *Am J Hosp Palliat Care*, *40*(5), 480-491. PMC9772355

Ventura, J., Downer, B., Li, C. Y., & Snih, S. A. (2023). Nativity differences in the relationship between handgrip strength and cognitive impairment in older Mexican Americans over 20 years of follow-up. *Arch Gerontol Geriatr*, *107*, 104903. PMC9974812

Minority Trainee(s):

- Monique Pappadis, PhD, MEd, Assistant Professor
  Mexican Americans have an increased risk of stroke in comparison to non-Hispanic Whites and report worse cognitive, functional, and neurological outcomes following stroke. It is well established that older adults with greater levels of mobility are likely to have lower rates of re-admissions and decreased mortality. Spatial mobility was initially conceptualized as 'life space', the space in which a person travels/moves over a specific time point. However, the initial assessment excluded the need for assistance. The Life-Space Mobility Assessment (LSA), developed at University of Alabama Birmingham, is a validated measure of community mobility in older adults during the 4 weeks prior to assessment. In addition, LSA accounts for assistance needed from a device or person. Using data from the Hispanic EPESE wave 7 (2010-2011) on Mexican Americans, the majority had restricted life-space, with nearly 80% limited to their home or neighborhood. To date, no study has identified the role of life space mobility as a potential protective factor in determining discharge destination, 30-day re-admission, and mortality following a stroke.
- Rafael Samper-Ternent, MD, PhD, Assistant Professor
  Dr. Samper-Ternent is a Clinician Scientist with a unique background in both patient care and research. Both his clinical and research activities focus on improving care and quality of life of older adults. He uses a multidisciplinary approach to analyze health disparities in different countries in Latin American and Hispanic adults in the United States. As an OAIC REC Scholar, he will focus on functional and cognitive decline of community dwelling older adults from different ethnic groups. Dr. Samper-Ternent is also serving as project manager for the UTMB clinical site of the D-CARE Study.

- Sadaf Milani, PhD, Assistant Professor

  Dr. Sadaf Arefi Milani's research focuses on how sociodemographic, behavioral, and health characteristics influence cognitive decline in old age. She works on the prevalence of diabesity, the co-occurrence of obesity and diabetes, among older adults in Mexico and its relationship with cognitive impairment. Additionally, Dr. Milani conducts research on pain and cognitive decline among older adults in Mexico, with a focus on gender differences.

No minority grant information specified.

WAKE FOREST UNIVERSITY SCHOOL OF MEDICINE
Claude D. Pepper Older Americans Independence Center

Stephen Kritchevsky, Ph.D.   336-713-8548   skritche@wakehealth.edu
Principal Investigator

Dalane Kitzman, MD   dkitzman@wakehealth.edu
Co-Principal Investigator

Kimberly Kennedy, MS, CCRC   336-713-8567   kkennedy@wakehealth.edu
Program Administrator

CENTER DESCRIPTION

The WF OAIC Leadership and Administrative Core (LAC) sets the scientific direction, optimizes administrative and fiscal operations, and ensures the scientific integrity and coherence of the WF OAIC. LAC co-leaders Drs. Kritchevsky and Kitzman will use a proven collaborative leadership model that fosters operational efficiency, high productivity, and innovative translational and multidisciplinary research focused on our theme, "Integrating pathways affecting physical function for new approaches to disability treatment and prevention".

The **Specific Aims** of the Leadership and Administrative Core are to:

1. Provide overall scientific leadership and direction for the WF OAIC. The LAC co-leaders will synthesize information regarding the local and national research environment with input from the OAIC Executive Committee, the OAIC External Advisory Board, the REC Advisory Committee and WF's senior administrative leadership to guide the direction of the OAIC through: the mix of Core services; the focus of research development projects; the tailoring of pilot award RFAs; interactions with the OAIC Coordinating Center, other OAICs and other aging-focused research centers; and the selection of early- career faculty for Research Education Component (REC) support. The LAC will integrate WF OAIC Core activities to advance the OAIC's scientific agenda, improve efficiency, and foster translation between basic and clinical research.

2. Efficiently manage the resources of the WF OAIC in compliance with applicable institutional and NIA/NIH policies. The LAC will: 1) provide administrative and budgetary support to the WF OAIC according to OAIC priorities; 2) seek additional institutional resources to extend the scope of its activities; 3) arrange for the scientific review of pilot and research development projects and candidates seeking REC support; 4) monitor all OAIC activities for timely completion and achievement of targeted goals and milestones, and intervene to remove roadblocks or (if necessary) redirect resources; and 5) assure all OAIC-supported activities follow federal and institutional rules, regulations, and guidelines and promote the responsible conduct of research and participant safety.

3. Increase WF OAIC's impact by attracting new investigators, capturing new resources, and translating findings beyond traditional research settings. The LAC will attract new researchers and research capabilities to OAIC-supported research by engaging the local and regional academic communities, in coordination with resources from WF's Sticht Center for Healthy Aging and Alzheimer's Prevention, the Section of Gerontology and Geriatric Medicine, and other academic and service units. The LAC will also promote the NIA's goals for the OAIC program by translating its research to affect the clinical care of older adults and the health and well-being of older adults in the community.

During the current cycle, the WF OAIC achieved high productivity and innovation, and enhanced its strategic positioning and prominence within Wake Forest and enhanced its local and national impact. **Compared to the previous cycle, publication productivity was increased 5% and OAIC-related extramural funding increased 91%.** The outstanding productivity of OAIC investigators occurred despite the challenging funding environment and is attributable (in part) to our innovative strategies to promote efficiency (e.g., thematic alignment, the OAIC Integrated Aging Studies Databank and Repository), and the LAC's success in leveraging $4.3 million in institutional funds in support of the OAIC mission.

WF OAIC involvement was critical in securing high-impact awards that enhance the breadth and depth of research resources available to the OAIC, including a new CTSA and a new Alzheimer's Disease Core Center. As an Associate Director of the Wake Forest Clinical and Translational Science Institute and director of its KL-2 program, Dr. Kritchevsky aligned CTSI resources with the OAICs for their mutual benefit. His role as Associate Dean for Research Development provides him with influence over WF's research priorities. Locally, the OAIC has successfully expanded our research partnerships to deliver interventions in innovative settings (Meals-on-Wheels, Agricultural Extension Service, YMCA's and Continuing-Care communities). WF OAIC leaders have been national advocates for the OAIC's mission and have helped develop multi-centered trials testing hypotheses generated from OAIC work (e.g. LIFE, ENRGISE, PCORI/STRIDE) and pivot large multi-center trials towards OAIC relevant outcomes (e.g., SPRINT, Look AHEAD). The WF OAIC, under the leadership of Drs. Kritchevsky and Kitzman, will use OAIC support to sustain the LAC's continual innovation through the 2018-2023 cycle.

To address these objectives our OAIC is composed of seven cores, which currently supports 4 REC Scholars, 17 clinical studies (all which are funded by the NIH), 2 research development projects, and 8 pilot studies.

CORES

Leadership and Administrative Core (LAC)

Leader 1:	Stephen Kritchevsky, PhD	skritche@wakehealth.edu
Leader 2:	Dalane Kitzman, MD	dkitzman@wakehealth.edu

The Leadership and Administrative Core is responsible for scientific leadership and direction of the center. It coordinates the functions of the OAIC cores and projects in order to facilitate communication and foster translation between basic and clinical research and ensure access of investigators to core resources. It assures the coordination of OAIC resources and functions with other research and training grants and institutional resources. It is supported by the OAIC Executive Committee, the Joint Scientific Review Panel, and the External Advisory Committee. The core communicates with other OAICs and the NIA and fosters collaborations with other OAICs including UTMB, University of Maryland and Duke. Maintains the OAIC web-based tracking and monitoring system and promotes the use of uniform assessment batteries in all OAIC supported studies. The LAC works with Core leaders to identify, review, and support projects and activities which serve to advance the scientific goals of the OAIC. The LAC and Executive Committee actively identify promising projects and REC candidates through informal networks, review of all new faculty hires at WF, and all new grant awards to WF faculty. WF OAIC overarching resource allocation priorities are based on: 1) scientific merit; 2) theme relevance; 3) REC scholar/junior faculty involvement; 4) Pilot/Exploratory study support; 5) research development projects; and 6) externally supported projects. This priority maintains our thematic coherence and enhances support for projects that may need it.

Research Education Component (REC)

Leader 1:	Stephen Kritchevsky, PhD	skritche@wakehealth.edu
Leader 2:	Denise Houston, PhD	dhouston@wakehealth.edu
Leader 3:	Heidi Klepin, MD	

The Research Education Component (REC) continues to promote the development of future research leaders in the area of focus of this OAIC application, integrating pathways affecting physical function for new approaches to disability treatment and prevention. The core emphasizes development of skills for translating basic findings into clinical research, and clinical findings into basic research. Resources of this core are integrated with other external sources for career support, such as NIH career development and research awards, fellowships, and non-NIH career and research awards. Resources of the REC are also leveraged with assets of the Wake Forest Clinical and Translational Science Institute (CTSI); Dr. Kritchevsky is a Core Faculty member of the CTSI's KL2 program. The CTSI has a Translational Research Academy, a Mentor Academy, and a K and R Award Writer's Series, which provide added value to the REC through courses, facilitation of grants, navigating regulations, and evaluating competencies. All REC scholars are encouraged to participate in the Translational Research Academy to help optimize the relative contributions of the CTSI and REC programs. The REC co-leaders are Drs. Kritchevsky and Houston; Dr. Klepin, REC leadership intern, will specifically recruit and advise promising clinical faculty. Dr. Kritchevsky is a national leader in aging research, whose expertise spans the translational spectrum from basic science to policy formulation. Dr. Houston is a national leader in nutrition and aging research with expertise in both epidemiologic studies and clinical trials. Dr. Klepin is a national leader in geriatric oncology with expertise in conducting patient-oriented

research, including both pharmacologic and behavioral interventions. Each of the Core Leaders is accomplished in interdisciplinary and team-based research, and well positioned to assure that REC programs and activities are well integrated with other internal and external career development activities. All REC projects continue to utilize Pepper Core support to signify the integration of resources and disciplines. This includes: Ellen Quillen, PhD (Integrative Biology Core) and Atalie Thompson, MD, MPH (Biostatistics and Data Management Core and Clinical Research Core). The REC currently supports five REC scholars which includes two REC scholars that began in the summer/fall of 2021 (Quillen, Thompson) and three new REC scholars (Genesio Karere, PhD; Lindsay Reynolds, PhD; and Jaime Hughes, PhD) that started in April 2022. The three new REC scholars were selected in response to an RFA for REC scholars distributed across the institution in October 2021. Two REC developmental scholars (Chinenyenwa Usoh, MD, and Philip Kramer, PhD) were also selected with the purpose of helping them refine and develop their research ideas and strengthen their research portfolios.

Pilot and Exploratory Studies Core (PESC)

Leader 1:   Dalane Kitzman, MD   dkitzman@wakehealth.edu
Leader 2:   Tom Register, PhD   register@wakehealth.edu
Leader 3:   Jingzhong Ding, MD, PhD   jding@wakehealth.edu

Effective pilot and exploratory studies (PES) play a critical role in the development of successful, externally-funded research proposals, particularly for early stage investigators who often lack other means to obtain preliminary data. The Wake Forest OAIC Pilot and Exploratory Studies Core (WF PESC) proposes to continue our coordinated, multi-faceted group effort to promote PESs, and to further innovate to optimize our processes. Through support from the OAIC grants, Wake Forest University has been very active in efforts to enhance aging related research activities. These activities have focused on the mechanism, treatment and outcomes associated with functional decline and disability and have had a profound impact on the research culture at our institution with greater awareness and interest in addressing these important yet understudied issues of geriatric research.

The overall goal of the WF OAIC PESC is to develop key information needed for the design of definitive, externally funded, translational research studies that promote the WF OAIC mission of advancing our understanding of pathways influencing physical function and developing new approaches to disability prevention and treatment.

This will be achieved by executing the following Specific Aims to:

1) Identify and promote promising key areas of research
2) Identify and recruit talented investigators from complementary fields to focus on OAIC-themed aging research
3) Solicit and facilitate competitive research proposals and conduct peer review to select those with the best science and career development opportunities
4) Coach and mentor investigative teams to maximize the quality of research proposals and projects
5) Team with other WF OAIC cores to facilitate successful completion of the selected pilot projects and mentor junior early career investigators to advance their development as successful translational scientists

Continuously evaluate, refine, and optimize OAIC PESC processes and procedures.

Clinical Research Core (CRC)

Leader 1:	Jack Rejeski, PhD	rejeski@wfu.edu
Leader 2:	Anthony Marsh, PhD	marshap@wfu.edu
Leader 3:	Jeff Williamson, MD, MHS	jwilliam@wakehealth.edu
Leader 4:	Kristen Beavers, PhD	beaverkm@wfu.edu

The Clinical Research Core (CRC) provides institution-wide guidance on the design and conduct of clinical research consistent with the WF OAIC theme (present and past) and involving older adults. The CRC also performs validated, standardized assessments of physical and cognitive function, strength, and disability. Assistance is provided to investigators at all levels of experience and all sizes of research studies with integration of these OAIC measures into their research involving older adults. The Core's scientific focus is the advancement of physical function based clinical research methods and the design, implementation, and evaluation of interventions designed to measure whether specific interventions developed in this or other cores preserve the independence of older adults. Functional assessment instruments and trial design encompass both community and clinic-based settings. Additionally, members of the core are involved in cross-disciplinary translational research with other cores within the center. The overall hypothesis for this CRC is that the inclusion of efficient, standardized measures of functional assessment will promote translation of the OAIC research into clinical research and care through improved understanding of function as both a risk factor and an outcome (see below). The Core also includes both 1) a recruitment unit and 2) a muscle and adipose tissue biopsy unit for OAIC supported studies. In addition, if including aging-related measures is required as part of specific studies, the Core supported staff will assist investigators by training them or their staff and/or collecting these assessments. Currently the standard assessment battery includes: 1. Anthropometry (Height, Body Mass, Abdominal Circumference) 2. Grip strength (Jamar hand grip dynamometer) 3. Lower extremity muscle power (Keiser knee extension and leg press) 4. The Short Physical Performance Battery (SPPB: three tests of physical function - standing balance, usual pace gait speed over 4 meters, time to rise from a chair and sit down five times) 5. 400 meter walk test (400MWT: study specific protocols for either usual or fast pace gait speed) 6. Pepper Assessment Tool for Disability (PAT-D: self-report instrument) 7. Mobility Assessment Tool – short form (MAT-sf: 10 or 12-item computer based self-report assessment of mobility using animated video clips) 8. Digit Symbol Substitution Test (DSST: validated cognitive assessment that is strongly correlated with walking speed) 9. Montreal Cognitive Assessment© (MoCA: global cognitive assessment that aids in interpreting DSST performance) The core also has the capacity to assess muscle strength of various muscle groups (Biodex isokinetic dynamometer), gait speed and spatiotemporal parameters of gait (GAITRite instrumented mat), and postural sway descriptors (AMTI portable force platform).

BioImaging

Leader 1:	Leon Lenchik, MD	llenchik@wakehealth.edu
Leader 2:	Christina Hugenschmidt, PhD	chugensc@wakehealth.edu
Leader 3:	Ashley Weaver, PhD	asweaver@wakehealth.edu

This core supports independently funded studies, pilot studies, and research development studies in the accurate in vivo measurement of body composition, specifically focusing on skeletal muscle mass and composition, fat mass and distribution, and bone mineral density. This core collaborates with other OAIC cores in the development of new, multidisciplinary, and translation research projects directed at elucidating the etiology, consequences, prevention and treatment of sarcopenia

and its sequelae. The BRC has contributed to the success of the WF OAIC by helping to quantify structural and functional tissue-related measures, developing novel bio-imaging techniques, integrating imaging assessments with other OAIC cores, and using imaging technologies for studies of physical function and disability in older persons. The BRC has also provided early-career and experienced investigators access to a broad range of imaging methods relevant to disability and age-related physical decline including dual x-ray absorptiometry (DXA), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasonography (US) as well as access to expertise and mentoring in bio-imaging including image acquisition, analysis, interpretation, archival, and dissemination. The Bioimaging Resource Core (BRC) has contributed to the success of the WF OAIC by helping to quantify structural and functional tissue-related measures, integrating imaging assessments with other OAIC cores, and using imaging technologies for studies of physical function and disability in older persons. The BRC has also provided early-career and experienced investigators access to a broad range of imaging methods relevant to age-related physical decline including dual x-ray absorptiometry (DXA), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasonography (US) as well as access to expertise and mentoring in bio-imaging including image acquisition, analysis, interpretation, archival, and dissemination. Over the past year, the BRC has added an emphasis on expanding the imaging infrastructure. The infrastructure initiative has two parts: 1) updating hardware and software and harmonizing archiving with other OAIC and ADRC cores to increase access to data already collected and 2) adding new bone imaging capability to the suite of imaging techniques available to OAIC investigators. The BRC received an administrative supplement (in response to NOT-AG-17-008 and PA-16-287) to develop research on Alzheimer's disease and Alzheimer's-related dementias (ADRD). The goal was to harmonize imaging data workflow between the WF OAIC and WF ADRC. In the past year, the BRC made progress on: 1) archiving of past imaging studies using a newly acquired Vendor Neutral Archive (VNA), 2) harmonizing imaging data storage, processing, and archiving between the OAIC and ADRC, and 3) harmonizing imaging data request process between OAIC and ADRC. Such harmonization will allow investigators to ask cutting-edge questions about the brain-body integration including the trajectory of physical decline in people with ADRD and the trajectory of cognitive decline in older adults with mobility disability, obesity, and frailty.

Biostatistical Design and Analysis Core (BIC)

Leader 1:	Iris Leng, PhD	ileng@wakehealth.edu
Leader 2:	Nicholas Pajewski, PhD	npajewsk@wakehealth.edu
Leader 3:	Dan Beavers, PhD	dbeavers@wakehealth.edu

The goal of the Wake Forest OAIC Biostatistics and Research Information Systems Core (BIC) is to build on our outstanding success in biostatistical collaboration and to expand a broad class of statistics/informatics tools tailored to research in aging. The BIC team has highly qualified investigators/staff with expertise in design and management of observational, pilot, and interventional studies; centralized and decentralized data management; forms design and data processing, psychometrics; statistical analysis of data from multiple study designs; and development of novel statistical methods. The BIC team is committed to the WF OAIC's programmatic aims to: (1) discover new common pathways contributing to age-related declines in physical function and disability; (2) develop, evaluate, and refine strategies for disability treatment and prevention; (3) translate proven strategies beyond traditional research environments; and (4) train the next generation of research leaders focused on disability treatment and prevention. The

BIC provides expertise and critical infrastructure essential to the mission of the WF OAIC, and promotes efficiency through centralized data management. BIC members will play a key role in study design, analysis, and interpretation for WF OAIC projects, will be integral members of mentoring teams for REC Scholars and early-stage faculty, and continue their intellectual contributions that strengthen research on aging through the development of novel measurement, statistical, and research informatics tools. During the past year, members of the Biostatistics and Research Information Systems Core (BIC) have continued to provide support for numerous studies performed within the WFU OAIC. Efforts include developing web-based data entry systems for individual studies, harmonizing common measurements taken across multiple studies, performing analyses of pilot/developmental studies and existing data bases, and collaborating on the development of pilot studies and grant submissions resulting from WFU OAIC pilot studies. In addition, faculty in the Core continue to be involved with mentoring committees for REC fellows, collaboration on career development award submissions, reviewing pilot studies and applications of prospective REC fellows. During the past year, members of the BIC collaborated with WFU OAIC investigators in the submission of several R01s, a U24, and a K76 grant. During the past year, members of the BIC collaborated with WFU OAIC investigators in the submission of several R01s, a U24, and a K76 grant. As of October 2021, the BIC has also undergone a planned change in leadership, with Drs. Miller and Ip stepping down from their roles.

Integrative Biology Core

Leader 1:   Barbara Nicklas, PhD   bnicklas@wakehealth.edu

Leader 2:   Osvaldo Delbono, PhD   odelbono@wakehealth.edu

Leader 3:   Jamie Justice, PhD   jjustice@wakehealth.edu

Over the past year, the Integrative Biology Core (IBC) advanced the science of our OAIC by adding biological measures to facilitate translational research for OAIC investigators and by advising and mentoring REC scholars and early-career faculty. We also continued maintenance of our centrally collected and stored Biological Specimen Repository from aging-related studies. The Core provided resources and personnel in support of several externally-funded studies (SOMMA, HALLO-P, U01 Aging Biomarkers, SECRET2, VARIA, INVEST, UPLIFT, B-NET, HOPE and EMPOWER), and externally-funded and OAIC-supported pilots. Core Resource Use and Development of New Services: Repository, Biomarker, and tissue biopsy services—IBC personnel assist study investigators with the proper collection, transfer, and central storage of human biological tissue specimens and facilitate their later use in ancillary studies by other investigators. In the past year the Core supported labeling, tracking and storage of blood samples from participants enrolled in 6 externally-funded studies (INVEST, SOMMA, B-NET, SECRET2, HOPE, and UPLIFT), and assisted with collection, processing, and storage of muscle (SOMMA) and adipose tissue (SOMMA). The Core also expanded its biomarker services through purchase of two instruments for biomarker determination: Ella SimplePlex and Luminex LX200. Ella SimplePlex is a semi-automated device with integrated cartridge system used for targeted biomarkers – which will form the basis for an expanded 'Pepper Common Battery' for biomarkers, and Luminex LX200 has advanced multiplexing capability that permits a discovery-based biomarker approach. The two systems work well in tandem, providing industry-standard biomarker multiplexing via Luminex LX200 which can be used to identify specific markers for analysis using Ella SimplePlex. Resources and personnel advanced the science of our OAIC theme by adding measures to externally-funded studies and pilots to facilitate translational research for OAIC investigators, and by advising and mentoring of the REC scholars. In the past year, the Integrative Biology Core (IBC) advanced the science of our OAIC by adding biological measures to facilitate

translational research for OAIC investigators, and by advising and mentoring REC scholars and early-career faculty. We also continued maintenance of our centrally collected and stored Biological Specimen Repository from aging-related studies. The Core provided resources and personnel in support of several externally-funded studies (SOMMA, HALLO-P, U01 Aging Biomarkers, SECRET2, VARIA, INVEST, UPLIFT, B-NET, HOPE and EMPOWER), and externally-funded and OAIC-supported pilots.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications

Lindsay Reynolds, PhD
Assistant Professor / Department of Epidemiology and Prevention
<u>Dietary Patterns and Biological Aging in the Women's Health Initiative</u>

Years / Publications: 2022-2024 / 1 (total) 0 (1st/Sr)

To examine epigenetic aging measures as a mediator between adherence to healthy dietary patterns and incidence of frailty over ~ 10 years using existing data from the Women's Health Initiative.

- (Pending Funding) Title: MARVEL: A Multidisciplinary Assessment of Risks from Vaping during Early Life Project Number: P01CA269048-02 Name of PD/PI: Sutfin/Donny MPIs Source of Support: NCI/NIH Submission date: 5/19/2022 Role: Co-I (co-lead Project 3) Project/Proposal Start and End Date: 04/01/23 - 03/31/28
- Title: Epigenetics of COPD - SPIROMICS pilot Name of PD/PI: Reynolds, LM Source of Support: Wake Forest Tobacco Control Center of Excellence Year 03/01/2022 - 03/31/2023 1.80 Calendar months
- Title: Women's Initiative Health (WHI) - Regional Center (RC) Project Number: 75N92021D00005 Name of PD/PI: Vitolins, M. Source of Support: NHLBI Year 10/15/2022 - 10/14/2023 1.8 Calendar months

Genesio Karere, PhD
Assistant Professor / Department of Internal Medicine, Section on Molecular Medicine
<u>MicroRNA biomarkers and pathways underlying response to exercise intervention in older adults</u>

Years / Publications: 2022-2024 / 1 (total) 0 (1st/Sr)

To identify a panel of circulating miRNA biomarkers and coordinately regulated miRNA-gene networks and pathways indicative of response to exercise in older obese adults from prior WF OAIC supported intervention studies. Specific aims: Using stored samples from the IASDR, 1) Identify a panel of circulating miRNA biomarkers indicative of response to exercise intervention in older adults with obesity; and 2) Identify coordinately regulated miRNA-gene networks and pathways underlying response to exercise intervention in older adults with obesity.

Jaime Hughes, PhD
Assistant Professor / Department of Implementation Science
<u>Promoting healthy sleep-wake behaviors across a 24-hour cycle in frail older adults</u>

Years / Publications: 2022-2024 / 7 (total) 5 (1st/Sr)

1) describe frail older adults' sleep-wake behaviors across a 24-hour cycle and explore the association between co-occurring poor sleep and low activity with functional status; 2) explore older adults' and providers' attitudes towards a comprehensive sleep-wake intervention, including treatment knowledge and preferences as well as potential intervention and implementation barriers and facilitators; and 3) explore the feasibility and acceptability of daytime intervention components for a comprehensive sleep-wake intervention in frail older adults in a pilot trial.

Ellen Quillen, PhD
Assistant Professor / Department of Internal Medicine, Section on Molecular Medicine
<u>A multiomic approach to profiling muscle contractility and mobility in healthy adults</u>

Years / Publications: 2021-2023 / 2 (total) 1 (1st/Sr)

- Wake Forest Pepper Pilot award: Monkeys, muscle, and mobility: a multi-omic approach to understanding the biology of muscle aging (1/22 – 12/22)

Atalie Thompson, MD, MPH   2021-2023 /
Assistant Professor / Department of Ophthalmology, Section on Glaucoma   3 (total)
<u>Exploring visual impairment and physical dysfunction in older adults</u>   1 (1st/Sr)
To determine if age-related differences in both the brain structure and functional brain networks explain age-related differences in visual function and how these differences in visual function relate to differences in physical function.

Past Scholars
Kathryn Callahan, MD, MS, Gerontology and Geriatric Medicine (2014-2018)
Candace Parker-Autry, MD, Obstetrics-Gynecology (2015-2019)
Rita Bakhru, MD, MS, Pulmonary, Critical Care, Allergy and Immunologic Diseases (2016-2021)
Jamie Justice, PhD, Gerontology and Geriatric Medicine (2017-2018)
Amber Brooks, MD, Anesthesiology (2017-2018)
Sam Lockhart, PhD, Gerontology and Geriatric Medicine (2018-2019)
Hariom Yadav, PhD, Molecular Medicine (2019-2021)
Jason Fanning, PhD, Health and Exercise Science (2019-2021)

PILOT/EXPLORATORY PROJECTS (4 Pilot Projects Listed)

1. Project Title: **PESC 2020.1 Application of the Novel D3Cr Dilution Method to Better Understand Weight Loss Associated Changes in Muscle Mass and Physical Performance Among Older Adults with Obesity**

Leader: **Kristen Beavers, PhD (Health & Exercise Science)**

The number of older adults living with obesity is growing at an unprecedented rate. Intentional weight loss (WL) can reverse obesity but concerns develop as WL decreases muscle mass. Counter-intuitively, despite decreased muscle mass; older adults can significantly improve muscle strength, physical performance, and mobility following intentional WL. We posit these paradoxical observations originate from indirect bioimaging methods commonly used to approximate muscle mass in clinical research. In contrast to these methods, the D3-Creatine (D3Cr) dilution method directly measures whole-body muscle mass. Consequently, D3Cr muscle mass displays stronger associations with physical function (i.e. strength, physical performance, and mobility) than dual energy x-ray absorptiometry (DXA) lean mass. However, given the novelty of this method, D3Cr muscle mass has not been examined in an intentional WL RCT; thus, the effects of intentional WL on changes in D3Cr muscle mass remain unclear. To address this knowledge gap, and as an appropriate next step in this line of research, we propose to add the D3Cr muscle mass measure to the ongoing NIA and Claude D. Pepper Older Americans Independent Center supported RCT (NCT04076618), Incorporating Nutrition, Vest, Education and Strength Training trial (INVEST). This pilot will leverage the current INVEST assessment schedule to add the D3Cr muscle mass measure at baseline and six-months. The primary objective of this pilot is to determine the feasibility of the D3Cr muscle mass measure as part of a clinical WL trial. We hypothesize this method for measuring muscle mass will be feasible among participants enrolled in INVEST. Additionally, our secondary objectives aim to (i) quantify the associations between six-month change in D3Cr muscle mass and change in 1) physical function, and 2) computed tomography (CT) muscle density and cross-sectional area (CSA), and DXA lean mass among 30 INVEST participants and (ii) examine the ability of baseline D3Cr muscle mass, CT muscle density and CSA, and DXA lean mass to predict six-month change in physical function among 90 INVEST participants. Overall, we hypothesize stronger associations will be observed between change in D3Crmuscle mass and physical function, compared to DXA and CT; and that baseline D3Cr muscle mass will predict intervention-related changes in muscle physical function; and, to a greater degree than DXA or CT parameters. These data will provide first of its kind data identifying the feasibility of the D3Cr method in a WL trial, support a prior R01 application (AG070169; 35%; MPIs: Cawthon/K. Beavers), and provide a unique training opportunity for Dr. Miller (T32 AG033534).The number of older adults living with obesity is growing at an unprecedented rate. Intentional weight loss (WL) can reverse obesity but concerns develop as WL decreases muscle mass. Counter-intuitively, despite decreased muscle mass; older adults can significantly improve muscle strength, physical performance, and mobility following intentional WL. We posit these paradoxical observations originate from indirect bioimaging methods commonly used to approximate muscle mass in clinical research. In contrast to these methods, the D3-Creatine (D3Cr) dilution method directly measures whole-body muscle mass. Consequently, D3Cr muscle mass displays stronger associations with physical function (i.e. strength, physical performance, and mobility) than dual energy x-ray absorptiometry (DXA) lean mass. However, given the novelty of this method, D3Cr muscle mass has not been examined in an intentional WL RCT; thus, the effects of intentional WL on changes in D3Cr

muscle mass remain unclear. To address this knowledge gap, and as an appropriate next step in this line of research, we propose to add the D3Cr muscle mass measure to the ongoing NIA and Claude D. Pepper Older Americans Independent Center supported RCT (NCT04076618), Incorporating Nutrition, Vest, Education and Strength Training trial (INVEST). This pilot will leverage the current INVEST assessment schedule to add the D3Cr muscle mass measure at baseline and six-months. The primary objective of this pilot is to determine the feasibility of the D3Cr muscle mass measure as part of a clinical WL trial. We hypothesize this method for measuring muscle mass will be feasible among participants enrolled in INVEST. Additionally, our secondary objectives aim to (i) quantify the associations between six-month change in D3Cr muscle mass and change in 1) physical function, and 2) computed tomography (CT) muscle density and cross-sectional area (CSA), and DXA lean mass among 30 INVEST participants and (ii) examine the ability of baseline D3Cr muscle mass, CT muscle density and CSA, and DXA lean mass to predict six-month change in physical function among 90 INVEST participants. Overall, we hypothesize stronger associations will be observed between change in D3Crmuscle mass and physical function, compared to DXA and CT; and that baseline D3Cr muscle mass will predict intervention-related changes in muscle physical function; and, to a greater degree than DXA or CT parameters. In May 2022, baseline and six-month pre-dose/post-dose urine sample collect was completed on our target 24 participants, and samples were sent to Dr. Bill Evan's group (co-I) for processing. An abstract describing the quantification of total body muscle mass was submitted by Allison Avery (HES graduate student) accepted for presentation at the 2023 Southeastern American College of Sports Medicine (SEACSM) annual meeting (2.24.22; Greenville, SC). A second abstract describing associations between D3Cr muscle mass and DXA lean mass was submitted in December 2022 to the 2023 National American College of Sports Medicine (ACSM) annual meeting by Dr. Daniel Beavers. Collectively, data will serve the basis of Ms. Avery's thesis and corresponding manuscript (targeting submission to the Journal of Cachexia, Sarcopenia, and Muscle by April 2023).

2. Project Title:	**PESC.2020.3 Real-world monitoring of limb loading for bone preservation during weight loss**	
Leader:	**Ashley Weaver, PhD, Katherine Hsieh, PhD (Biomedical Engineering)**	

Obesity is a serious health concern among older adults that is associated with a loss of physical function and increased disability. Despite known medical complications that accompany obesity, there is reluctance to recommend intentional weight loss for older adults. This hesitation is partly due to reduced bone mineral density (BMD) that is observed with weight loss in this population, which can exacerbate the potential for development of osteoporosis and osteoporotic fracture. Reduced BMD because of weight loss is thought to occur due to less mechanical stress on the bone with reduced body weight. Although resistance training increases mechanical loading and attenuates BMD loss, compliance is challenging among older adults. A novel method to increase mechanical loading and improve BMD is through wearing weighted vests. This mode of increasing external load is currently being evaluated in an active OAIC-investigator led clinical trial (INVEST). However, the INVEST trial does not contain a direct measure of limb loading. The lack of direct limb loading metrics combined with uncertainty as to which loading metrics are associated with improved bone health likely contributes to observed variation in individual levels of preserved BMD with external loading interventions. Therefore, the overarching goal of this study is to evaluate the feasibility of using

innovative force-sensing insoles to compare limb-loading response between external loading during intentional weight loss and intentional weight loss alone. Force-sensing insoles are a portable, valid, and reliable wearable technology that measures force at the foot-shoe interface and provides an indicator of overall limb loading. These insoles can be used outside of a research or clinical setting and measures real-world activities for continuous hours. Leveraging the investigator's ongoing clinical trial, the primary goal of this study is to evaluate the feasibility of measuring daily limb loading using force-sensing insoles in 45 overweight or obese older adults (ages 60-85 years) in an intentional weight loss program combined with weighted vest use (VEST+WL) or resistance training (RT+WL) compared to intentional weight loss alone (WL). We hypothesize we will be able to recruit participants into the study with high adherence and satisfaction when wearing the insoles. We will also compare a) daily loading metrics with the insoles and b) femoral stress and strain between groups using CT imaging and finite element (FE) modeling. Last, we will identify associations and between limb loading metrics, changes in physical function and BMD change. The results of this study will expand the ability for remote home-based assessment and intervention delivery through force-sensing insoles, a necessity during the COVID-19 pandemic. Moreover, these findings will understand how to tailor external loading during weight loss for older adults to maximize their physical function and prevent disability associated with aging. Recent Updates: 44 participants have completed baseline insole assessment: 43 of those have been randomized, 37 participants have competed at-home wear, and 36 have completed follow up assessment. Data collection will be completed by the end of January 2023. Limb loading metrics (cumulative loading, loading rate, peak loading) are being processed and analyzed as data collection is on-going. Baseline data processing is completed, and at-home wear and follow-up data are currently being processed. Subject specific FE models of the dominant leg for randomized subjects have been generated. Simulations have been conducted using a well-validated full human body FE model in the mid-stance stance of the gait cycle to quantify how loads measured at the insole (foot) transfer to loading at the mid-femur level. From this, a translation value was derived to appropriately associate the insole forces to the mid-femur shaft of the isolated femoral FE model. Relationships derived from literature are being used to simulate the mid-femur in the maximal force configuration corresponding to each subject (i.e. heel strike or toe off), which was determined through visual inspection of the force v. time data. Subject-specific FE simulations are in progress, and virtual instrumentation is being developed for the FE models to extract strain metrics from the simulations. As data is being continuously processed, a feasibility paper (Aim 1 of the pilot) is currently drafted and will be submitted in Spring 2023.

3. Project Title: **PESC.2020.4 (Ignition Pilot) MicroRNAs biomarkers and miRNA-gene networks associated with exercise-modulated weight loss**

Leader: **Genesio Karere, PhD (Internal Medicine)**

The prevalence of overweight and obesity is increasing in the US and the world-wide. Obesity is associated with comorbidities, including cardiovascular disease, diabetes and hypertension. Exercise is a proven approach to weight loss and is accompanied by physiological changes in skeletal muscles. Identification of skeletal muscle miRNAs associated with weight loss and measured in circulating biofluids is important for elucidating molecular indicators of weight loss and exercise-modulated molecular mechanisms underlying the weight loss. MicroRNAs (miRNAs) are post-transcriptional regulators of gene expression that results in alteration of mRNA and protein abundance, impacting diverse biological processes including cell growth, proliferation, differentiation and apoptosis. These processes are fundamental to maintenance of

tissue cellular homeostasis. miRNAs expression is responsive to external stimuli, including exercise. Consequently, miRNAs are emerging potential biomarkers because are readily dateable in biofluids, including plasma/serum, saliva and urine, and potential therapeutic targets. Dysregulation of a few specific miRNAs (miR375. 126-3p, 663, 30c-p, 100-5, 27-3p, and 590-5p) has been implicated in weight loss after bariatric surgery (Doyon L et al. 2020). Inhibition of miR-324-5p resulted in reduction of adipose tissue and overall body weight loss in juvenile mice (Li D et al 2019). Other studies have revealed miRNAs dysregulated after exercise. For example, the expression of skeletal muscle-specific miRNAs (miR-1, miR-133a and b, miR-208b and miR-206) measured in plasma increased after chronic exercise (Banzet et al. 2013). In another study, serum circulating levels of miR-486 decreased after chronic versus acute exercise, and the expression was negatively correlated with VO2 max (Aoi et al. 2013). Together these studies separately suggest that miRNAs are responsive to weight loss and exercise. However, a comprehensive study revealing miRNA biomarkers of and molecular mechanisms underlying weight loss due to exercise is lacking. The objective of the proposed pilot study is to evaluate the feasibility of using miRNAs to predict weight loss after exercise and to provide potential mechanistic insights. We hypothesize that miRNAs are potential biomarkers predicative of weight loss after exercise, providing potential insights to molecular mechanisms underlying exercise outcomes.

We will test the hypothesis using the following specific aims:

1. Identify circulating miRNAs in plasma that correlate with weight loss after exercise. We will use small RNA Seq to assess miRNAs in plasma at baseline and post intervention in two groups: a group that showed weight loss after exercise (n= 5 pairs) and another group that exhibited no change (n= 5 pairs). Outcomes will be identification of miRNAs differentially expressed between baseline and post interventions in each group and miRNAs that are differentially expressed between the groups post intervention.

2. Identify skeletal muscle miRNA-gene regulatory networks associated with weight loss. We use the same study design in Aim 1 and small RNA Seq to identify differentially expressed miRNAs. In addition, we will identify miRNA-gene regulatory networks by integrating miRNA data and existing skeletal muscle transcriptomic data from the same individuals. Outcomes will be identification of skeletal muscle differentially expressed miRNAs and miRNA-gene networks dysregulated in exercise-modulated weight loss, providing potential biomarkers and insights to molecular mechanisms underlying weight loss after exercise.

4. Project Title:	**PESC.2021.1 Epigenetics of an intensive lifestyle intervention: the Look AHEAD study.**
Leader:	**Lindsay Reynolds, PhD (Epidemiology and Prevention), Mark Espeland, PhD (Gerontology and Geriatric Medicine), Timothy Howard, PhD (Biochemistry), Carl Langefeld, PhD (Biostatistics)**

Diabetes and obesity increase the risk of age-related health deficits and may accelerate epigenetic aging. Lifestyle interventions promoting weight loss, such as the Action for Health in Diabetes (Look AHEAD) trial intervention, can potentially buffer against decline in age-related health status in overweight or obese adults with type 2 diabetes. However, significant variation exists among who benefits from intensive lifestyle intervention (ILI) programs. Better understanding of the biological impact of ILI could help lay the foundation for personalized

medicine approaches to predict individual responses to ILI. Epigenetic aging measures (the difference between a DNA methylation-based measure of biological age vs. chronological age) capture aspects of biological aging, and have potential as biomarkers of impact of ILI. We hypothesize that an ILI is more beneficial for participants with higher baseline measures of epigenetic aging, and that changes in epigenetic aging mediate benefits of ILI on accumulation of health deficits over time. To test our hypothesis, we are proposing to test epigenetic aging measures as predictors and biomarkers of the impact of the Look AHEAD ILI in adults with diabetes and obesity. We will assess baseline epigenetic age acceleration as a predictor of impact of an ILI on frailty in adults with diabetes and obesity. The goal of this pilot study is to generate preliminary data establishing feasibility and estimates for sample size calculations for an R01 application. We will generate epigenomic data and DNA methylation-based estimates of epigenetic aging in samples from a subset (n=32) of participants of the Look AHEAD trial at baseline and ~16 years after baseline. We will generate descriptive statistics for baseline epigenetic aging measures (epigenetic age acceleration and rate of aging) and for the change in epigenetic aging measures from baseline to Year 16 visit. Baseline epigenetic aging and change in epigenetic aging from baseline to Year 16 visit will be compared between intervention arms: ILI (n=16) vs. diabetes support and education (control condition; n=16). We will also compute associations of baseline epigenetic aging measures with change in frailty index from baseline to Year 16 visit (n=32). Our experienced and multi-disciplinary team, led by an Early Career Investigator, is well-positioned to perform the proposed pilot study, and future studies aiming to better understand the biological basis of benefit of an intensive lifestyle intervention for aging adults with diabetes who are overweight or obese. Most recently the pilot study has received the samples, DNA extracted, methylation arrays run, methylation data generated, DNAm GrimAge has been calculated, and data analysis has begun to generate the pilot data to support planned R01 proposal to be submitted in the fall of 2023.

DEVELOPMENT PROJECTS (0 Development Projects Listed)

No development projects.

RESEARCH (27 Projects Listed)

1. Project Title: **SENESCENT CELL BURDEN IN HUMAN AGING AND OBESITY: FUNCTIONAL CONSEQUENCES AND REDUCTION BY CALORIC RESTRICTION**

Leader(s): **JUSTICE, JAMIE NICOLE**

WAKE FOREST UNIVERSITY HEALTH SCIENCES

NIH K01AG059837 / (2018 - 2023)

Core(s): - Pilot and Exploratory Studies Core (PESC)

Project SummaryA key aim of this proposal is to equip the candidate, Dr. Jamie Justice, with the expertise to become anindependent investigator who can advance interventions that extend healthy lifespan to randomized, controlledtrials in older persons. Specifically, cellular senescence is a biologic hallmark of aging that emerging preclinicalevidence indicates could have profound consequences on aging-related disease and function, and removal ofsenescent cells results in robust improvements in healthspan in rodents. Translation of these interventions toclinical trial has been proposed, yet health consequences of cell senescence and therapeutic potential has notbeen evaluated in humans. Dr. Justice's preliminary data in a small number of older women are the first toshow that cells expressing tumor suppressor protein and senescence biomarker p16INK4a are present inadipose tissue from older adults and related to worse physical function, but exercise and weight loss by caloricrestriction may mitigate this burden. The proposed research project represents a critical next step byexamining the effects of caloric restriction (CR) on cell senescence in a prospective randomized controlled trial(RCT). The primary hypothesis is that a CR intervention will reduce senescent cell burden and this reductionwill be related to improvement in functional and metabolic outcomes. This will be accomplished by capitalizingon a recent NIH-funded RCT (VEGGIE, R01DK103531) and the candidate's engaged inter-disciplinaryprimary mentoring team (Drs. Nicklas, Ding, Kritchevsky, Kirkland). VEGGIE will determine the effects of CRdesigned to achieve 10% weight loss vs. health education control in 200 men and women aged 40-65 yearswith obesity (BMI 30-45 kg/m2), to characterize epigenetic and transcriptomic effects of CR in adipocytes andperipheral blood monocytes and T cells, and associations with physical and metabolic function. We propose anancillary investigation in a subset of 90 participants (50-65 years, n=45 per grp) to determine the effects ofCR on senescent cell burden (Aim 1): a) proportion of p16INK4a expressing senescent cells(immunohistochemistry) in subcutaneous abdominal adipose tissue; b) expression of senescence biomarkersin isolated adipocytes and monocytes (RNAseq) and T cells (p16INK4a expression); and c) SASP biomarkers inplasma (cytokine/chemokine panel). We will also examine cross-sectional associations of age and obesity withcell senescence (Aim 2), and relationships between changes in senescence biomarkers and physical functionand metabolic outcomes (Aim 3). The research proposed is aligned with an approved NIA concept todevelop markers of aging-related biologic mechanisms for human studies. Additionally, it will provide essentialtraining for the candidate, who will establish expertise in cell senescence and translational research, anddevelop competencies in leading clinical trials with biological outcomes. This approach provides the idealplatform to advance the candidate's career as an independent investigator, and provide the foundation toestablish the role of cell senescence in human age-related functional decline.

2. Project Title: **Effect of protein supplementation during weight loss on older adult bone health**

Leader(s): **WEAVER, ASHLEY**

WAKE FOREST UNIVERSITY HEALTH SCIENCES

NIH K25AG058804 / (2019 - 2023)

Core(s):

Project Summary. Dr. Weaver seeks this K25 mentored training award to expand her bioengineering research background in medical imaging and finite element modeling of trauma towards pursuit of an independent research career focused on reducing osteoporosis and fracture in older adults. Weight loss poses an increased risk of bone loss and fracture in older adults. The proposed research will test the overall hypothesis that higher dietary protein intake during and following weight loss will attenuate bone loss in older adults with obesity. Guided by an accomplished multidisciplinary mentoring team with expertise in aging, clinical trials, bone metabolism, nutrition, and radiology, the PI will: (1) Develop knowledge of gerontology and geriatric medicine, (2) Acquire training in the design and execution of clinical trials, 3) Obtain in-depth knowledge on bone metabolism and structure, including the influence of nutrition and weight loss, and 4) Develop expertise in dual-energy computed tomography (CT) acquisition and post-processing to measure volumetric bone mineral density,

cortical thickness, and bone marrow adipose tissue. Dr. Weaver's training and research will take place at Wake Forest School of Medicine which has a strong history of clinical research in aging and an exceptional radiology infrastructure. The partnership with her co-mentor at Rutgers within the Department of Nutritional Sciences will provide additional resources and expertise related to the nutritional regulation of bone metabolism. The proposed ancillary study to the ongoing clinical trial, UPLIFT: Utilizing Protein During Weight Loss to Impact Physical Function, will examine bone health over 6 months of active weight loss, followed by 12 months of weight maintenance. Musculoskeletal phenotypes will be compared in older adults with obesity randomized to either: (1) a lower protein diet for weight loss and follow-up, (2) a higher protein diet for weight loss only, or (3) a higher protein diet for weight loss and follow-up. The ancillary study expands the UPLIFT trial by adding dual-energy CT scans of the lumbar spine and proximal femur at baseline, 6 months, and 18 months to compare the influence of a higher versus lower protein intake on: vertebral and femoral trabecular volumetric bone mineral density and cortical thickness (Primary Aim), bone marrow adiposity which may alter the trabecular matrix and affect bone strength (Secondary Aim 1), and bone strength and fracture risk predicted with subject-specific finite element modeling (Secondary Aim 2). The study will test if a higher protein diet improves bone outcomes during active weight loss (evaluated at 6 months), and if maintaining higher protein intake during weight maintenance further preserves bone (evaluated at 18 months). The proposed training and research plan will launch Dr. Weaver's career as an independent investigator focused on applying bioengineering techniques to: 1) develop translational tools for fracture prediction, and 2) assess osteoprotective interventions in clinical trials ultimately leading to improved diagnostics, prognostic tools, clinical recommendations, and therapies for preventing osteoporosis and fracture in older adults.

3. Project Title: IDENTIFYING FRAILTY IN PRIMARY CARE: IMPLEMENTATION OF AN ELECTRONIC MEDICAL RECORD-BASED FRAILTY INDEX

Leader(s):   CALLAHAN, KATHRYN
WAKE FOREST UNIVERSITY HEALTH SCIENCES
NIH K76AG059986 / (2018 - 2023)

Core(s):   - Clinical Research Core (CRC)

Project SummaryThis Beeson award seeks to equip the candidate, Dr. Kathryn E. Callahan, with the expertise to become anindependent investigator to advance use of aging-related metrics and interventions to promote health, function,and quality of life in frail and at-risk older adults. Frailty is prevalent among older adults, and associated withnegative outcomes, including hospitalizations, mobility disability, admission to skilled nursing facilities, andmortality. Despite efforts to define and quantify frailty, time and resource constraints limit the feasibility of frailtymeasures in clinical practice. Dr. Callahan's preliminary work supports the feasibility of translating anEMR-based Frailty Index, or eFI into the Wake Forest Baptist Health (WFBH) EMR, and demonstrates an initialassociation between eFI score and hospitalizations and mortality. The proposed research project representscritical next steps: (1) to adapt and refine the eFI using ambulatory care data, (2) assess its predictive value forhealthcare outcomes for older adults, and (3) conduct a pilot of implementation in Medicare Shared SavingsProgram/Next Generation Accountable Care Organization primary care practices, to collect critical dataregarding feasibility, acceptability, and effectiveness. The scientific goal is to develop and implement an indexto define a population of frail older adults who would benefit from personalized evidence-based interventions.This work is essential to inform larger-scale implementation trials of interventions to mediate negative andcostly health outcomes for frail older adults. We hypothesize that self-report and functional data from AnnualWellness Visits (AWVs) in the EMR will further refine the predictive value of the eFI; and that implementation ofthe eFI will be feasible and acceptable. This project is supported by engaged mentors (Drs. Williamson andBoustani) and a highly interactive, inter-disciplinary advisory committee (Drs. Foley, Rejeski, and Pajewski)whose expertise and complementary skills are a noteworthy asset to this project. We propose the adaptationand refinement of the eFI within the WFBH EMR, using data from older adults enrolled in the WFBH MSSP/Next Gen ACO (Aim 1): we will integrate AWV data, and refine the predictive value of eFI scores in thispopulation. We will then conduct a pilot study implementing the adapted eFI score in six MSSP/Next Gen ACOprimary care practices, and follow health outcomes. The research proposed aligns with an NIA priority toimprove the health, well-being, and independence of adults as they age. It will also provide essential trainingfor the candidate, who will establish expertise in implementation science, achieve fluency in clinical informatics,and develop competencies in leading implementation trials. This approach provides the ideal platform toadvance the candidate's career as an independent investigator and provides the foundation to establish frailtymetrics in practice, leveraging the learning health system to implement interventions to improve health andfunction.

4. Project Title: Blood Base Bioenergetic Profiling: A Novel Approach for Identifying Alzheimer's Disease Risk and Pathology

Leader(s):   **NICKLAS, BARBARA J; MOLINA, ANTHONY J;**
                     WAKE FOREST UNIVERSITY HEALTH SCIENCES
                     NIH R01AG054523 / (2017 - 2024)

Core(s):

7. Project Summary/Abstract In Alzheimer's disease (AD), irreversible neurological damage takes place years before the onset of clinical symptoms. Therefore, it is recognized that the development of AD dementia treatment and prevention strategies relies on the early detection of presymptomatic pathology. Previous studies demonstrate that mitochondrial dysfunction plays a key role in the pathophysiology of AD and precedes the formation of plaques and tangles that are hallmarks of this disease. The premise of this study is based on the unique sensitivity of the brain to systemic bioenergetic decline due to its exceptionally high metabolic demand. We hypothesize that bioenergetic capacity is related to early AD pathology and that bioenergetic decline is associated with the long term progression and severity of this disease. Recent work by our group and others demonstrate that blood- based bioenergetic profiling, utilizing cellular respirometry, provides a reliable measure of systemic mitochondrial function. The proposed study will determine whether blood cell bioenergetics is related to AD risk, pathology, cognitive performance, and changes in these parameters over time. Our long term goal is to develop a minimally invasive screening tool that can be used in a clinic/community setting to identify candidates for more intensive diagnostic testing, such as CSF biomarker analysis and brain imaging. This project will be completed in an efficient and cost-effective manner by leveraging resources provided by the NIA-funded Wake Forest Alzheimer' Disease Center Clinical Core (ADCCC). Participants in the ADCCC represent a spectrum of AD risk and disease progression and are being extensively characterized for AD pathologies at baseline and 3 year follow ups. Our preliminary data from ADCCC participants indicate that bioenergetic capacity, measured in blood cells, is lower in participants with mild cognitive impairment. Moreover, our data suggest that bioenergetic deficits are already apparent in cognitively normal participants at high risk for AD. The aims of the proposed study are: 1) To determine bioenergetic profiles most strongly associated with AD risk and reporters of AD pathology (cognitive performance, CSF A 42/tau, hippocampal volume, brain amyloid, and cerebral glucose metabolism); 2) To determine the changes in bioenergetic profiles related to the 3 year progression of cognitive decline and reporters of AD pathology; and, 3) To determine the relationships of mitochondrial content and inflammation with bioenergetic capacity, and reporters of AD pathology at baseline and at follow-up. A central goal of the proposed study is to determine the specific bioenergetic parameters that are most closely associated with AD risk and pathology. Therefore, in addition to convention analytical approaches, we will employ state of the art Machine Learning analyses to identify individual parameters or multivariate signatures that are most closely associated with AD risk and pathology. Completion of this project can impact the detection of presymptomatic AD, provide insights into mechanisms underlying bioenergetic decline associated with AD, and broadly advance translational bioenergetics research.

5. Project Title: INCORPORATING NUTRITION, VESTS, EDUCATION, AND STRENGTH TRAINING IN BONE HEALTH (INVEST IN BONE HEALTH)

Leader(s):   **BEAVERS, KRISTEN MARIE**
                     WAKE FOREST UNIVERSITY
                     NIH R01AG059186 / (2019 - 2024)

Core(s):   - Pilot and Exploratory Studies Core (PESC)
                     - Clinical Research Core (CRC)
                     - BioImaging (BioImaging)

PROJECT SUMMARYOld age and obesity are prevalent risk factors for morbidity and mortality. Weight loss (WL) ameliorates manyclinical consequences of obesity; yet despite its benefits, recommendation of intentional WL in older adultsremains controversial. Reluctance stems, at least in part, from loss of bone mass known to accompany overallWL and the potential for exacerbation of age-related risk of osteoporosis and fracture. Addition of resistanceexercise training (RT) to WL is an effective means to attenuate, but not stop, WL-associated reductions in bonemineral density (BMD); however, conventional RT interventions present barriers to long term feasibility (i.e.,expensive equipment, on-site participation, safety supervision by trained staff, and waning compliance).Alternately, treating the WL-associated decrease in mechanical stress by replacing lost weight externally mayalso preserve bone mass. Pilot data from our institution signal that weighted vest use (designed to mimicweight stability) during WL is both feasible and likely efficacious in reducing WL-associated hip BMD loss whileincreasing biomarkers of bone formation. If confirmed, the greater availability, ease of administration, andreduced cost of weighted vest use to offset WL-associated bone loss, as compared to RT, holds significantpublic health potential as a translatable strategy to maximize the cardiometabolic benefits of WL, whileminimizing negative implications for the

musculoskeletal system. The main goal of the proposed R01 study isto compare the effects of WL alone and with weighted vest use or RT on several indicators of bone health andsubsequent fracture risk. We propose a 12 month trial in 192 older (65-79 years) adults with obesity (BMI=30-40 kg/m2) randomized to one of three interventions (n=64/group): WL alone (WL; caloric restriction targeting10% WL and following national obesity treatment guidelines); WL plus weighted vest use (WL+VEST; =6hours/day, weight replacement titrated up to 10% WL); or, WL plus structured RT (WL+RT; 3 days/week, 10exercises, 10-12 repetitions). Our primary study outcome is 12 month change in total hip trabecular volumetricBMD (vBMD) and we hypothesize that despite similar reductions in total body weight: (1) participants in theWL+VEST group will show attenuated losses of total hip trabecular vBMD versus WL, and (2) loss in total hiptrabecular vBMD will be no greater in WL+VEST compared to WL+RT. Led by a talented New Investigator, thisproposal is a natural extension of the work accomplished during the PI s current MRSDA (K01 AG047291), andconfers public health impact by testing a translatable strategy aimed at optimizing intentional WL in older adultswith obesity while elucidating mechanisms governing musculoskeletal response to WL.

6. Project Title: **STUDY OF MUSCLE, MOBILITY AND AGING (SOMMA)**

Leader(s):   **CUMMINGS, STEVEN RON; HEPPLE, RUSSELL T ; KRITCHEVSKY, STEPHEN B. ; NEWMAN, ANNE B. ; CALIFORNIA PACIFIC MED CTR RES INSTITUTE**
NIH R01AG059416 / (2018 - 2023)

Core(s):   - Clinical Research Core (CRC)
- BioImaging (BioImaging)
- Integrative Biology Core (Integrative Biology Core)

Mobility inevitably declines with age, more in some than other people, often leading to mobility disabilitywith dependency, decreased quality of life, and enormous health care costs. The role of age-related biologicalchanges in skeletal muscle on the decline in mobility is poorly understood. We hypothesize that muscle massand the capacity to produce ATP are strong determinants of the mobility disability in older adults. Based onadvances from laboratory studies of muscle aging, we also hypothesize that denervation, oxidative damage,and decreased autophagic flux interact and contribute to declines in fitness, endurance and an increased riskof mobility disability. We will also use transcriptomic profiling by RNAseq to discover patterns of geneexpression that play important roles in the loss of mobility with aging. In the Study of Muscle Mobility and Aging (SOMMA), a prospective, longitudinal study of men andwomen age 70 to 90, our team of experts in clinical and laboratory sciences will use innovative and state-of-the-art technologies with rigorous quality control to test these hypotheses and discover new pathways for theloss of mobility with aging. We will measure quadriceps contractile volume by MRI and total muscle mass byd3 creatine dilution. We will use 31PMRS to assess the capacity of the quadriceps to generate ATP (ATPmax).In tissue form, muscle biopsies quantify denervation and oxidative damage to contractile proteins. SOMMA willbe the first to quantify autophagic flux to assess the role of autophagy in the loss of mobility with aging. We userespirometry on fresh tissue to quantify the contribution of mitochondria to ATPmax and mobility disability.These properties interact: for example, decreased autophagic flux promotes the accumulation of oxidativedamage and denervation, and understanding these relationships will guide the analysis and interpretation ofour results. Furthermore, we will use unbiased RNA-sequencing (RNA-seq) to profile the entire transcriptometo discover new associations between clusters of genes and individual variation in rates of loss of fitness (peakVO2), muscle mass, and risk of mobility disability. Field centers at Wake Forest and Pittsburgh, with exceptional track records for recruiting and retainingolder adults in complex studies, will enroll 875 women and men age 70 89 with a gait speed = 1.0 m/s,providing sufficient power to identify important relationships between individual and combinations of propertiesand the risk of mobility disability. SOMMA may identify and prioritize targets for new therapeutics and tailored exercise regimens. Wealso will create a unique archive of tissue, blood, with longitudinal data about important clinical outcomes thatthe scientific community can use to efficiently test new hypotheses about muscle and loss of mobility withaging.

7. Project Title: **Dietary Effects on Imaging and Fluid-based Biomarkers of the Adipose-Brain Axis in Alzheimers Disease**

Leader(s):   **BRINKLEY, TINA E**
WAKE FOREST UNIVERSITY HEALTH SCIENCES
NIH R01AG064014 / (2019 - 2024)

Core(s):

PROJECT SUMMARY The present proposal, in response to PAR-17-029, seeks to advance our understanding of how crosstalk between adipose tissue (AT) and the brain may contribute to the pathophysiology of Alzheimer's disease (AD). The scientific premise is based on the fact that while body mass index (BMI) is an independent predictor of AD in both mid- and late-life, the association with this crude global measure of obesity is confounded by aging- related changes in AT distribution and function. Although the underlying mechanisms remain to be elucidated, it is clear that BMI is not sufficient to fully understand the obesity-associated risks for AD. Diet influences the risk of both obesity and AD, and investigating dietary interventions that can modulate both AT and the brain may provide critical insight into the overlapping molecular pathways linking these diseases. Our preliminary data suggest that greater amounts of AT in central / visceral (VAT) depots and lower amounts of AT in peripheral / subcutaneous (SAT) depots are associated with a cerebrospinal fluid (CSF) biomarker profile indicative of increased AD pathology. Moreover, minimizing the loss of protective SAT depots following a ketogenic diet may favorably impact AD pathology. To confirm and extend these findings, we propose to conduct an ancillary study to the Brain Energy for Amyloid Transformation in AD (BEAT-AD) trial, a phase 2 randomized clinical trial designed to examine the effects of a 4-month Modified Mediterranean Ketogenic (MMK) diet versus an American Heart Association (AHA) low-fat diet on brain health in 120 adults (age: 55 to 85 years) with amnestic mild cognitive impairment (aMCI) (R01AG055122; PI: Craft). The proposed study will leverage ongoing study procedures, data, and samples to generate new data on AT distribution and function, including their relationship with AD biomarkers and their modulation by diet. Specifically, CT imaging will be leveraged to quantify changes in the cross-sectional area and density of VAT, SAT, and intermuscular AT in the abdomen and thigh, as well as fatty infiltration of liver and skeletal muscle. FDG-PET imaging will also be leveraged to quantify changes in glucose uptake (i.e., metabolic activity) in AT depots of interest. Finally, stored blood and CSF will be used to assess changes in circulating adipokines and AT-derived exosomes. To complement the ongoing collection of CSF, FDG-PET, amyloid PET, and structural/functional MRI, the proposed study will also add 18F-AV-1451 tau PET in a subset of participants (n=60), which will enhance the categorization of participants across the AD spectrum as defined by the NIA-AA Research Framework. This timely, cost-effective, and innovative study will not only expand the scope and impact of the parent trial, but will also address important gaps in the field. Investigating AT distribution and function in the context of the MMK diet may reveal novel targets that are amenable to intervention and new therapeutic agents that can alter the trajectory of AD.

8. Project Title: **Investigating the role of adipose tissue in mobility and aging (SOMMA-AT)**

Leader(s):   **SPARKS, LAUREN MARIE; KERSHAW, ERIN E.; ADVENTHEALTH ORLANDO**
NIH R01AG066474 / (2020 - 2025)

Core(s):

Project Summary/Abstract Targeted therapies for aging-related mobility disability are urgently needed to preserve quality of life and pre- vent morbidity/mortality in the rapidly expanding aging population. Progressive decline in mobility with aging has been partially attributed to loss of skeletal muscle (SM) mass and function, as well as an increase in the quantity of adipose tissue (AT). The quality of AT and AT-secreted factors are also likely to influence this pro- cess, yet meager evidence exists for this notion. Cellular senescence, a phenomenon by which normal healthy cells cease to divide and therefore become programmed for cellular death, occurs in adipose tissue and is as- sociated with poorer mobility. Furthermore, secreted factors from AT, potentially from senescent or dying cells, induces insulin resistance and atrophy in human skeletal muscle cells. Collectively, these data demonstrate that AT quality (i.e., structure and function) can directly impact skeletal muscle function. This adipose-skeletal muscle crosstalk has been increasingly implicated in poor functional and metabolic outcomes in younger hu- man populations. The unique contributions of AT structure and function and AT-secreted factors to mobility de- cline and skeletal muscle function in the context of human aging have not been addressed. The proposed stud- ies will fill a critical knowledge gap by directly assessing structural and functional components of AT in aging and using their associations with mobility to identify AT-secreted proteins that negatively impact skeletal mus- cle function. The long-term goal of this ancillary study is to leverage and add to the outstanding resources of the parent SOMMA project to understand the contribution of AT quality, AT-secreted factors and AT-skeletal muscle crosstalk to mobility disability and other complications of aging in humans. Our overall objective is to identify key structural and functional components of AT quality - including necrosis, senescence, inflammation, self-renewal and metabolic flexibility - and AT-secreted proteins that influence mobility via direct effects on skeletal muscle. We hypothesize that AT structure and function influences AT-secreted proteins that contribute to aging-related mobility outcomes by directly impacting skeletal muscle function. The stated purpose of Aim 1 is to determine which structural and functional components of AT are associated with slower walking speed. We posit that increased cellular senescence, increased necrosis, increased inflammation, decreased capacity for self-renewal and metabolic inflexibility will be associated with slower walking speed. For Aim 2, we antici- pate that incubation of human muscle cells with known and novel secreted proteins - identified

through stand- ard immunoassay panels and unbiased proteomics and shown to be associated with aberrations in AT struc- ture and/or function - will worsen mitochondrial respiration, increase oxidative stress, decrease contractility and muscle cell diameter. This work will have a positive translational impact by improving strategies for prevention and/or treatment of aging-related mobility disability and by promoting knowledge and facilitating future studies to understanding AT-skeletal muscle crosstalk across the lifespan.

9. Project Title: **The PREVENTABLE Physical Performance Ancillary Study**
Leader(s): **HOUSTON, DENISE KATHRYN**
WAKE FOREST UNIVERSITY HEALTH SCIENCES
NIH R01AG071807 / (2021 - 2027)

Core(s):

Project Summary/Abstract Aging is associated with significant declines in muscle mass, strength, and physical performance, which often lead to disability, loss of independence, and adverse clinical outcomes including multimorbidity and mortality. At present, health care providers have no therapeutic options to offer their patients to slow aging-related declines in physical function. Importantly, evidence is emerging that statins could be an effective treatment for preserving physical function by preventing disabling events such as stroke, heart failure, or myocardial infarction. In addition, statins have pleiotropic properties including anti-inflammatory, anti-oxidant, and immuno- modulatory effects, which may slow or prevent aging-related declines in physical function. However, reports of muscle pain and weakness in patients on statins has led to a significant number of patients discontinuing statins. Thus, the proposed study is critical to establish whether statins may help to preserve physical function and independence in older adults, or whether statin-associated muscle symptoms portend a statin-related decline in physical function. The PREVENTABLE trial (U19 AG065188) provides an ideal opportunity to definitively determine the effect of statins as a treatment for aging-related declines in physical function. PREVENTABLE is a placebo-controlled pragmatic clinical trial designed to investigate whether randomization to a statin can prevent dementia and prolong disability-free survival in 20,000 participants aged 75+ years without clinically evident coronary heart disease. While the PREVENTABLE trial will help clarify the effects of statins on self-reported disability, the proposed ancillary study will extend and validate the physical disability data by investigating the effects of statins on changes in physical performance, which are typically observed earlier in the trajectory of functional decline and may be a more sensitive marker for the effects of statin. To determine if statins affect longitudinal change in physical performance, the proposed ancillary will add the Short Physical Performance Battery (SPPB), a validated measure of lower-extremity performance comprised of balance tasks, a 4-m walk, and repeated chair stand test, over 3 years of follow-up in 2,500 PREVENTABLE participants (1,250 per intervention arm). Self-reported information on patient-centered outcomes relevant to physical function including statin-associated muscle symptoms, fatigue, and pain will also be collected. The specific aims of this ancillary study are to: 1) determine whether randomization to statin slows the aging- related decline in usual gait speed; 2) determine whether randomization to statin slows aging-related declines in lower-extremity function (SPPB score) and strength (chair rise time); and 3) explore whether randomization to statin is associated with self-reported statin-associated muscle symptoms, fatigue, and pain. By leveraging the rich resources and infrastructure of PREVENTABLE, this timely and cost-effective study provides a unique opportunity to significantly expand the scope and impact of the parent trial on self-reported physical disability by determining the therapeutic potential of statins to slow aging-related declines in physical performance.

10. Project Title: **The relationship between blood based bioenergetics and muscle function, mobility, and aging**
Leader(s): **SHIVA, SRUTI ; MOLINA, ANTHONY J;**
UNIVERSITY OF PITTSBURGH AT PITTSBURGH
NIH R01AG072734 / (2022 - 2026)

Core(s):

As people age, they experience declining physical performance, which is associated with diminished quality of life, augmented health care costs, and is a strong predictor of morbidity and mortality. Thus, uncovering mechanisms that underlie age-associated mobility decline and identifying reliable biomarkers to predict this decline is imperative for the development of interventions to maintain physical ability with age. Mitochondria generate chemical energy to support homeostatic function of most cells in the body, and mitochondrial dysfunction is linked to age-associated decline in physical performance. This has been studied predominantly in skeletal muscle mitochondria since muscle function is central to physical ability. However, it is recognized that muscle function is not the sole determinant of mobility, and that

input from other organ systems (cardiovascular and central nervous system) is also required. While age associated mitochondrial dysfunction has been observed across all organ systems, the contribution of this systemic bioenergetic dysfunction to age-associated mobility decline has not been assessed. The current study brings together two PIs with expertise in mitochondrial biology who have independently optimized and validated complementary assays (high resolution respirometery and Seahorse extracellular flux analysis) for the measurement of systemic bioenergetic function utilizing blood cells (platelets and peripheral blood mononuclear cells). Preliminary data using these assays show that blood cell mitochondrial function reflects bioenergetics of solid tissues (e.g. skeletal muscle, heart, lung, brain) and correlates with multiple measures of physical ability. However, it is unknown whether blood cell bioenergetics reflect skeletal muscle function or are predictive of mobility decline in older adults. The Study of Muscle, Mobility and Aging (SOMMA) is a multi-site longitudinal study of older adults (=70 years; n=875). SOMMA focuses on the relationship between skeletal muscle mitochondria and mobility decline and will obtain skeletal muscle biopsies to measure mitochondrial function in all participants. Physical performance measures will at baseline and three years follow-up. The current proposal is an ancillary study that synergizes with SOMMA to add blood cell bioenergetic measurements in all SOMMA participants at baseline as well as at the three year follow up visit. Using these data, we will test whether blood cell bioenergetics are 1) reflective of skeletal muscle mass and function, 2) are associated with physical performance measures (400 m walk), and 3) are predictive of physical performance decline in older adults. Completion of this study will elucidate systemic mitochondrial changes that are associated with age-related physical decline, and potentially establish blood cell bioenergetics as a biomarker of systemic mitochondrial function that can be utilized as a surrogate for muscle biopsies, and as a predictor of mobility decline in the aging population.

11. Project Title: **Establishing the optimal frequency of dance movement for neurocognitive and physical outcomes in people at risk of Alzheimer's disease**

Leader(s): **HUGENSCHMIDT, CHRISTINA E; SORIANO, CHRISTINA T; WAKE FOREST UNIVERSITY HEALTH SCIENCES NIH R01AG076669 / (2022 - 2027)**

Core(s):

PROJECT SUMMARY Dance movement is a form of physical activity that may benefit the brain as much or more than structured aerobic exercise. Despite the potential of dance as an intervention to promote neurocognitive health, gaps in knowledge about essential intervention components are a barrier to definitive trials, specifically:1) a lack of specificity on key prescription parameters including how many times a week dance classes should be taught, 2) need for better estimates of how large an effect dance has on fitness and the brain, and 3) little understanding of the expected time course for change in fitness and the brain in response to dance. The primary aim of this proposal is to test whether weekly dance frequency differentially modifies key outcomes, and from this to test effect sizes to determine sufficient sample sizes for a larger-scale trial. Physical activity promoting interventions tested in older adults have traditionally focused on exercise, i.e., structured physical activity of at least moderate intensity with the express purpose of improving health or fitness. However, in 2003, epidemiological evidence showed that social dance was the only leisure time physical activity associated with lower Alzheimer s disease risk. Since then, multiple smaller studies have shown benefits of dance movement and dance therapy on mobility and neurocognitive health in older adults, including cardiorespiratory fitness, balance, white matter health, and cognition. Dance movement inherently involves simultaneous cognitive stimulation through motor learning and dual-tasking; social interactions; aerobic physical activity that elevates heart rate and improves cardiorespiratory fitness; and improves balance and reduces fall risk. Dance also satisfies key antecedents of lasting behavior change outlined in contemporary behavioral theories including self-efficacy, intrinsic motivation, autonomy, and relatedness. Dance is also culturally relevant and has been practiced spontaneously for thousands of years. This means dance may result in better long-term adherence than more commonly studied forms of aerobic exercise like brisk walking, where data from our group and others shows that adherence drops significantly after intervention ends. This proposal plans to assess outcomes of 1x/weekly, 2x/weekly, and 3x/weekly dance movement classes and 1x/week music appreciation class control at 4 time-points over 6 months to determine the time course of changes in cardiorespiratory fitness, cognition, and key secondary outcomes in 160 adults = 65 years old at risk for Alzheimer s disease due to subjective cognitive decline. 1x/weekly is common for community classes and has been tested in multiple dance studies; 2x/weekly is most common in dance research; and 3x/weekly is most common for aerobic exercise interventions like treadmill walking that target CRF. We aim to determine the optimal frequency of dance movement intervention for a Phase III trial that will effect change in relevant outcomes while maintaining attendance.

12. Project Title: **Physical Rehabilitation for Older Patients with Acute HFpEF-The REHAB-HFpEF Trial**

Leader(s):   **KITZMAN, DALANE W**
                            WAKE FOREST UNIVERSITY HEALTH SCIENCES
                            NIH R01AG078153 / (2022 - 2027)

Core(s):

Acute decompensated heart failure (ADHF) is the leading cause of hospitalization in older persons, and is associated with marked physical disability, poor health-related quality of life (HRQOL), frequent rehospitalizations, loss of independence, high mortality, and enormous health care costs. However, most of the trials testing a wide range of medications and strategies in ADHF have been neutral. In our recently completed NIA-funded phase 2 trial (REHAB-HF), an innovative, early, transitional, tailored, and progressive multi-domain physical rehabilitation intervention produced a large improvement in the primary outcome of Short Physical Performance Battery (+1.5 points) in older patients with ADHF. At baseline, the participants (53%) with HF with preserved ejection fraction (HFpEF), had significantly worse impairments in physical function, frailty, HRQOL, and depression than those with HF with reduced EF. They also appeared to derive greater benefit from the intervention, with ~50% larger effect sizes in physical function, frailty, HRQOL, and depression. Patients with HFpEF also appeared to have much greater reductions in rehospitalizations and death and potential for reduced medical resource use. The finding of potentially greater benefit in HFpEF is noteworthy as HFpEF is highly relevant to older persons and has the most urgent need for new treatments since it is: 1) the most common form of HF, nearly unique to older persons, and disproportionately affects older women and Black persons; 2) increasing in prevalence; 3) accepted as a geriatric syndrome; 4) associated with marked impairments in physical function and HRQOL and high rates of frailty; 5) has high morbidity and mortality which are worsening over time; and 6) has limited evidence-based treatments. The phase 3 REHAB- HFpEF trial will focus on this large, growing, vulnerable, underserved population. The 5-year, randomized, attention-controlled, single-blinded trial will enroll 880 older adults age >60 years with ADHF and HFpEF across 20 geographically dispersed clinical centers. We will test the hypothesis that the innovative REHAB-HF intervention will improve the clinically compelling combined primary endpoint of all-cause rehospitalizations and mortality during 6-month follow-up, the most vulnerable time period following ADHF hospitalization (Aim 1) and the secondary endpoint of prevalence of major mobility disability, a clinically meaningful outcome in trials of older adults, at 6-months (Aim 2). We will also assess the intervention s impact on HRQOL, frailty, depression, physical activity, and health care costs. Our diverse, cohesive, multi-disciplinary team and experience from the phase 2 trial will ensure efficient and effective execution and dissemination. REHAB-HFpEF directly addresses the key recommendations of several recent NIA and NHLBI sponsored workshops. Its results could improve key outcomes that are meaningful to patients, caregivers, health systems, and payers. The trial has strong potential to change clinical guidelines, reduce health care costs, and influence national coverage decisions for the large, growing, underserved, high-risk population of older patients with acute HFpEF.

13. Project Title: **ASPIRE: A Study Promoting Critical Illness Recovery in the Elderly**

Leader(s):   **BAKHRU, RITA NANIK**
                            WAKE FOREST UNIVERSITY HEALTH SCIENCES
                            NIH R03AG060076 / (2019 - 2023)

Core(s):

ASPIRE: A Study Promoting critical Illness Recovery in the Elderly Project Abstract: Older people have a higher risk of developing a critical illness requiring invasive mechanical ventilation than younger people. Additionally, muscle wasting, which occurs quickly and progresses rapidly in all patients who are critically ill and on mechanical ventilation, is more severe in older adults. This results in long-term physical impairments, particularly in older survivors of critical illness. ICU rehabilitation, when administered early, has been shown to be effective at attenuating the degree of physical function impairment in survivors. However, there are barriers to the provision of early ICU rehabilitation, including delirium and coma. Additionally, older patients have been routinely excluded from critical care trials even though they make up the majority of the critically ill population. We recently performed a pilot feasibility trial of a novel, early ICU rehabilitation protocol in older adults utilizing an in-bed cycle ergometer. The in-bed cycle ergometer allowed for ICU rehabilitation to start at a particularly early point in the ICU course when muscle wasting begins, and allowed delivery of rehabilitation even when patients were comatose or delirious. We hypothesize that the novel, early ICU rehabilitation protocol using an in-bed cycle ergometer will improve functional outcomes in older survivors of critical illness. As such, the specific aims of

the proposal are to evaluate the effect of the early ICU rehabilitation intervention on 1) physical function (as measured by the SPPB at ICU discharge), 2) muscle mass (as measured by ultrasound at ICU discharge), and 3) quality of life (measured with the SF-36 at 6 months post-discharge). This will be the first randomized controlled trial to test this novel early ICU rehabilitation intervention in older patients. This project and period of training with the GEMSSTAR award will be critical in my transition to becoming a clinical trialist with a focus on improving older adults' physical function following critical illness.

14. Project Title: **Novel Computed Tomography (CT) Imaging Biomarkers in Older Adults for Predicting Adverse Geriatric Health Outcomes**

Leader(s): **CAWTHON, PEGGY MANNEN; LENCHIK, LEON ; CALIFORNIA PACIFIC MED CTR RES INSTITUTE NIH R21AG070804 / (2021 - 2024)**

Core(s):

Blood-based biomarkers have been widely used in studying various metabolic pathways contributing to aging, including energy metabolism, chronic inflammation, cellular senescence, and endothelial function. Like blood- derived biomarkers, imaging-based biomarkers can be evaluated as potential predictors of aging outcomes. For study of non-neurologic aging, biomarkers derived from computed tomography (CT) offer great promise. Recent advances in scanner technology and image processing mean that most CT examinations can be obtained in less than one minute, lowering participant burden. In addition, radiation doses have been lowered and the intra- and inter-scanner variability has improved. In parallel, machine learning tools allow for automated image processing and segmentation, increasing efficiency of image analysis, and reducing bias. For these reasons, CT is increasingly being used to study skeletal muscle and adipose tissue. On CT, muscle quantity is typically measured by cross-sectional area (CSA). Muscle quality is traditionally quantified by skeletal muscle density (SMD) and intermuscular adipose tissue (IMAT) cross-sectional area. In addition to being a measure of muscle quality, IMAT may be considered as a measure of fat quantity. We recently developed and validated an automated machine learning tool to determine traditional CT measures of muscle and adipose tissue quantity and quality. To better characterize tissue quality, we have also applied radiomic texture analysis to muscle tissue on CT images. Texture analysis refers to the quantification of image voxel inter-relationships and provides a measure of tissue heterogeneity. To our knowledge, this technique has never been applied to CT images from community-based epidemiological studies. We propose to relate these CT-based assessments of muscle and adipose tissues to important geriatric outcomes, focusing on hip and other fractures as well as falls, physical performance, and strength. We will complete these analyses on archived CT images in MrOS (a prospective cohort study of healthy aging in older men, with a particular focus on osteoporosis) and Health ABC (a prospective cohort study of non-disabled Black and White older adults). Abdominal CT images were collected at the baseline exam for MrOS men in the United States (N~3700 in 2000-2), MrOS men in Hong Kong (N~400 in 2001-3), and Health ABC (N~3000 in 1997-8). Health ABC also collected CT images at the mid-thigh. In Health ABC, mid-thigh and abdominal CT images were repeated in a subset five years later (N~600 in 2000-3). We will add three aims: 1) test the hypothesis that that greater muscle and fat tissue heterogeneity features at the abdomen and mid-thigh are associated with increased risk of hip and other fractures, 2) test the hypothesis greater muscle and fat tissue heterogeneity features at the abdomen and mid-thigh are associated with lower strength and poor physical performance (walking speed and chair stands); their decline over time; and risk of falls, and 3) characterize changes in muscle and fat tissue heterogeneity features at the mid-thigh over 6 years.

15. Project Title: **Geroscience Education and Training (GET) Network**

Leader(s): **KUCHEL, GEORGE A; AL-NAGGAR, IMAN ; JUSTICE, JAMIE NICOLE; UNIVERSITY OF CONNECTICUT SCH OF MED/DNT NIH R25AG073119 / (2021 - 2024)**

Core(s):

Summary In developing educational materials and meeting with our GET Network advisory committees we often discuss where the educational boundaries of the GET Network may dovetail with existing or upcoming training programs in aging (both basic and clinical) and geroscience. For example, the NIA's Division of Aging Biology recently published an approved concept informed by the Trans-NIH GeroScience Interest Group (GSIG) to create short-term educational programs with a primary focus on courses that enhance and expand Geroscience skills and development at all levels of professional career development. This concept is aligned with the mission of the GET Network, yet independent. Similarly, other NIA-supported R25's (eg, R25AG071488) are also creating educational content or delivery methods highly relevant to other groups. We hope to share resources, update on our progress, and get input from a wider group of people working on similar concepts, as we all have much to learn for long-standing educational programs in aging. An opportunity presented itself when we were approached by the CEO of GSA, James Appleby, about disseminating GET Network content and scope at the society's 2022 meeting. During our discussions, we realized that more than just presenting work completed within the GET Network, there is a real advantage to engaging with investigators and educators beyond the GET Network. We are therefore requesting an administrative supplement to support a preconference workshop at the 2023 GSA meeting to allow us to harmonize with other educational programs, introduce key concepts for teaching and training programs in geroscience, and disseminate our work. This is directly aligned with the goals of the GET Network, but represents additional work beyond what was proposed in the parent award. We will invite 50 interdisciplinary participants to attend and contribute as speakers and discussants, including students, early career contributors and key stakeholders. Additionally, we plan to hold meetings for our Content and Dissemination committee members on the same day. Finally, three junior faculty or postdocs will be selected to record the discussions and participate in a separate whitepaper writing retreat to develop a manuscript of the meeting proceedings for submission to a GSA-affiliated journal.

16. Project Title: **AIDS and Aging Research Platform (AARP)**
Leader(s): **CRANE, HEIDI M.; AUSTAD, STEVEN N.; KRITCHEVSKY, STEPHEN B.;**
UNIVERSITY OF WASHINGTON
NIH R33AG067069 / (2020 - 2025)
Core(s):

ABSTRACT Effective antiretroviral therapy (ART) for people living with HIV (PLWH) has dramatically reduced mortality resulting in many surviving into middle and old age. Despite this success, PLWH experience high rates of comorbidities, multimorbidity (>1 major chronic illness), and functional decline at ages 10-15 years younger than uninfected controls. Geriatric syndromes, such as frailty and falls, are becoming more prevalent in PLWH. Thus, there is an urgent need to focus on the healthspan of PLWH rather than just mortality. Healthspan, in contrast to lifespan, is defined as the time someone is healthy not just alive. The Claude D. Pepper Older American Independence Centers (OAlCs) were established to help define aging phenotypes and advance research into the causes, prevention and treatment of functional decline with age. OAlCs have developed and validated functional assessments in aging, but lack depth and breadth of HIV expertise. In contrast, Centers for AIDS Research (CFARs) have unparalleled expertise in HIV-related basic, clinical and social/behavioral research, but lack robust resources and expertise in aging biology, geriatric clinical phenotypes and functional assessments. Our R24 project, Developing Research At The Interface Of HIV And Aging was in response to PA-12-064 Network and Infrastructure Support for Development of Interdisciplinary Aging Research. Through this R24 we successfully linked CFARs and OAICs to support pilot projects in high-priority focus areas and mentor researchers at the interface of HIV and Aging. Our vision for this proposal is to build on this success deepening the ongoing linkage of CFARs and OAICs and expanding the network to include Nathan Shock Centers of Excellence in the Basic Biology of Aging (NSCs) and the McKnight Brain Institutes (MBIs). By bringing together OAICs expertise on functional decline in aging, with NSC expertise in aging biology and the mechanisms underlying function decline, with MBI expertise on age-related cognitive decline, and CFAR expertise on HIV, we create an integrated approach to advancing and accelerating investigation at the interface of HIV and aging via the following Aims: Aim 1. Provide specific training models and a brief inventory of tools to efficiently collect data to improve HIV clinical care and outcomes research. Aim 2. Using a geroscience approach, provide a platform for pilot studies to determine the links between molecular hallmarks of aging with functional decline, and the development of common comorbidities among aging PLWH. Aim 3. Develop infrastructure for evaluating interventional approaches and their application to HIV care. Aim 4. Provide educational support, implementation advice and mentoring for emerging investigators to establish/advance research programs in HIV and aging. These synergistic aims leverage and expand the infrastructure and close ties built in the R24 of HIV expertise from CFARs with the gerontology and functional assessment expertise within the OAlCs and expand them with inclusion of NSCs and MBIs to enhance and accelerate investigation at the interface of HIV and aging.

17. **Project Title:** **Effects of Western and Mediterranean Diets on Metabolic and Neuropathologic Risk Factors for Alzheimer's Disease in Nonhuman Primates**

Leader(s): **SHIVELY, CAROL A.; CRAFT, SUZANNE ;**
WAKE FOREST UNIVERSITY HEALTH SCIENCES
NIH RF1AG058829 / (2018 - 2023)

Core(s):

Summary This study examines the effects of diet on peripheral metabolism and central nervous system (CNS) phenotypes and pathways implicated in early-stage Alzheimer's disease (AD) pathology in nonhuman primates (NHPs). The premise for the study is based on evidence that dietary patterns are powerful modulators of brain aging. Habitual consumption of simple sugars and saturated fat, characteristic of a Western diet, is associated with chronic diseases and increased risk of AD and vascular cognitive impairment. Conversely, high intake of dietary fruits and vegetables, fish, and healthy fats, characteristic of a Mediterranean diet, is associated with reduced risk of chronic diseases, AD, and vascular cognitive impairment. Evidence supporting these associations comes from population-based studies that may be affected by confounders, or from rodent studies with limited translational relevance. Identification of specific mechanisms underlying dietary effects has been challenging to date. However, in our 1-month randomized trial in older adults comparing Western and prudent diet, we observed changes in AD and pathologic aging markers (e.g. cerebrospinal fluid A 42, lipoproteins, insulin, and oxidative stress markers), suggesting that Western diet composition may alter the brain in ways that promote AD-related neuropathologies. Nonhuman primates offer unique opportunities to model complex human diseases, and we and others have shown that they develop AD pathology and diet- related metabolic and vascular disorders with aging. The proposed study leverages a NIH-funded investigation in which adult female cynomolgus monkeys were randomized to consume a Western or Mediterranean-like diet for 30 months. Metabolic, vascular, and behavioral phenotyping, MR imaging, and serial collections of cerebrospinal fluid occurred in the Baseline and Treatment phases. At necropsy, multiple peripheral and vascular tissues were obtained and the brains collected using a protocol adapted from human AD guidelines. We now propose to use these archived tissue, images, and data to determine the effects of Western vs. Mediterranean diet on structural and functional CNS characteristics relevant to AD risk. Our overarching hypothesis is that, compared to a Western diet, consuming a Mediterranean diet protects against neuropathologic, vascular, inflammatory, oxidative, and other phenotypes associated with increased risk of AD. Our Specific Aims are to determine effects of Western and Mediterranean diets on: AD neuropathology, neurovascular pathophysiology, neuroinflammation, oxidative stress, and gene expression to identify the peripheral mediators of diet effects on the CNS, and novel pathways and mechanisms which may be involved in diet/AD interactions.

18. **Project Title:** **Translational Training in Aging and Alzheimer?s Disease Related Disorders**

Leader(s): **KRITCHEVSKY, STEPHEN B.**
WAKE FOREST UNIVERSITY HEALTH SCIENCES
NIH T32AG033534 / (2009 - 2027)

Core(s):

Translational Training in Aging and Alzheimer s Disease Related Disorders This renewal application seeks to sustain our T32-supported Training Program to continue training postdoctoral fellows in the conduct of translational research focused on optimizing cognitive and physical function with aging and Alzheimer s disease-related disorders (ADRD). This T32 has been continuously funded since 2009; in November, 2019, its scope and number of trainees increased from 3 to 5 fellows to include specific training in research related to ADRD, in alignment with the newly funded P30 Alzheimer s Disease Research Center. Of the 19 trainees appointed or who are pending appointment since the T32 began in 2009, 10 have an ADRD focus (53%). Of the 9 trainees appointed or who are pending appointment since the T32 was revised to include an ADRD focus in 2019, 6 have an ADRD focus (66.7%).Nationwide, there is a dearth of competent investigators trained in the appropriate skills to conduct research on prevention and treatment of mobility disability, ADRD, and other conditions that lead to loss of independence with aging. Thus, the research of our T32-supported trainees has been, and will continue to be, instrumental in advancing knowledge regarding the prevention of cognitive and functional disability and the best health care for older adults. The overall goal of our T32 Training Program is to help develop a new generation of researchers by providing an integrated career development path centered on training PhD/MD fellows in the skills and competencies needed to conduct translational research with a focus on the prevention of physical and cognitive disability. Importantly, the unique and seamless integration of both aging and ADRD research within the Wake Forest School of

Medicine (WFSM) Section on Gerontology and Geriatric Medicine, and the supporting ADRC and Pepper Older Adult Independence Center, provides the ideal environment to facilitate trainees knowledge of the biological contributions and risk factors for aging- and ADRD-related changes in physical and cognitive function, and their inter-connectedness. Our scholars acquire 1) scientific knowledge in the fields of aging and brain biology, geroscience, and ADRD; 2) competencies needed to successfully and ethically conduct preclinical experiments, clinical trials, and/or longitudinal cohort studies of relevance to aging and ADRD; 3) experience and expertise in the measurement of cognitive and/or physical disability outcomes; and 4) specific technical or methodological skills in line with their individual interests. This training will place them in a position to successfully transition to an early-stage faculty position and to be highly competitive for new funding to continue their path towards independence. With a current research portfolio of funded grants totaling $73.96 million in direct costs ($55.7 million from NIA) awarded to our T32 Program Faculty, we have the scientific expertise, resources, and research opportunities available for training the next generation of investigators for success in aging and ADRD research.

19. Project Title: **Aging Biomarkers: Integrating Omic Profiles with Mechanistic Measures**

Leader(s):   **DING, JINGZHONG ; DELBONO, OSVALDO ; MOLINA, ANTHONY J;**
WAKE FOREST UNIVERSITY HEALTH SCIENCES
NIH U01AG060897 / (2018 - 2023)

Core(s):

Project Summary The objective of this study is to develop and validate biomarkers that reflect mechanisms of biological aging. At least five pharmacologic compounds approved for human use extend health span and life span in rodent models. Parallel approaches in humans would require studies lasting 40+ years and are infeasible. Rather, the field needs reliable human biomarkers that indicate beneficial (or adverse) effects of an intervention on aging-related pathways over shorter time periods. Epigenomics and resultant transcriptomic changes may unite mechanisms of biological aging implicated in animal studies and unravel novel pathways. In a genome- wide analysis of monocyte samples in 1,200 persons (aged 55-94 years) from the Multi-Ethnic Study of Atherosclerosis (MESA), we identified 1,794 age-associated methylation sites and 2,704 age-associated transcripts, which over-represented several networks, including mitochondrial bioenergetics and autophagy. We further demonstrated associations of these gene networks with aging-related diseases independent of age. In addition to omic profiles, functional phenotyping may provide further advantages as biomarkers of the aging process. For example, our studies in older adults indicate the bioenergetic capacity of peripheral blood mononuclear cells is positively associated with physical function measures even when controlling for age. We predict that these epigenetic, transcriptomic, and functional markers will be associated with the development of aging-related comorbidities and are responsive to caloric restriction. We propose to utilize existing longitudinal assessments of monocyte epigenetic/transcriptomic profiles and age-related health outcomes from 1,800 middle-aged and older adults (55-94 years) in the MESA study. Leveraging an ongoing randomized clinical trial (VEGGIE) of caloric restriction in 200 adults (40-70 years), we also propose to add skeletal muscle biopsy (N=80). The specific aims are: 1) to determine whether aging-related monocyte transcriptomic/epigenomic pathways individually or in combination predict changes in aging-related diseases over an 8-year follow up (N=1,800); and 2) To determine whether caloric restriction shifts aging-related monocyte transcriptomic/epigenomic pathways (N=200) and bioenergetic measures in circulating cells and skeletal muscle (N=80) towards a younger pattern and whether these changes individually or in combination correlate with changes in aging-related metabolic, physical and cognitive health outcomes. The proposed study will generate a panel of biomarkers reflecting a comprehensive battery of aging pathways by integrating transcriptomic and epigenomic profiles with bioenergetics in circulation and skeletal muscle, from an existing longitudinal cohort study and an ongoing clinical trial of caloric restriction, to efficiently and cost-effectively validate potential biomarkers through multiple convergent strategies.

20. Project Title: **Health Aging & Later-Life Outcomes Planning (HALLO-P)**

Leader(s):   **KRITCHEVSKY, STEPHEN B.; MILLER, MICHAEL E.; NICKLAS, BARBARA J; REJESKI, WALTER JOHN;**
WAKE FOREST UNIVERSITY HEALTH SCIENCES
NIH U01AG073240 / (2021 - 2024)

Core(s):   - Clinical Research Core (CRC)
                      - BioImaging (BioImaging)
                      - Biostatistical Design and Analysis Core (BIC)
                      - Integrative Biology Core (Integrative Biology Core)

The Health, Aging and Later-Life Outcomes Planning Grant (HALLO-P) is submitted in response to RFA-AG-21-016. Collectively, HALLO-P affiliated investigators have led 17 clinical trials of caloric restriction (CR; 3 ongoing), enrolling 2,773 adults (ages 55-91) with BMIs = 27 kg/m2, showing multiple beneficial physiologic changes associated with lower disease and disability risk. Whether this translates to actual reductions in disease and disability is unclear. A large multi-year trial with definitive clinical outcomes is needed to fill this evidence gap. Time restricted feeding (TRF) could be an attractive alternative to CR if it produced similar health benefits, was more easily sustained, and mitigated CR s undesirable loss of muscle and bone. The overall goal of this 3-year HALLO planning grant is to develop a protocol for a rigorous, multi-site, randomized clinical trial (RCT) comparing clinically-relevant health outcomes in older persons randomized to daily CR, a TRF regimen, or a non-dietary attention control group employing innovative mHealth tools to promote adherence. We will complete a 12-month pilot study enrolling 120 older adults (age =60 years; 50% women; =23% minority) to provide critical information on feasibility, intervention delivery, and data informing effect size determination. HALLO-P s Objectives are to: 1. Establish a scientific advisory board and other structures to guide planning activities and the design of a full- scale RCT that engage a wide range of stakeholders and build a national constituency for the project. 2. Refine our mHealth behavior-change and adherence tracking platform the HALLO-P Companion App to optimize delivery of both the CR and TRF interventions. 3. Conduct focus groups and a 12-month pilot RCT of: 1) 20% CR delivered in-person; 2) 20% CR delivered remotely via video conferencing; and 3) TRF (8-10 hours) with ad libitum caloric intake. Pilot data will help refine recruitment criteria, estimate recruitment yields, and refine intervention approaches. We will use doubly- labeled water to measure achieved CR and continuous glucose monitoring to assess adherence to TRF. 4. Model aging biomarker changes for differing CR doses using WF OAIC repositories and the HALLO-P pilot. Existing epidemiological databases will be used to estimate the anticipated effect of these biomarker changes on clinical outcomes and to derive key design metrics related to inclusion/exclusion criteria, and event rates related to multi-morbidity, health deficit accumulation, and functional decline/disability; and 5. Integrate new data, the scientific literature .and expert advice to prepare a protocol, and develop informed consent forms, manuals of operation, study forms, and related systems to permit the rapid launch of the larger trial upon completion of the pilot activities in coordination with the other U01 project funded by this mechanism.

21. **Project Title:**   **The Wake Forest Nonhuman Primate Radiation Survivor Cohort**
    Leader(s):   **CLINE, J. MARK**
                            WAKE FOREST UNIVERSITY HEALTH SCIENCES
                            NIH U01AI150578 / (2020 - 2027)

Core(s):

Abstract/Summary Acute effects of radiation exposures are the focus of emergency medical responses and mitigation efforts, but the major burden of radiation injury lies in delayed effects. These late and usually long-term effects of exposure on normal healthy tissues include cellular, molecular, and metabolic changes leading to organ dysfunction and failure; fibrosis; and neoplasia. The Radiation Survivor Cohort (RSC) is a unique and irreplaceable population of nonhuman primate (NHP) radiation survivors, which serves the nation s need to identify and understand the late effects of radiation exposure; provides long-term outcome validation of acute biomarker measurements; and provides critical data regarding tissue damage and recovery. RSC investigators at Wake Forest have assessed adverse effects of single-dose whole-body exposures of 1-8.5 Gy in over 140 rhesus monkeys observed for up to 15 years after irradiation, with 38 controls. The cohort includes juvenile and adult exposures, males and females, and subsets of animals that did or did not receive mitigating treatments such as hematopoietic growth factors or antibiotics. Observations have included an annual cycle of clinical examinations, imaging (ultrasound, CT and MRI), clinical pathology, and ultimately necropsy examinations. Major diseases identified to date include (1) metabolic disease and type II diabetes mellitus; (2) myocardial diastolic dysfunction with fibrosis; (3) neurologic disorders with MRI-detected brain lesions; (4) chronic renal disease with fibrosis; (5) gastrointestinal disease resulting in chronic diarrhea; (6) immune compromise with impaired response repertoire; (7) neoplasms, primarily including sarcomas, hematopoietic, epithelial, and neuroendocrine types. Other stereotypical radiation effects are seen, such as cataracts and gonadal atrophy at higher doses. Multiple disorders in the same animal were common, up to 8 in high-dose animals, with diabetes being the most common co-morbid condition. The overarching goal for the proposed new funding period is to identify and study relevant patterns of post-irradiation morbidity and mortality in this unique, controlled, well- defined NHP population, by collaborating and sharing data with NIH-funded and other federally-funded investigators. Sharing will include samples (blood, tissue, body fluids, microbiome) and data

(clinical, imaging, pathology, gene sequence, gene expression, immunophenotyping and other data types) with an active investigator community currently consisting of 62 investigators across 18 institutions, including outreach to new investigative teams. The specific aims of this program are to (1) identify and share patterns of post-irradiation morbidity; (2) identify genomic and biomarker characteristics of animals with differing radiation-induced disorders; (3) assess late effects of prior mitigator treatment; and (4) refine the cohort to balance age, sex, dose, and mitigator type, in order to maximize the scope of inference of data derived from the cohort.

22. Project Title: Bisphosphonate Use to Mitigate Bone Loss Secondary to Bariatric Surgery

Leader(s):   **BEAVERS, KRISTEN MARIE; ARD, JAMY D;**
WAKE FOREST UNIVERSITY
NIH U01AR080969 / (2022 - 2027)

Core(s):

PROJECT SUMMARY Despite well recognized improvements in obesity-related comorbidities, mounting evidence implicates sleeve gastrectomy (SG) in the onset of skeletal fragility. Bisphosphonate therapy reduces osteoporotic fracture risk and may also be effective in minimizing bone loss associated with SG. Once-monthly oral risedronate is a commonly prescribed bisphosphonate with a favorable gastrointestinal profile that acts by inhibiting the activity of osteoclast cells, thereby decreasing the rate of bone resorption. Because SG is associated with a significant increase in bone resorption, we hypothesize that risedronate use will counter bone loss in this clinical scenario, ultimately reducing long-term fracture risk. Indeed, pilot data from our group signal that six months of risedronate use is both feasible and likely effective at reducing bone resorption and bone mineral density (BMD) loss post- SG as compared to placebo. Intriguingly, we also observe a signal for appendicular lean mass preservation with risedronate use. This novel finding aligns with data from animal models of clinical pathology and limited observational data in humans, suggestive of a bisphosphonate-induced lean-mass sparing effect. If true, confirmatory data from a definitively designed trial is poised to influence clinical management of the SG patient, while also providing a platform upon which to interrogate mechanisms of bone-muscle crosstalk. To fill these knowledge gaps, the main objective of the proposed study is to definitively test whether risedronate use can effectively counter SG associated bone loss. To do this, we propose to randomize 120 middle-aged and older (=40 years) SG patients to six months of risedronate or placebo treatment, with bone and muscle outcomes assessed at baseline, six, and 12 months. Due to its robust change following SG and clinical utility in predicting fracture, our primary outcome is change in total hip areal (a)BMD measured by dual energy x-ray absorptiometry (DXA). This will be complemented by DXA-acquired aBMD assessment at other skeletal sites and appendicular lean mass, as well as quantitative computed tomography (QCT) derived changes in bone (volumetric BMD, cortical thickness, and strength) and muscle (cross sectional area, fat infiltration) at the hip and spine allowing for novel assessment of intervention effectiveness on several state of the art bioimaging metrics as well as select physical function tasks. Biomarkers of bone turnover and bone-muscle crosstalk will also be assessed in a tertiary aim, providing mechanistic insight into intervention-related changes to the bone-muscle unit. Definitive data has the potential to shift current clinical practice while also offering insight into underlying biologic mechanisms.

23. Project Title: Wake Forest Atrium HeartShare Clinical Center

Leader(s):   **KITZMAN, DALANE W**
WAKE FOREST UNIVERSITY HEALTH SCIENCES
NIH U01HL160272 / (2021 - 2026)

Core(s):

Project Summary Heart Failure with Preserved Ejection Fraction (HFpEF) is the most common form of HF in the US and is associated with high morbidity and mortality. However, its pathophysiology is incompletely understood, and most trials have been neutral such that few evidence-based treatments exist. In response, NIH convened 2 workshops co-led by Dr. Kitzman (PI). The highest priority research recommendation was a coordinated effort to create a large cohort of HFpEF patients and controls and perform comprehensive, deep phenotyping. This became the basis for HeartShare, whose ultimate goals are to discover novel HFpEF mechanisms, subtypes, and therapeutic targets. Our Wake Forest - Atrium HFpEF team is highly qualified to serve as a Clinical Center and make robust, over-arching contributions to HeartShare. Dr. Kitzman is internationally recognized as a thought-leader in HFpEF with a sustained track record of developing novel concepts regarding HFpEF pathogenesis, mechanisms, and outcomes and designing and conducting innovative studies to

test them. His team has extensive experience in all key aspects of the HeartShare program, particularly in recruiting, retaining, and phenotyping diverse populations of HFpEF patients and controls, often significantly exceeding goals for racial and gender diversity. Our institutions have ~15,000 HFpEF clinical visits annually. In all, our team has led or helped lead recruitment and phenotyping for 69 studies, mostly NIH-sponsored, with 15,354 participants, demonstrating our ability to fulfill HeartShare recruitment and phenotyping goals. Data from these studies will be contributed to the Cohort phase of HeartShare. We will make robust contributions to HeartShare by achieving 4 Specific Aims: Aim 1) Provide thought leadership in collaboration with the HeartShare Steering Committee; Aim 2) Contribute data, images, and stored specimens cohort phase of HeartShare from our numerous studies of HFpEF and controls, and identify and phenotype HFpEF patients and controls from the electronic health record using robust bioinformatics tools; Aim 3) Recruit, consent, enroll and follow at least 250 HFpEF patients plus controls (type and number to be determined by consensus); Aim 4) Conduct state-of- the-art deep phenotyping exams using a collaboratively determined protocol. Our phenotyping proposal is highly innovative, with advanced echo-Doppler and cardiac magnetic resonance imaging, CPET, physical activity monitoring, remote and artificial intelligence electrocardiography, sampling of skeletal muscle, adipose, blood, and microbiome, and mitochondrial energetics, and brain structure/function. Our diverse, cross- disciplinary team has the full range of complementary expertise and access to the robust resources of two large, closely affiliated health systems to ensure fulfillment of all HeartShare s goals. We will help accelerate and optimize the program s success with our insight, creativity, and sustained track record of collaboration, innovation, and dissemination.

24. Project Title: PRAGMATIC EVALUATION OF EVENTS AND BENEFITS OF LIPID-LOWERING IN OLDER ADULTS (PREVENTABLE)

Leader(s): **ALEXANDER, KAREN P; AMBROSIUS, WALTER T ; HERNANDEZ, ADRIAN ; WILLIAMSON, JEFF DOUGLAS ; DUKE UNIVERSITY**
NIH U19AG065188 / (2019 - 2026)

Core(s):   - Clinical Research Core (CRC)

There is an urgent need for evidence to guide clinical care of older adults due to demographic shifts, includinglonger life expectancy and a recent doubling of the older adult population. Statins reduce recurrent CVD eventsand prevent initial events in patients younger than 75 years. However, clinical research has often excludedpersons older than 75 years due to a higher prevalence of comorbidity and frailty so little to no evidence isavailable to guide care in this population. For older adults living longer, the promise of preventing cognitiveimpairment is as compelling as preventing a CVD event, but some evidence suggests statins maycontribute to memory difficulty or muscle symptoms. There is equipoise regarding the usefulness of statinsfor primary CVD, dementia, and disability prevention in adults older than 75 years, especially in the settingof multiple chronic conditions, advanced age, or frailty. Evidence to improve cognitive and functionaloutcomes in older populations with diverse race/ethnicity and health status will require new clinical trialapproaches with sustainable methodology and infrastructure. We propose PREVENTABLE (PRagmaticEValuation of evENTs And Benefits of Lipid-lowering in oldEr adults), the first statin trial with a non-CVDprimary outcome survival free of dementia or persisting disability. Using a placebo-controlled pragmaticclinical trial (PCT) design across PCORnet and VA network, the trial will be under the leadership of Dr. KarenAlexander at DCRI, Dr. Jeff Williamson at WFSM, Dr. Adrian Hernandez at DCRI, and Dr. Walter Ambrosius atWFSM. This team has established experience and track-record of accomplishment in the design and conductof PCTs, trial expertise in ascertaining cognitive and disability outcomes in older adults, and is supported by arobust administrative infrastructure for coordinating these shared responsibilities for success. The overarchinggoal of PREVENTABLE is to generate knowledge about the role of statins in older adults, a population in whichrisk/benefit for primary prevention has been under studied. The hypothesis is that a large trial conducted in anolder adult population will demonstrate the benefit of statins for reducing dementia, disability, and CV events.We further hypothesize that extensive genomic, biochemical and imaging ancillary studies will offer uniqueinsights into these key outcomes. PREVENTABLE has the following specific aims: AIM 1: Determine the roleof a moderate-intensity statin in preventing dementia and prolonging disability-free survival in patients 75 yearsand older without clinically evident coronary heart disease, including those with frailty, impaired physicalfunction, mild cognitive impairment, polypharmacy, and multi-morbidity. AIM 2: Determine the role of moderate-intensity statin in preventing hospitalization for myocardial infarction/acute coronary syndrome, stroke, heartfailure, revascularization or cardiovascular-related death, and preventing either mild cognitive impairment ordementia. AIM 3: Test the safety and tolerability of statins in older adults and collect 17,000 bio-specimens toadvance precision health.

25. Project Title: Research Centers Collaborative Network Renewal

Leader(s):   **KRITCHEVSKY, STEPHEN B.; LEDERMAN, STEPHANIE ;**
WAKE FOREST UNIVERSITY HEALTH SCIENCES
NIH U24AG058556 / (2018 - 2026)

Core(s):

The problems of an aging society transcend the boundaries of any specific discipline and play out across multiple biologic and societal domains. The six National Institute on Aging center programs address these problems but typically from a specific disciplinary perspective. To provide a mechanism to foster cross-disciplinary collaborations the Research Centers Collaborative Network (RCCN) was established in 2008. It is led by the American Federation for Aging Research and the Wake Forest School of Medicine. The RCCN addresses the challenge of building multidisciplinary collaborations by employing 5 complementary strategies: 1) identifying intellectual opportunities that are best advanced by inter-center collaboration; 2) stimulating the development of cross-center collaborations; 3) providing new opportunities for early career researchers to expand their multidisciplinary collaborative network; and 4) leveraging RCCN activities to bring additional resources to multidisciplinary aging research. Its first two years were highly successful. In a highly praised workshop series, it brought together key thought leaders from each of the 6 NIA center programs, offered didactic programs for early career researchers, established a Webinar series, worked with NIA center coordinating centers to coordinate activities and promote dissemination, and worked with the CTSA s Inclusion of Older Adults workgroup to increase recruitment of older adults to clinical research among other achievements. Its goals going forward build on these achievements and introduce important innovations and refinements. The RCCN s specific aims for the next cycle are to: 1. Stimulate cross-center collaboration through: a) Workshops focused on cross-cutting scientific themes each relevant to 4 or more center programs; and b) Pilot grants supporting the initiation of cross-center collaborations. 2. Provide educational opportunities for early career investigators to build competencies in multidisciplinary and cross-institutional research. 3. Work with NIA Center program coordinating centers and other NIA supported research networks to: a) disseminate cutting edge multidisciplinary science; b) foster connections between the 6 NIA center programs and other NIA-supported research networks; and c) develop tools, standards and guidelines to promote multi-disciplinary and multi-institutional research. 4. Expand its impact through fostering applications to foundations, the CTSA program and other potential sponsors whose interests align with NIA Center programs. The RCCN employs multiple evaluation strategies designed to strengthen and adapt its programs and to gauge its impact in fostering multidisciplinary approaches to solving the problems facing older adults.

26. Project Title: MoTrPAC Consortium Coordinating Center

Leader(s):   **ESSER, KARYN A; MILLER, MICHAEL E.; PAHOR, MARCO ;**
REJESKI, WALTER JOHN; TRACY, RUSSELL P;
UNIVERSITY OF FLORIDA
NIH U24AR071113 / (2016 - 2023)

Core(s):

Summary Physical inactivity is a major public health challenge underlying a broad range of health problems at all ages. While physical activity (PA) has shown to produce relevant health benefits, the underlying molecular mechanisms are poorly known. The coordinated effort of clinical and animal studies supported by bioinformatics and chemical analyses will achieve the Molecular Transducers of Physical Activity Consortium (MoTrPAC) goals of assessing the molecular changes that occur in response to PA. The Consortium Coordinating Center (CCC) for the MoTrPAC will provide support for the organization, administration, planning, standardization, documentation, monitoring and reporting activities relating to the MoTrPAC. The CCC will play a pivotal role in ensuring the cohesion of the MoTrPAC by enhancing communication and integration across all study components, including the Clinical Sites, the Preclinical Animal Study Sites, the Bioinformatics Center, the Chemical Analysis Sites, and the various study committees. The CCC will develop strategies and strategic planning processes by integrating activities of the MoTrPAC investigators with the input provided by the Data Safety Monitoring Board, the External Scientific Advisors, outside experts, and the NIH. The CCC will facilitate interactions and communications with junior and senior investigators outside the consortium to maximize the use of the MoTrPAC resources toward achieving the overall research goals. To accomplish these goals and maximize the progress and productivity of the MoTrPAC, the CCC will promote team science, team leadership, and innovative leadership approaches across all study components. Strategic planning that follows the principles of the dynamic theory of strategy will be fostered to evaluate alternative approaches, maintain the cutting-edge scientific focus, leverage state-of-the-art coordination technologies, anticipate challenges, and maximize future opportunities to ensure the success of the consortium. The CCC will comprise four integrated components led by four highly qualified PIs who have a long-lasting track record of successfully working in synergy. The four CCC components comprise the Administrative

Coordinating Center (PI Dr. Pahor), the Data Management, Analysis, and Quality Control Center (PI Dr. Miller), the Biospecimens Repository (PI Dr. Tracy), and the Exercise Intervention Core (PI Dr. Rejeski). The CCC will employ innovative project management tools and web-based tracking of exercise adherence and diet, and will capitalize on the outstanding track record and expertise of its investigators in: (a) working together; (b) successfully coordinating, managing, and leading large long-term multicenter clinical trials involving PA and other interventions; (c) implementing rigor and transparency in research, (d) acquiring, managing, storing and analyzing biological samples; (e) conducting animal exercise studies; (f) sharing resources; (g) publishing results; and (h) leading multidisciplinary teams. The CCC will ensure and promote the continued success of the MoTrPAC in advancing knowledge about the molecular changes that occur in response to PA, and relating these changes to the health benefits of PA.

27. Project Title: Mapping and validating senescent cells in human muscle, ovary and breast

Leader(s): MELOV, SIMON
BUCK INSTITUTE FOR RESEARCH ON AGING
NIH U54AG075932 / (2021 - 2026)

Core(s):

BIOLOGICAL ANALYSIS CORE - PROJECT SUMMARY This Buck Institute Tissue Mapping Center (TMC) proposes to map senescent cells in three human somatic and reproductive tissues; ovaries, breast tissue and skeletal muscle. A major gap in the field has been to define specific cellular senescence markers for distinct cells and tissue types. We propose to fill this gap by defining markers of cellular senescence in the context of aging in human tissues. The capabilities of this core include a deep knowledge of multiple aspects of senescence encompassing the SASP, novel senolytics, and preliminary data defining senescent cells in human muscle tissue. Tissues received in the Biospecimen Core will be conveyed to the Biological Analysis Core and subjected to multiple procedures designed to identify senescent cell signatures (either protein or mRNA) in nuclei or biofluids, and confirmed in tissue sections. The results from the Biological Analysis Core will be conveyed to the Data Analysis Core, and coordinated through the Administrative Core. The Biological Analysis Core will spatially map and determine the signatures of cellular senescence in healthy human ovaries, breast, and muscle in both sexes across an aging continuum through four specific aims. 1) Determine the unique transcriptional signature of large senescent cells. We will determine the transcriptional signatures of large senescent cells, which are lost during conventional single cell workflows and use this data to determine the prevalence of such signatures in the breast, ovary, and muscle. 2) Determine senescent protein signatures of the breast, ovary, and skeletal muscle. We will comprehensively analyze secreted senescence-associated secretory phenotype (SASP) proteins from bio fluids, and cell culture systems from muscle, breast, and ovaries using different senescence inducers and senolytics. 3) Determine senescent transcriptional signatures of the breast, ovary, and skeletal muscle. We will use a bootstrapping strategy on key cell types from the tissues in this aim, to determine unique single cell senescent signatures derived from a range of senescent inducers on prototypical cell cultures from each tissue. We will use these data to map similar signatures back to complex fully profiled data sets derived from intact tissues using snRNA-seq, cell assignment, and expression analysis. 4) Determine spatial relationship and frequencies of senescent cells in tissue sections. We will take advantage of emerging technologies from Nanostring (Digital Spatial Profiling), and 10X technologies (Visium) to build on our knowledge discovered in the first three aims to better understand frequency and subtypes of senescent cells within tissue sections from tissue sections. In conjunction with other cores we expect to create a comprehensive spatial map and signatures of senescence in reproductive tissues (breast and ovary) and also the sex-specific and longitudinal differences in muscle, a somatic tissue, with age.

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2023

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Citations: 23 | AltScore: 12.4

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Citations: 25 | AltScore: 3.95

4. **Daily Low-Dose Aspirin and Risk of Serious Falls and Fractures in Healthy Older People: A Substudy of the ASPREE Randomized Clinical Trial.**
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Citations: 30 | AltScore: 2.5

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Citations: | AltScore: NA

27. **Improvisational Movement to Improve Quality of Life in Older Adults With Early-Stage Dementia: A Pilot Study.**
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Citations: 69 | AltScore: 4.7

28. **The geriatrics research instrument library: A resource for guiding instrument selection for researchers studying older adults with multiple chronic conditions.**
Tisminetzky M, Delude C, Allore HG, Anzuoni K, Bloomstone S, Charpentier P, Hepler JP, Kitzman DW, McAvay GJ, Miller M, Pajewski NM, Gurwitz J
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Citations: 16 | AltScore: 3

29. **Predictors of Clinically Meaningful Gait Speed Response to Caloric Restriction Among Older Adults Participating in Weight Loss Interventions.**
Tse K, Neiberg RH, Beavers DP, Kritchevsky SB, Nicklas BJ, Kitzman DW, Rejeski WJ, Messier SP, Beavers KM
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Citations: 26 | AltScore: 3.25

30. **Defining the Specific Skeletal Muscle Adaptations Responsible for Exercise Training Improvements in Heart Failure With Preserved Ejection Fraction.**
Tucker WJ, Kitzman DW
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Citations: 15 | AltScore: NA

31. **Skeletal muscle sympathetic denervation disrupts the neuromuscular junction postterminal organization: A single-cell quantitative approach.**
Wang ZM, Messi ML, Rodrigues ACZ, Delbono O
Mol Cell Neurosci, 2022 May, 120: 103730
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Citations: 36 | AltScore: 2.35

32. **Older Patients With Acute Decompensated Heart Failure Who Live Alone: An Analysis From the REHAB-HF Trial.**
Warraich HJ, Kitzman DW, Nelson MB, Mentz RJ, Rosenberg PB, Lev Y, Whellan DJ
J Card Fail, 2022 Jan, 28(1): 161-163
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Citations: 5 | AltScore: 5.1

33. **Severity of functional impairments by race and sex in older patients hospitalized with acute decompensated heart failure.**
Ye F, Nelson MB, Bertoni AG, Ditzenberger GL, Duncan P, Mentz RJ, Reeves G, Whellan D, Chen H, Upadhya B, Kitzman DW, Pastva AM
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34. **Cardiac troponin T and autoimmunity in skeletal muscle aging.**
Zhang T, Feng X, Dong J, Xu Z, Feng B, Haas KM, Cawthon PM, Beavers KM, Nicklas B, Kritchevsky S
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https://doi.org/10.1007/s11357-022-00513-7 | PMID: 35034279 | PMCID: PMC9616986
Citations: 131 | AltScore: 3.8

EXTERNAL ADVISORY BOARD MEMBERS

Nir Barzilai
Albert Einstein College of Medicine
Serving since 2012 (11 years)

Heather Whitson
Duke University
Serving since 2018 (5 years)

Kirk Erickson
University of Pittsburgh
Serving since 2018 (5 years)

Nathan LaBrasseur
Mayo Clinic
Serving since 2018 (5 years)

RECOGNITION AND AWARDS (2022-2023)

<u>Ashley Weaver</u> (2022)

- Research Excellence Awards, WFUSM

<u>Atalie Thompson</u> (2022)

- Translational Research Academy Scholar, WFUSM
- Translational Science Leadership Academy, WFUSM

<u>Gagan Deep</u> (2022)

- Research Excellence Award, Wake Forest University School of Medicine

<u>Jaime Speiser</u> (2022)

- Top 8 Cited Paper in the Past 3 Years, Expert Systems with Applications Journal (Publication 1c, Speiser et al.)

<u>Jaime Speiser, PhD</u> (2022)

- Top 8 Cited Paper in the Past 3 Years, Expert Systems with Applications Journal (Publication #5, Speiser et al.)

<u>Jamie Justice, PhD</u> (2022)

- AFAR Vincent Cristofalo Rising Star in Aging Research Award
- Travel Awardee, NIA / AFAR Research Centers Collaborative Network (RCCN), Measuring Biologic Age Workshop
- Jarrahi Research Scholars Fund in Geroscience Innovation
- Early Career Investigator in Basic/Translational Science Award, Wake Forest University School of Medicine

<u>Stephen Kritchevsky, PhD</u> (2022)

- Special Achievement Award, Wake Forest School of Medicine Faculty Award

<u>Tina Brinkley, PhD</u> (2022)

- WFUSM Department of Internal Medicine – Top Papers Published in 2021

MINORITY RESEARCH

General Brief Description of Minority Activities:
The Maya Angelou Research Center for Health Equality (MA-RCHE) has been established by the WFUSM to address issues related to racial and ethnic health disparities. Its overarching goal is to enhance wellness, improve quality of life, and reduce the burden of disease in underrepresented minorities through a comprehensive program in four core areas: health education, career/leadership development, research, and dissemination/application of new research findings for more effective and efficient health care approaches.

A key feature of the MA-RCHE is its model campus/community partnership involving WFUSM, the Reynolda Campus of Wake Forest University, Winston-Salem State University (a historically Black college/university) and the Forsyth County community at-large. This partnership brings the vast experiences, knowledge base and resources of each partner to bear on health problems of underrepresented minorities.

Minority Trainee(s):

- Gagan Deep, PhD, Associate Professor, Cancer Biology
  PESC Pilot 2019.1 Isolation and molecular characterization of exosomes secreted by visceral adipose tissue
- Genesio Karere, PhD, Assistant Professor, Department of Internal Medicine, Section on Molecular Medicine
  Current REC scholar Project title: MicroRNA biomarkers and pathways underlying response to exercise intervention in older adults
- Raghunatha Yammani, PhD, Associate Professor, Internal Medicine, Molecular Medicine
  PESC 2019.2 Is Restoring Protein Homeostasis A Viable Therapy For Age-Related Osteoarthritis?

Minority Grant(s):

1. Project Title:	**PROSOCIAL BEHAVIOR AND EXERCISE AMONG OLDER ADULTS**
Leader(s):	**FOY, CAPRI G**
	WAKE FOREST UNIVERSITY HEALTH SCIENCES
	NIH R21AG027413 / (2008-2011)

DESCRIPTION (provided by applicant): Regular physical activity has been shown to enhance physical function and health-related quality of life and reduce morbidity and mortality among older adults. Unfortunately, compliance rates to physical activity programs are distressingly low, even among asymptomatic populations. Many traditional exercise interventions do not provide the self-regulatory skills necessary for long-term behavioral change. These issues become more prominent as the population of older Americans continues to increase. Although only a small percentage of older adults engage in habitual physical activity, there are episodic charity events involving moderate physical activity that attract large numbers of participants of all age ranges. These actions are a form of prosocial behavior, defined as voluntary, intentional behavior that results in benefits for another. The opportunity to help others seems to be a motive to inspire these individuals to at least engage in acute moderate physical activity. In previous

pilot work (Section 4.1.a), we found that participants randomized into a prosocial behavior physical activity group demonstrated increased physical activity at 3 months compared to those in a standard exercise group. Our current research question contemplates whether prosocial behavior may be implemented as a viable behavioral incentive for long-term physical activity. Therefore, the primary aim of this investigation is to determine the feasibility of conducting a 9-month prosocial behavior intervention to increase physical activity among 80 underactive older adults. To our knowledge, the use of prosocial behavior as a motivational tool for physical activity has not been investigated, and represents a novel approach. The PBPA program will allow participants to earn boxes of food for donation to the Second Harvest Food Bank of Northwest North Carolina based upon their weekly physical activity. Other specific aims include determining the ability to successfully recruit participants into the study, the ability of participants to adhere to the PBPA program, and the ability to retain participants throughout the study. If successful, preliminary data from this study will be used to seek R01 funding to conduct a fully powered, longitudinal trial.

2. Project Title: **MOBILE INTERVENTION TO REDUCE PAIN AND IMPROVE HEALTH (MORPH) IN OBESE OLDER ADULTS**

Leader(s): **BROOKS, AMBER K ; FANNING, JASON ;**
WAKE FOREST UNIVERSITY HEALTH SCIENCES
NIH R21AG058249 / (2017-2020)

PROJECT SUMMARY Chronic pain has emerged as an urgent age-related health issue that significantly compromises physicalfunctioning and quality of life, with the adverse effects amplified by both obesity and sedentary behavior. The annualcost of pain in the United States is nearly 30% higher than the combined costs of cancer and diabetes. In 2016, the NIHcalled for a National Pain Strategy to: 1) expand non-pharmacological treatment options in older adults, who areparticularly susceptible to the side effects of opioid and other pain medications; 2) develop accessible treatments that aretailored to individuals; and 3) increase the development of self-management programs for chronic pain. The purpose ofthis R-21 is to develop and test the feasibility and acceptability of a novel, patient-centered intervention to reducechronic pain and improve physical functioning in older adults, leveraging the combination of telecoaching andindividually-adaptive mHealth tools to decrease both body mass and sedentary behavior. The proposal consists oftwo phases. The first phase will use an iterative user-centered design process to develop the mHealth application, to adaptthe weight loss and sedentary behavior components of the intervention to a telecoaching model, and to evaluate theusability and feasibility of the intervention for obese, older adults with chronic pain. In the second phase we will conducta pilot randomized controlled trial to provide initial evidence for effect sizes (pain and physical function) associated withthe proposed intervention, and to estimate the sample size needed for a full scale randomized controlled trial design thatcompare the effects of the intervention versus usual care on pain ratings and physical function in overweight/obese olderadults with chronic pain.

3. Project Title: **THE ENRGISE STUDY**

Leader(s): **PAHOR, MARCO ; AMBROSIUS, WALTER T ;**
UNIVERSITY OF FLORIDA
NIH U01AG050499 / (2015-2019)

DESCRIPTION (provided by applicant): Growing evidence from our group and others shows that low-grade chronic inflammation, characterized by elevations in plasma C-reactive protein, tumor necrosis factor alpha, and particularly Interleukin-6 (IL-6), is an independent risk factor o disability, impaired mobility, and lower walking speed. Low-grade chronic inflammation is a modifiable risk factor. However, it is unknown whether interventions that reduce the levels of inflammatory markers per se improve mobility, or avert decline in mobility in older persons. To address this gap in evidence we propose the randomized clinical trial ENRGISE (ENabling Reduction of low-Grade Inflammation in SEniors) to test the ability of anti-inflammatory interventions for preventing major mobility disability by improving or preserving walking ability. We have maximized the public health impact of our proposed interventions by selecting interventions that are safe, tolerable, acceptable, and affordable for vulnerable older persons. Based on an extensive literature review, we propose to test the efficacy vs. placebo of the angiotensin receptor blocker losartan and omega-3 polyunsaturated fatty acids in the form of fish oil, alone and in combination. Both angiotensin receptor blockers and omega-3 polyunsaturated fatty acids have shown to reduce IL-6 in clinical trials and preliminary data suggest that they may improve physical function. We plan to recruit older persons who are at risk for, or with, mobility impairment, as measured by slow gait speed and self-reported mobility difficulty, and who have elevated levels of IL-6, the marker most consistently associated with mobility limitations. Preliminary data regarding feasibility need to be gathered before such a tria can be effectively designed and implemented. We propose to conduct a feasibility phase that includes performing meta-analyses of existing trials and cohorts, and conducting a pilot trial to assess the effects of the interventions on several inflammatory markers and walking speed. This will allow us to refine the design, recruitment yields, target population, adherence, retention, tolerability, sample-size, and cost for the main ENRGISE trial. We will assemble the multicenter research infrastructure needed for the ENRGISE pilot and main trials, including the biorepository, and we will develop the materials needed for implementing the trials, including the protocol, manual of operations, data and safety monitoring plan, forms, quality control and quality assurance plan, and recruitment and retention materials.

YALE UNIVERSITY
Claude D. Pepper Older Americans Independence Center

Thomas M. Gill, M.D.   203-688-9423   thomas.gill@yale.edu
Principal Investigator

Mary Geda   203-737-1800   mary.geda@yale.edu
Program Administrator

CENTER DESCRIPTION

The overarching mission of the Yale Older Americans Independence Center (OAIC), established in 1992, is to provide intellectual leadership and innovation for aging research that is directed at enhancing the independence of older persons. The unifying theme of the Yale OAIC is the investigation of multifactorial geriatric conditions, encompassing single conditions resulting from multiple contributing factors or affecting multiple outcome domains and multiple conditions occurring simultaneously.

The central Yale OAIC hypothesis is that geriatric conditions are determined by the co-occurrence of multiple predisposing and precipitating factors. These conditions and factors, in turn, affect a range of health outcomes. The predisposing factors may be at the genetic, molecular, physiologic, impairment, disease, or socio-demographic level, while the precipitating factors may be behavioral, environmental, social, medical, or psychological. The Yale OAIC theme requires designs and models (e.g. molecular, animal, and statistical) that inform the study of multiple, simultaneously interactive factors and outcomes. As a prominent subtheme, the Yale OAIC also aims to advance the science of clinical decision making in the face of trade-offs and multiple competing outcomes. This includes developing strategies to elicit older persons' health outcome priorities.

The Specific Aims of the Yale OAIC are to

1. Foster the career development of future academic leaders, from multiple disciplines, in aging research;
2. Train investigators, biostatisticians and other methodologists in the skills necessary to design, conduct, analyze, and disseminate findings from studies of multifactorial geriatric conditions;
3. Develop and disseminate design and analytic techniques for conducting studies of multifactorial geriatric conditions;
4. Develop strategies for recruiting into, and retaining, a broad spectrum of older persons, including minorities, into studies of multifactorial geriatric conditions;
5. Investigate the causative mechanisms of, and develop and test effective treatments for, geriatric conditions from a multifactorial research perspective;
6. Develop strategies to enhance clinical decision making in the setting of multiple competing outcomes;
7. Encourage and facilitate interdisciplinary research (basic, translational and clinical) that connects to our focus on multifactorial geriatric conditions; and further strengthen collaborations with other OAICs.

The Yale OAIC cores include: 1) Leadership and Administrative; 2) Research Education; 3) Pilot/Exploratory Studies; 4) Operations; and 5) Biostatistics.

CORES

Leadership and Administrative Core (LAC)

Leader 1:	Thomas M. Gill, MD	thomas.gill@yale.edu
Leader 2:	Terri Fried, MD	terri.fried@yale.edu
Leader 3:	Denise Acampora, MPH	denise.acampora@yale.edu
Leader 4:	Mary Geda, RN, BSN, MSN	mary.geda@yale.edu

The overarching objective of the Leadership and Administrative Core (LAC) is to advance the scientific knowledge base of multifactorial geriatric conditions. The LAC, which is led by two board-certified geriatric physician investigators with complementary expertise, is responsible for strategic planning, organization, administrative operations and evaluation of the OAIC research and training program. A special effort is devoted to ensuring the cohesion of the Center and maintenance of an interdisciplinary and translational research focus on the common research theme, which is "the investigation of multifactorial geriatric conditions". The key LAC tasks are achieved by the LAC leadership administrators, and three committees: the Executive Committee, the Internal Advisory Committee, and the External Advisory Committee.

Research Education Component (REC)

Leader 1:	Terri Fried, MD	terri.fried@yale.edu
Leader 2:	Albert Shaw, MD PhD	albert.shaw@yale.edu
Leader 3:	Denise Acampora, MPH	denise.acampora@yale.edu
Leader 4:	Andrew Cohen, MD, DPhil	andrew.b.cohen@yale.edu

The objective of the Research Education Core (REC) is to identify highly promising early-stage investigators and provide support to promote their development as independent investigators and leaders in aging research. The REC seeks to provide three groups of investigators, designated as Pepper Scholars, Small REC Awardees, and REC Affiliates, with the knowledge and skills to conduct biological, translational, and clinical studies of multifactorial geriatric conditions and to obtain subsequent funding from a broad range of sources. The outcomes and career advancement goals for the Pepper Scholars include: 1) publication of research results in high-impact journals; 2) success in obtaining independent funding, both to support further career development (e.g. K08 and K23 awards) and specific projects (e.g. R21 and R01 awards); and 3) development of leadership skills necessary to manage research teams and to become successful mentors themselves.

Pilot and Exploratory Studies Core (PESC)

Leader 1:	Albert Shaw, MD PhD	albert.shaw@yale.edu
Leader 2:	Terri Fried, MD	terri.fried@yale.edu
Leader 3:	Denise Acampora, MPH	denise.acampora@yale.edu

The primary goal of the Pilot/Exploratory Studies Core (PESC) is to facilitate the development of innovative and rigorous research studies that will enhance our understanding of the pathogenesis, etiology, diagnosis, prevention, and management of multifactorial geriatric conditions, leading ultimately to the development of efficacious and cost-effective interventions to increase or maintain the independence of older Americans.

Operations (RC1)

<u>Leader 1:</u>	Katy Araujo, MPH	katy.araujo@yale.edu
<u>Leader 2:</u>	Mary Geda, RN, BSN, MSN	mary.geda@yale.edu
<u>Leader 3:</u>	Lauren Ferrante, M.D., M.H.S.	lauren.ferrante@yale.edu

The Operations Core (OC) supports OAIC investigations of multifactorial geriatric conditions by recruiting and retaining diverse populations of older persons, seeking input from the local community in research, planning and dissemination, monitoring participant safety, ensuring regulatory compliance, developing surveys and instruments, designing Information Technology (IT) systems to implement research, collecting and preparing data for statistical analysis, and providing continuity and shared knowledge across projects. The overall goal of the OC is to ensure the successful implementation of research focused on multifactorial geriatric conditions. This goal will be accomplished by leading, managing, and coordinating the effective, efficient and innovative use of facilities, data, staff, resources, and space. There is a consistent demand for experienced personnel with the ability to quickly execute aging-focused research and an increasing need for informatics skills and technology to streamline work.

Biostatistical Design and Analysis Core (RC2)

<u>Leader 1:</u>	Denise Esserman, PhD	denise.esserman@yale.edu
<u>Leader 2:</u>	Brent Vander Wyk, PhD	brent.vanderwyk@yale.edu

The overarching goals of the Biostatistics Core (BC) are to provide design and analytical services to OAIC investigators conducting studies of multifactorial geriatric conditions; to develop and disseminate new design and analytical techniques for conducting studies with older persons; and to train a cadre of clinical investigators, biostatisticians, and epidemiologists in the skills necessary to design, conduct, and analyze gerontologic studies.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications

Minhee Sun
Instructor of Medicine (General Medicine) / Yale University
<u>Opioid Use Disorder Management of Older Adults with Multimorbidity: a Delphi Study</u>

2023-2025 /
0 (total)
0 (1st/Sr)

Specific Aim 1 to perform a scoping review of the existing literature to characterize the populations and outcomes studied. Part of the scoping review will also be to examine existing publicly available datasets of older adults to determine whether and how Opioid Use Disorder (OUD) was evaluated and its prevalence, in order to evaluate suitability for further epidemiologic studies of OUD among older persons. Specific Aim 2 will be to bring together the existing experts in aging and OUD in a Delphi panel to address several important clinical questions for which there are insufficient data to inform practice. These include: 1) should an older adult being treated with OUD who develops delirium with an acute illness remain on therapy? What factors, in terms of comorbid conditions and risks, should be considered in the decision?; 2) how should treatment for OUD in the older person be modified if the patient develops a geriatric syndrome such as cognitive impairment or falls? Key benchmarks for this project will be two manuscripts presenting the findings of each aim and preparation of an advanced VA CDA award.

Michael Nanna
Assistant Professor of Internal Medicine (Cardiovascular Medicine) / Yale
<u>Multimorbidity and Shared Decision Making for Treatment of Stable Coronary Artery Disease</u>

2023-2025 /
9 (total)
3 (1st/Sr)

This work is predicated on several established findings: 1) there are no mortality differences between the two approaches; 2) each of the two approaches has a unique set of treatment burdens and potential for harm, and these are modified by patients' unique set of comorbid conditions; and 3) patients have unrealistic expectations regarding the treatment options. The goal of the tool is to help clinicians and patients consider these treatment options in the context of the individualized risks, preferences and priorities of the older person. The knowledge gap is a lack of understanding about how patients and clinicians factor these considerations into their decisions and the specific aspects of the therapies that matter to decision making. Specific Aim 1 will use qualitative methods to understand the concerns and priorities of older persons with cardiovascular disease related to the use of medical therapy and PCI, including views regarding relevant benefits and harms of each therapy and the importance of these to decision making. Specific Aim 2 will use consensus methods with a group of experts in geriatric cardiology to establish methods for identifying older adults with elevated likelihood of experiencing the outcomes elucidated in Specific Aim 1. Specific Aim 3 will involve the iterative design of a decision support tool with feedback from the participants in Aims 1 and 2 as well as general cardiologists
- HA-2021C3-24767

Guido Falcone
Assistant Professor of Medicine (Neurology) / Yale University
<u>Multi-Phenotype Big Data Approach to Cerebral Small Vessel Disease Genomics</u>
- P30AG021342
- R03NS112859

2017-2024 /
62 (total)
3 (1st/Sr)

Edward Manning
Instructor / Yale University
Aging of the Human Pulmonary Artery: Analyzing Gene Expression to Tissue

2021-2023 /
4 (total)
1 (1st/Sr)

There is a knowledge gap in the underlying mechanisms of how the pulmonary artery changes with age. Evidence from an aging mouse model shows that pulmonary arteries stiffen with an age. Pulmonary arterial stiffening in humans is associated with lung diseases including chronic obstructive pulmonary disease, pulmonary hypertension, and disease associated with dyspnea; dyspnea occurs in over 10 million Americans over the age of 65. Yet, the association between age and pulmonary arterial stiffening is poorly described. Dyspnea is associated with frailty and poor health in the older population, but the etiology of dyspnea in many of these older individuals is unexplained. Therefore, this study aims to identify an association between age and pulmonary arterial stiffness in the human pulmonary artery and investigate underlying mechanisms of human pulmonary arterial stiffening. These aims are based on findings from a mouse model of pulmonary arterial aging and will employ similar investigational techniques as those successfully used in the mouse model. The first aim is to characterize the association of material stiffness of the pulmonary artery with age by mechanically testing 20 disease-free pulmonary arteries from deceased human donors ranging from 18 to 80 years old. Material stiffness will be calculated from measurements of deformation of the pulmonary arteries, including diameter, pressure, and force, while mounted on cannulas and submerged in physiologic solution. An additional aim is to use 2-photon imaging of 20 disease-free pulmonary arteries from deceased human donors ranging from 18 to 80 years old to characterize the association of extracellular collagen fiber orientation with age. The orientation of collagen fibers will be calculated from using 2-photon imaging and fast fourier transform analysis. The final aim is to identify whether pulmonary arterial cell gene expression changes as a function of age by performing single cell RNA sequencing on 20 disease-free pulmonary arteries from deceased human donors ranging from 18 to 80 years old. This aim will be accomplished by performing single cell RNA sequencing, a unique tool to investigate cell populations in tissue with near complete genomic profile of individual cells. These cellular specific changes of genetic expression will identify multiple cellular pathways and mechanisms responsible for changes in the pulmonary artery as a function of age. This study will be the foundation for future clinical investigations to associate age-related pulmonary arterial stiffness and health outcomes. Additionally, a better understanding of underlying mechanisms related to increased pulmonary arterial stiffening will provide information to determine optimal non-invasive measurements of pulmonary arterial stiffening in clinical settings and potential therapeutic targets for slowing or reversing the aging process of the pulmonary artery in future studies.

Cameron Gettel
Assistant Professor / Yale University
Development and validation of the Patient-Reported Outcome Measure – Older adult care Transitions from the Emergency Department (PROM-OTED) tool

2021-2023 /
13 (total)
11 (1st/Sr)

Persons aged 65 years and older account for over 22 million emergency department (ED) visits annually. Recent efforts to reduce unnecessary hospitalizations following ED evaluation have resulted in approximately 65% of older adult ED patients being discharged home. This vulnerable time period post-ED discharge has significant clinical and public health importance as it has been associated with an increased likelihood of morbidity and mortality as well as unscheduled ED recidivism and hospital admission. Despite high rates of adverse outcomes in this period of transition, little is known regarding the experiences and specific challenges faced by older adults during transitions home from the ED. Having a clear understanding of patients' priorities regarding health-related quality of life, functional disability, communication barriers, and condition-specific symptoms after ED discharge is essential to inform clinical conversations and the development of interventions targeting care transitions for older adults. The overall objective of this proposal is to use a sequential exploratory mixed-methods approach to develop and validate the Patient Reported Outcome Measure - Older adult care Transitions from the ED (PROM-OTED) tool, a novel care transitions PROM for older persons experiencing ED discharge care transitions. We will achieve this objective with the following two aims: 1) To develop the PROM-OTED tool, characterizing outcomes of ED discharge care transitions prioritized by older persons. We will use an iterative qualitative approach including concept development, item generation, member checking, cognitive debriefing, and expert panel item-reduction by a modified Delphi process; and 2) To conduct internal validity testing of the PROM-OTED tool. We will perform quantitative survey evaluation of the tool's initial psychometric properties and feasibility among older persons who recently experienced an ED discharge care transition. Specifically, this work will have significant impact by developing a measure to assess whether outcomes prioritized by older adults experiencing ED discharge care transitions are currently met and identify opportunities for improvement in

the clinical and research arenas. Findings of this proposal will improve our understanding of the needs of an aging society to inform intervention development and policy decisions. During the award period, the candidate will acquire relevant skills and benefit from mentorship by accomplished clinician-researchers with complementary skill sets. This investigation will serve as preliminary work towards a future NIA K award application, in line with the candidate's long-term objectives of assessing the PROM-OTED tool in a larger national ED sample, including those with Alzheimer's disease and related dementias (ADRD), and subsequently developing care transition interventions to help older adults successfully navigate ED discharge care transitions.

- ARCOM-22-878456

Past Scholars
Xi Chen, Yale University (2016-2020)
Janice Hwang, Yale University (2018-2020)
Morgan Levine, Yale University (2018-2020)
Joan Monin, Yale University (2018-2020)
Brienne Miner, Yale University (2019-2021)
Maor Sauler, Yale University (2019-2021)
Gregory Ouellet, Yale University (2020-2022)
Zachary Levine, Yale University (2020-2022)

PILOT/EXPLORATORY PROJECTS (10 Pilot Projects Listed)

1. Project Title: **Genetic Predisposition to Cardiovascular Disease and Risk of Death, Dementia and Disability in Older Persons: PESC (2021-2022) - carryover 2022-2024**

Leader: **Guido Falcone**

Statins constitute a powerful treatment for hyperlipidemia, one of the most important risk factors for cardiovascular disease (CVD). While the benefit of statins in primary prevention has been clearly established for middle-aged persons, there is no definitive evidence supporting their use in older adults. The PREVENTABLE clinical trial will enroll 20,000 older adults to test the hypothesis that statins increase survival free of dementia or disability in persons aged >75 years without clinically-evident CVD. Through the support of this Yale Pepper Pilot Award, we will evaluate whether a higher genetic predisposition to CVD increases the risk of this composite outcome in this age group. The results from this pilot study will provide key preliminary data to support an R01 application for an ancillary genetic study to PREVENTABLE that will test the hypothesis that information on known genetic risk factors for CVD can identify persons aged >75 who may preferentially benefit from statin treatment. Genomic information is emerging as a powerful precision medicine tool to identify persons at highrisk of human disease. There are numerous genetic risk variants that contribute to the pathophysiological processes that lead to the endpoints evaluated by PREVENTABLE. These genetic variants constitute an excellent basis for developing precision medicine tools, as they remain constant throughout life and immune to confounding by post-natal exposures due to their random assignment during meiosis. While promising, the field still lacks evidence on whether these genetic risk factors retain their effect and predictive ability in older adults, a crucial prerequisite to explore genomic-based precision medicine strategies in this age group. We will address this knowledge gap by evaluating the role of genetic predisposition to CVD in determining the risk of death, dementia or disability in persons aged >75 years without clinically-evident CVD. We will harmonize, quality control and analyze clinical and genetic data from 95,541 persons aged >75 years enrolled in the Health and Retirement Study and the UK Biobank to pursue the following specific aims: (1) Determine whether a higher genetic predisposition to CVD is associated with higher composite risk of death, dementia and disability (primary PREVENTABLE endpoint) in persons aged >75 years without clinically-evident CV disease; and (2) determine whether a higher genetic predisposition to CVD is associated with a higher composite risk of acute myocardial infarction, stroke or death of any cause (secondary PREVENTABLE outcome) in persons aged >75 years without clinically-evident CVD. The proposed research will significantly advance our understanding of the role of high genetic predisposition to CVD in determining death, dementia, disability and acute vascular events in older adults without clinically-evident CVD.

2. Project Title: **Aging of the Human Pulmonary Artery: Analyzing Gene Expression to Tissue: REC (2021-2023) Carryover 2023-2024**

Leader: **Edward Manning**

There is a knowledge gap in the underlying mechanisms of how the pulmonary artery changes with age. Evidence from an aging mouse model shows that pulmonary arteries stiffen with an age. Pulmonary arterial stiffening in humans is associated with lung diseases including chronic obstructive pulmonary disease, pulmonary hypertension, and disease associated with dyspnea; dyspnea occurs in over 10 million Americans over the age of 65. Yet, the association between age and pulmonary arterial stiffening is poorly described. Dyspnea is associated with frailty and poor health in the older population, but the etiology of dyspnea in many of these older individuals is unexplained. Therefore, this study aims to identify an association between age and pulmonary arterial stiffness in the human pulmonary artery and investigate underlying mechanisms of human pulmonary arterial stiffening. These aims are based on findings from a mouse model of pulmonary arterial aging and will employ similar investigational techniques as those successfully used in the mouse model. The first aim is to characterize the association of material stiffness of the pulmonary artery with age by mechanically testing 20 disease-free pulmonary arteries from deceased human donors ranging from 18 to 80 years old. Material stiffness will be calculated from measurements of deformation of the pulmonary arteries, including diameter, pressure, and force, while mounted on cannulas and submerged in physiologic solution. An additional aim is to use 2-photon imaging of 20 disease-free pulmonary arteries from deceased human donors ranging from 18 to 80 years old to characterize the association of extracellular collagen fiber orientation with age. The orientation of collagen fibers will be calculated from using 2-photon imaging and fast fourier transform analysis. The final aim is to identify whether pulmonary arterial cell gene expression changes as a function of age by performing single cell RNA sequencing on 20 disease-free pulmonary arteries from deceased human donors ranging from 18 to 80 years old. This aim will be accomplished by performing single cell RNA sequencing, a unique tool to investigate cell populations in tissue with near complete genomic profile of individual cells. These cellular specific changes of genetic expression will identify multiple cellular pathways and mechanisms responsible for changes in the pulmonary artery as a function of age. This study will be the foundation for future clinical investigations to associate age-related pulmonary arterial stiffness and health outcomes. Additionally, a better understanding of underlying mechanisms related to increased pulmonary arterial stiffening will provide information to determine optimal non-invasive measurements of pulmonary arterial stiffening in clinical settings and potential therapeutic targets for slowing or reversing the aging process of the pulmonary artery in future studies.

3. Project Title: **Improving Hospital-Level Mortality Performance for Major Surgery in Older Adults: A Mixed Methods Study: small REC (2021-2022) carryover 2023-2024**

Leader: **Robert Becher**

Despite decades of efforts to improve care for patients undergoing major surgery, there remains substantial variation across hospitals in surgical mortality. For adult patients undergoing common general surgery operations, standardized mortality ratios range from an average of 1.7 at poor-performing hospitals to a mean of 0.5 at high-performing hospitals, more than a three-fold difference. For older persons, deficient surgical care is especially problematic. Major surgery is a common event in the lives of community-living older persons, with a 5-year cumulative incidence of 13.8%, representing nearly 5 million persons aged 65 years or older in the US. This value will increase substantially in the coming years based on the projected doubling of this age group to 98 million people by the year 2060. Therefore, despite the

importance of major surgery as a defining health issue for older persons, we know little about what distinguishes poor-performing from exceptionalperforming outlier hospitals with high-versus low-mortality. This lack of evidence about what accounts for hospital mortality variation for geriatric surgery is a critical gap in our current knowledge. To facilitate improvements and achieve truly optimal perioperative outcomes for older persons undergoing major surgery, quality improvement science espouses the concept that we must first accurately define the landscape of the quality problem. One novel approach to examining the variation in healthcare quality is called positive deviance. This mixed methods analytic strategy postulates that hospital structures, processes, and internal environments may influence clinical outcomes. While the positive deviance approach has proven instrumental in improving hospital-level quality for other fields of medicine, it has not previously been applied to surgery. Grounded in the tenets of positive deviance, we will employ both quantitative and qualitative research in a complementary fashion to: (1) evaluate hospital-level mortality performance for older persons undergoing major surgery; (2) compare the patient-, operation-, and hospital-level characteristics between the highmortality and low-mortality hospitals for older persons undergoing major surgery; and (3) develop the methods and processes necessary for a full-scale qualitative evaluation of the hospital-specific efforts that may explain hospital-level mortality performance at the high-mortality and low-mortality hospitals for older persons undergoing major surgery. By taking a mixed methods approach, the proposed Pepper Scholar project will provide information that is essential to understanding the hospital-level sources of variation in mortality for geriatric surgery. These results, coupled with a robust career development plan and experienced mentoring, are expected to lay the groundwork for a subsequent novel and innovative large-scale, mixed methods R01 grant, fully utilizing the positive deviance approach on a national level, to define, test, disseminate, and implement evidence-based, hospital-level efforts to elevate hospital performance for older persons having major surgery in the US.

4. Project Title: **Can Type 2 Acute Myocardial Infarction Be Classified as a Geriatric Syndrome? (PESC 2022-2023) Carryover 2023-2024**

Leader: **Alexandra Hajduk**

While the archetype of acute myocardial infarction (AMI) is a disruption of plaque in a coronary artery leading to atherothrombosis (type 1 AMI), it is increasingly recognized that AMI does not always follow this definition. Type 2 AMI, which does not involve atherothrombosis in its pathogenesis but instead arises from supply-demand imbalance in myocardial oxygen secondary to other conditions (e.g., respiratory failure, anemia) is aprevalent AMI phenotype among older adults, particularly those with multiple comorbidities. Despite differences in pathogenesis, type 2 AMIs are often treated with the same diagnostic and treatment cascades as type 1 AMI, including angiography and secondary preventive medications. These treatments may be, at best, not helpful, and at worst, harmful, particularly to those with underlying vulnerabilities. A lack of tailored treatment strategies for type 2 AMI may explain, in part, the worse prognosis for mortality and morbidity for this AMI type when compared to type 1 AMI. Given the multiple etiologic factors, the increased incidence among older adults, and the poorly defined diagnostic and treatment pathways (with resulting poor outcomes), the primary aim of this work is to evaluate the appropriateness of characterizing type 2 AMI as a geriatric syndrome, i.e., a multifactorial health condition that occurs when the accumulated effects of impairments in multiple systems render an older person vulnerable to situational challenges. The objectives of this work align well with the unifying theme of the Yale Pepper Center, i.e., the investigation of multifactorial health conditions. This pilot project

will consist of a secondary analysis of data from the "ComprehenSIVe Evaluation of Older Patients with Acute Myocardial Infarction" (SILVER-AMI), a large cohort study of older adults with AMI that is unique in its collection of risk factors for geriatric syndromes at the time of AMI hospitalization. In aim 1, we will identify type 2 AMI cases via medical chart review using a hierarchical algorithm and a team-based adjudication process. We will not only discern type 2 AMI from type 1 AMI but will also examine the underlying condition(s) that precipitated type 2 AMI (e.g., arrhythmia, sepsis), thereby establishing a multifactorial pathogenesis. In aim 2, we will evaluate the appropriateness of characterization of type 2 AMI as a geriatric syndrome by associating it with a high prevalence of shared risk factors for geriatric syndromes: older age, functional impairment, mobility impairment, and cognitive impairment. To do this, we will evaluate the probability of type 1 vs. type 2 AMI, contingent on the presence of these shared risk factors. The findings from this pilot project will be used as preliminary data for an R21 proposal to the National Institute on Aging to evaluate differences in treatments and outcomes between types 1 and 2 AMI in older adults. The totality of this work will increase visibility of type 2 AMI as a condition that transcends traditional organ- and discipline-based boundaries, improve timeliness and accuracy of diagnosis, and facilitate development of appropriate treatment pathways, while reducing use of inappropriate treatments.

5. Project Title: **Epigenetic Aging Clock, Metabolomic, and Health Profiles in Adulthood Following Early Life Adversities in Nonhuman Primates : PESC (2022-2023) Carryover 2023-2024**

Leader: **Amanda Dettmer**

Societal and familial early life adversities (ELAs), including neglect, maltreatment, and low socioeconomic status (SES) are associated with adverse health outcomes in adulthood, yet it is unclear precisely how ELA "gets under the skin" to impact lifelong health. Given the high prevalence in the U.S. of childhood maltreatment and neglect (at least 15-20%), and that of children living in low-income families (38%), millions of children possess unique risks to healthy aging. Identifying biological mechanisms that link ELAs and age-related health outcomes is crucial for developing therapeutic treatments to ameliorate health disparities within the burgeoning population of older humans. Two promising mechanisms in associative studies in humans are dysregulated metabolism and epigenetic aging, both of which are correlated with chronological age and are associated with increases in obesity, diabetes, depression, and mortality. However, experimentally testing the hypothesis that ELA causes dysregulated metabolism and accelerated epigenetic aging in human cohorts is challenging. Children cannot be randomly assigned to adverse early experiences, and genetic and environmental confounds exist. Moreover, poor health in children may precede maltreatment or neglect. Finally, humans' long lifespan makes repeated sampling across the life course difficult and necessitates several decades for age-related health outcomes to emerge. Studying nonhuman primates (NHPs) as models of human health and aging has the potential to fill these critical gaps. NHPs possess striking biological, genetic, and behavioral similarities to humans, they have faster (~4x) developmental trajectories, and they can be randomly assigned to different early life experiences. We and others have previously shown that rhesus macaques (Macaca mulatta) randomly assigned to the ELA of nursery rearing (NR) in infancy, which models caregiver absence during critical developmental periods, have poorer health outcomes and acquire lower social ranks in adolescence and adulthood compared to mother-reared (MR) macaques. Additionally, macaques that are naturally born into low social ranks, a good proxy of low SES in humans, exhibit greater risk for adverse health outcomes. This pilot project will leverage the

macaque model to simultaneously examine whether experimentally-induced and naturally-occurring ELA is associated with differential likelihood of biological and health outcomes in adulthood. Capitalizing on our archive of over 30,000 biological samples and health data collected on macaques across the life course, we will examine whether NR and low social status differentially influence metabolism, epigenetic aging, and health outcomes in adulthood. Aim 1 will analyze plasma samples collected in adolescence and middle age from NR (n=12) and MR (n=12) macaques using global (untargeted) metabolomics, and white blood cells collected in middle age using epigenetic aging clock analysis; these measures will be correlated with occurrence of medical interventions, weight fluctuations and BMI, and adverse reproductive outcomes (stillbirths, spontaneous abortions, infant deaths, and C-sections) in middle age. Aim 2 will correlate epigenetic aging clock measures with the same health outcomes in a separate colony of high-ranking (n=10) and low-ranking (n=10) macaques. Results from this pilot study will be leveraged to pursue independent funding to expand this research into mechanistic evidence for the associations between ELA and adult health.

6. Project Title: **Distressing Symptoms and Disability Among Older Adults Following Critical Illness: REC (2022-2024)**

Leader: **Snigdha Jain**

The number of older adults who survive critical illness, estimated at about 1.4 million a decade ago, is increasing with the aging of the US population, advances in treatment for critical illness, and the current pandemic. Critical care medicine societies, nationally and internationally, are increasingly acknowledging challenges associated with critical illness survivorship, and multiple studies have described distressing symptoms across domains of physical, cognitive, and mental health among patients who survive hospitalization with a stay in the intensive care unit (ICU). However, these studies have enrolled patients at or after ICU hospitalization, precluding an evaluation of how symptoms change in the context of critical illness. Surviving hospitalization with a stay in the ICU is also accompanied by new or worsening disability for older persons. Whether distressing symptoms are associated with functional decline after critical illness has not been investigated. Furthermore, prior studies of distressing symptoms have not taken into account two particularly vulnerable populations - older persons with 1) multimorbidity, who are known to have greater symptom burden in later stages of life, and 2) individual and neighborhood socioeconomic disadvantage, who are at increased risk for functional decline after critical illness. I will utilize a unique longitudinal study of older persons, the Precipitating Events Project (PEP), that has prospectively collected information on distressing symptoms and disability for more than two decades, linked with Medicare claims, to evaluate the occurrence of distressing symptoms before and after hospitalization (Specific Aim 1) and to examine the association between distressing symptoms and the course of disability after critical illness survival (Specific Aim 2). In both aims, I will specifically examine these changes among older persons with multimorbidity as well as individual- and neighborhood-level socioeconomic disadvantage. The proposed work will move our knowledge from description of symptoms in the period after critical illness to an understanding of how distressing symptoms change in the context of critical illness hospitalization and their relationship with disability following critical illness survivorship. Furthermore, it will identify specific symptoms and population groups with the greatest increases in occurrence and the largest associations with disability. These findings will serve as the first step towards accomplishing my long-term objective, which is to integrate evaluation of evidence-based determinants of disability after critical illness into routine clinical practice, with the goal of

improving functional outcomes among older survivors of critical illness. Support from the award will also allow me to acquire advanced skills in geriatric epidemiology and biostatistics that will guide my future work in aging research.

7. Project Title: **Multimorbidity and Shared Decision Making for Treatment of Stable Coronary Artery Disease: small REC (2022-2023)**

Leader: **Michael Nanna**

Older adults living with multiple chronic conditions and chronic coronary disease experience significant morbidity, disability, and mortality. Treatment options in patients with chronic coronary disease are varied and can include a variety of potential medical and invasive therapies, all of which carry unique risks and benefits. In older adults with multiple chronic conditions, these treatment decisions are particularly complex, with highly variable patient priorities, multifactorial symptoms, and interactions between other chronic conditions and treatments for chronic coronary disease. Clinicians are often forced to presuppose the individual importance and likelihood of these outcomes, while simultaneously navigating how best to incorporate the impact of non-cardiac conditions that modify the effect of these treatments on the outcomes that matter most to their patient. In the face of this uncertainty, the development of a dedicated decision support tool to help clinicians align treatment decisions for chronic coronary disease with their older patients' goals of care within the context of their multiple chronic conditions is a crucial step in improving the overall care of these individuals. Given the uncertainty surrounding treatment decisions for older adults with chronic coronary disease and MCCs, it is important to engage both clinicians and patients in identifying the information that should inform patient-specific decision-making. A necessary initial step is identifying, from both clinician and patient-care giver perspectives, what information should inform treatment decisions. The process should include input from including both clinicians who offer their judgement on treatments and patients who establish the full range of domains that matter most to them. Importantly, patient stakeholders must serve a central role in informing the most pressing priorities and preferences of older patients with chronic coronary disease. Thus, our Specific Aims are 1) To generate a summary of the factors influencing the treatment of older adults with MCCs with chronic coronary disease through a robust process including multiple stakeholders; and 2) To develop and test a shared decision-making tool to apply to older adults with multiple chronic conditions presenting for the treatment of chronic coronary disease. The study design will include an initial needs assessment, literature review, and a consortium of both patients and clinicians to conduct both participant-specific and multi-stakeholder groupings, in order to identify the factors influencing person-centered decisions in this population (Aim 1). We will then apply a user-centered design approach and established decision support frameworks, including the Ottawa Decision Support Framework (ODSF) and International Patient Decision Aid Standards (IPDAS), to develop a chronic coronary disease decision support tool tailored to the unique and complex needs of the older adult populations with MCCs (Aim 2). Beta testing and initial pilot feasibility testing of the decision aid will be measured by reported successful completion by both patient and clinician, along with additional measures of feasibility, acceptability, and appropriateness, and qualitative feedback from patient and clinician stakeholders. Ultimately, the pilot-tested decision-support tool generated from this project will serve as the groundwork for a future proposal to more broadly test and implement

8. Project Title: **Opioid Use Disorder Management of Older Adults with Multimorbidity: a Delphi Study: small REC (2023-2024)**

Leader: **Minhee Sun**

Among older adults, opioid use disorder (OUD) diagnoses have increased three-fold from 2013 to 2018[1,2] and is expected to rise substantially higher due to the aging Baby Boomer generation who have higher rates of substance use compared to previous generations.[1,3] Much attention has been paid to expanding the initiation of medications for opioid use disorder (MOUD) for individuals with OUD, effective treatments for curbing opioid overdose deaths and OUD-related hospital visits.[4] As a result, a growing number of individuals prescribed MOUD, including buprenorphine and methadone, are approaching older age.[5,6] However, limited attention has been paid to understand how to optimize long-term MOUD treatment among older adults. There have been increasing calls to address this knowledge gap due to a growing appreciation of the complexities and trade-offs of reducing OUD-related harms by continuing MOUD indefinitely.[7] Tradeoffs include adverse effects of MOUD including somnolence and cognitive impairment,[5,7-10] which may lead to falls and fractures, highly morbid events for older adults.[11] Lifelong MOUD use may also contribute to polypharmacy which is associated with frailty among other harms.[12,13] Furthermore common causes for medication nonadherence among older adults, such as cognitive impairment and lack of caregiver support,[14] may make it difficult to continue lifelong MOUD. To further inform decision making, certain MOUD such as buprenorphine provide the added benefit of analgesia due to its partial opioid agonist effects,[15] which may be desired in older adults as chronic pain is prevalent and causes functional impairment.[16] Buprenorphine has been the primary treatment used to expand MOUD access to treat OUD recently due to its office-based availability.[17] Therefore, our objective is to gain a comprehensive understanding of factors that impact the use of buprenorphine long-term among older adults with OUD using sequential mixed methods[18] by achieving the following Specific Aims: 1) to identify factors that impact the continuation/discontinuation of buprenorphine long-term among older adults with OUD by conducting a qualitative study of older Veterans with current/past receipt of buprenorphine for [3]1 year for OUD and buprenorphine-prescribing clinicians and 2) to quantify the geriatric conditions and experiences of older individuals with OUD prescribed long-term buprenorphine by conducting a cross-sectional survey among Veterans on long-term buprenorphine. I am well-positioned to conduct this proposal as a buprenorphine-prescribing Internal Medicine physician with imminent Addiction Medicine certification who treats and studies OUD in older adults and has experience with qualitative/quantitative methods.[19,20] I have been appointed to Instructor in the Yale Program in Addiction Medicine through a Veterans Health Administration (VHA) career development award to conduct this proposal. My mentors are experts in Addiction Medicine, aging, and mixed methods. Generating innovative knowledge on factors impacting OUD treatment among older adults through this proposal is timely and highly relevant with potential for long-term impact given the worsening opioid epidemic and growing cohort of individuals aging with OUD. Completion of my aims will lay the necessary foundation for me to build a prospective cohort to conduct longitudinal then intervention studies, leading me to become an independent clinical investigator focused on optimizing OUD care among older adults.

9. Project Title: **Exploring Novel Environmental and Climatological Determinants of Health for Aging Populations: small REC (2022-2023) Carryover 2023-2024**

Leader: **Natalia Festa**

Older adults are differentially susceptible to adverse environmental exposures, while those with age-related disability require intensive healthcare and custodial supportive services. Nonetheless, there is scarce information regarding the relationship between environmental exposures and aging outcomes. Because disabled older persons are often reliant upon local aging infrastructure, such as nursing homes and home and community-based services (HCBS), understanding the potential of environmental factors—ranging from climatological hazards to rurality—to affect access to these resources is vital. The interdependence of older persons and aging infrastructure renders environmental and climate adaptation more complex for this enlarging demographic group and has made appropriate modifications of aging infrastructure a national priority in the United States.1 The specific aims outlined in this small grant application are designed to evaluate novel environmental determinants of health for aging populations. Because our planned research focuses on nursing home residents and recipients of home and community-based services, our findings will have direct implications for older adults with multiple chronic conditions and disabilities. Each specific aim focuses on an area in which there are knowledge gaps in environmental gerontology, using three categories of environmental exposures. First, we will quantify potential changes in the relative risk of mortality due to cold temperature exposure during the 2022-2023 winter, adjusting for home heating oil prices as an effect modifier in the context of current energy shortages. Second, we will evaluate the geographic access of nursing homes to hospital care as a potential determinant of rehospitalizations and mortality. Because driving time to healthcare facilities and rurality have emerged as important environmental determinants of health for multiple conditions, we will evaluate these exposures and their interaction in relation to nursing home resident outcomes. Third, we will evaluate the magnitude and statistical significance of the association between administrative emergency preparedness and outcomes among nursing home residents exposed to Hurricane Matthew in 2016.

10. **Project Title:**   **Senescence-Associated Endosomes and Vascular Healthspan: Translational Geroscience (2023-2024)**

Leader: **Dan Jane-wit**

Age-related vascular conditions have had a devastating negative impact on the morbidity and mortality of elderly patients. In the U.S. alone, the aged population >65 years old encompasses ~56 million individuals, and this large cohort shows disproportionately increased risk for vascular disease. Improved understanding of the molecular underpinnings of vascular aging is urgently warranted to inform new anti-senolytic therapies for these at-risk individuals. Our extramurally-funded research lab uses patient-centered approaches to study how endothelial cells (ECs), cells that line blood vessels, contribute to the longevity of tissue allografts. Using humanized models and patient specimens, we discovered a new molecule in ECs called ZFYVE21. ZFYVE21 is an ancient protein whose functions are virtually unknown. We found that ZFYVE21 was expressed on intracellular vesicles called Rab5 endosomes. ZFYVE21 was capable of modifying the protein constituency of Rab5 endosomes to elicit inflammatory signaling, a process causal for vascular senescence, a key mediator of healthspan. To explore ZFYVE21 in vascular senescence, we generated ZFYE21 EC-/- mice using gene targeting technology. Mice lacking ZFYVE21 in ECs developed vascular dysfunction and sequelae of age-related vascular disease including failure to thrive, renal insufficiency, hepatic insufficiency, and HFpEF. Multi-system organ dysfunction in ZFYVE21 EC-/- mice

developed by 8-12 wks of age, equivalent to 20-30 yrs of age in humans, and occurred in association with increased markers of cellular senescence. Rab5 endosomes isolated from ZFYVE21 EC-/- mice showed dramatically reduced levels of various anti-senolytic proteins including pENOS. pENOS is an EC-specific enzyme that catalyzes the formation of nitric oxide (NO), a bioactive gas well known to support EC health by upregulating genes promoting growth and tissue repair. ZFYVE21 EC-/- mice showed systemic deficits in NO generation, and NO supplementation using isosorbide improved renal insufficiency. Our data showed that an altered cohort of endosomes which we call senescence-associated endosomes (SAEs) were unable to support the stability of anti-senolytic molecules including pENOS, resulting in accelerated aging and decreased healthspan. NO-modifying drugs including isosorbide and sildenafil are used in clinical practice to treat vascular conditions including heart failure and pulmonary hypertension, respectively. Our findings open the possibility that these FDA-approved therapies could be repositioned to support vascular healthspan in aged individuals by blocking the negative systemic effects of SAEs. Based on our studies we explore the hypothesis that SAEs regulate vascular senescence. In Specific Aim 1 we will characterize changes in SAEs in aged ZFYVE21 EC-/- mice which developed clinically relevant vascular disease. Informed by these studies, in Specific Aim 2, we will examine frequencies of SAEs isolated from patient tissues from solid organ transplant recipients, and we will calculate correlations of these molecules with patient parameters including use of NO-modifying therapies. My lab has had long-standing, multi-disciplinary collaborations with Dr. George Tellides in the Dept of Cardiovascular Surgery, Dr. Jordan Pober in the Dept of Pathology, Dr. Arnar Geirsson in the Dept of Surgery, and Dr. Sanjay Kulkarni in the Dept of Transplant Surgery. My lab has numerous publications and co-PI funding awards with all these investigators who are included in this proposal. Our proposal carries important implications for age-related vascular conditions and reflects a significant divergence from our current projects. By analyzing SAEs in patient specimens and focusing on new anti-senoltyic molecules amenable to drug manipulation, our application addresses vascular senescence, a problem relevant to translational geroscience.

DEVELOPMENT PROJECTS (3 Development Projects Listed)

1. Project Title: **NOSI YES3 Software (2021-2023)**

Leader: **Cynthia Brandt**

Core(s):

This year, we secured a supplemental NOSI grant funded by the Office of Data Science Strategy (ODSS). With the award, we are refactoring and refining high-utility software that has been used to support our most successful studies including DCare, STRIDE, SILVER-AMI, and VALIANT. The NOSI award consists of a Web Portal EM and Dashboard EM. The YES3 Web Portal EM provides researchers with an intranet platform to deliver customized group communications, study documents, announcements, and real-time performance reports. The YES3 Dashboard EM (see Diagram 1) provides a feature-rich control panel used to manage workflow; view, filter, and manage participant status; track visit windows; communicate with study staff, and monitor outcomes. The YES3 Dashboard provides the research team with an organized, real-time view into study activities and the necessary tools to manage the study protocol effectively. In turn, this can position the study to on-time data collection metrics and study milestones, improved data quality, and more efficient staff management. The code can be modified and repurposed by any REDCap software developer to allow future innovation. We will disseminate these EMs through the REDCap EM Repository and plan to feature our work within the National OAIC network and NIA Research Centers Collaborative Network (RCCN).

2. Project Title: **Multilevel Cosinor Analysis (2022-2023)**

Leader: **Margaret Doyle**

Core(s):

This DP will extend Ms. Doyle's work with the cosinor model[36,37] to allow for mul-tilevel modeling and will develop a SAS macro for implementation that will be disseminated through GRASP. This work will directly impact the analysis of the association between ambient light levels in the ICU and sleep disruption as captured by actigraphy and/or heart rate acrophase (EP-24).

3. Project Title: **YES3 Report Card- Ops (2022-2023)**

Leader: **Mary Geda**

Core(s):

Yale Study Support Suite (YES3): Dashboard and Web Portal Software Supporting Research Workflow through integrated, customizable REDCap External Modules Specific Aim 1: To refactor, refine and repackage high utility Yale Study Support Suite (YES3) External Modules: (1.) Web Portal and (2.) Dashboard External Modules and disseminate them through the REDCap EM Repository and feature within the National OAIC network and RCCN. Specific Aim 2: Ensure the access, dissemination, and evolution of the YES3 software by (1.) establishing an opensource integrated developer workflow process that incorporates the security and validation practices published by the EM community within the REDCap Consortium (2.) by developing the required detailed technical documentation (e.g. source code documentation, UX and UI design considerations, testing documents. This work is complemented by a

supplemental NOSI award which comprises a generalizable Web Portal and Dashboard EM whose software will be interoperable with the Exporter EM. The Biostatistics Core also has a Development Project to build software for data visualization. We are maximizing resources by implementing multiple simultaneous initiatives with the intent of creating high-utility software to support research operations and analysis.

RESEARCH (18 Projects Listed)

1. Project Title: **Assessment of a Novel Emergency Care Equity-Based Caregiver Outcome Measure**

Leader(s): **GETTEL, CAMERON**
YALE UNIVERSITY
ALZHEIMERS ASSOCIATION ARCOM-22-878456 / (2021 - 2023)

Core(s):

Dr. Cameron Gettel and colleagues will conduct a study to develop and validate the novel Caregiver-reported Outcome Measure for Emergency Care Transitions (COMET) tool and assess it across diverse racial, ethnic, and socioeconomic status populations. This novel measure will identify care transition outcomes that are meaningful to caregivers of people with dementia. The researchers will conduct interviews with older individuals and their caregivers recruited from emergency departments in New Haven, CT, to inform the development of the COMET tool. Then, they will test its feasibility and validity among caregivers of people with dementia who were recently discharged from an emergency department. Finally, the team will investigate the association between COMET tool scores and rates of emergency department return visits for people with dementia.

2. Project Title: **DEMENTIA AND DECISION-MAKING FOR OLDER ADULTS WITHOUT SURROGATES**

Leader(s): **COHEN, ANDREW B**
YALE UNIVERSITY
NIH K76AG059987 / (2018 - 2023)

Core(s):

PROJECT SUMMARY / ABSTRACTA growing number of older adults with dementia are unbefriended : they have impaired capacity and no familyor friends to make decisions on their behalf. Because such persons must be represented by a stranger most often a guardian, selected by the court they may receive care that is discordant with their preferences.Work by the candidate, for example, suggests that individuals with dementia who are under guardianship aremuch more likely to receive aggressive end-of-life treatment than those with family members available to makedecisions. Given the substantial difficulties involved in making decisions for a person with dementia whosevalues and priorities are unknown, the current application seeks to lay the groundwork for an innovative upstream approach among persons who still have capacity but do not have a potential surrogate, so that theyare at risk for becoming unbefriended. The candidate envisions an intervention whereby such persons wouldbe identified ahead of time and health professionals would elucidate their values and priorities. The proposedwork will address the key knowledge gaps that stand in the way of such an intervention. Because little isknown about the population that would be targeted, Aim 1 will use a unique national dataset to describe theprevalence and risk factors associated with older adults who are unable to name a surrogate. Aims 2 and 3take up the broader challenge of generating an advance care planning model tailored to the unique challengesof dementia. Aim 2 will involve using qualitative methods to ascertain the core information that shapestreatment decisions when an ideal surrogate is exercising substituted judgment. Aim 3 involves thedevelopment and validation of a tool, capturing this information, that can be used in clinical practice.The candidate, Dr. Cohen, is a geriatrician at the Yale School of Medicine with a track record of early success,including several high-impact original reports and a GEMSSTAR award from the NIA. He has engaged anexceptional mentorship team. His primary mentor, Dr. Terri Fried, is an internationally-recognized authority ondecision-making for older adults with serious illness. He has recruited three co-mentors and an advisor whosediverse academic backgrounds will contribute a remarkable richness of perspectives and expertise both to theproposed research and to the career development plan. Dr. Cohen has outlined a rigorous program of trainingthat draws upon resources from across Yale University as well as national training opportunities in mixedmethods research and leadership development. The extraordinary resources available from the Yale Sectionof Geriatrics and Program on Aging provide an ideal environment for the execution of the proposed researchand for Dr. Cohen s emergence as an independent investigator at the forefront of geriatrics, medical decision-making, and ethics.

3. Project Title: **NLRP3 Inflammasome Activation and Mitochondrial Function in the setting of Aging and HIV Infection**

Leader(s):   **ZAPATA, HEIDI J**
YALE UNIVERSITY
NIH K76AG064548 / (2019 - 2024)

Core(s):

Project Summary/Abstract: Both the aging and the aging HIV-infected population are characterized by increased rates of metabolic syndrome (defined by abdominal obesity, dyslipidemia, insulin resistance and hypertension). Notably, metabolic syndrome is associated with the dysregulated, age-associated pro-inflammatory environment termed Inflamm-aging characterized by elevated levels of cytokines, acute phase reactants, and clotting factors. Chronic stimulation of innate immune receptors by both pathogen-associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) is thought to contribute to age-associated chronic inflammation, but the mechanisms underlying the pathogenesis of metabolic syndrome in the context of aging and HIV disease remain an incompletely understood knowledge gap in the field. The NLRP3 (NOD- like receptor pyrin domain-containing 3) inflammasome is an intracellular protein complex, that is part of the innate immune response and mediates the caspase-1-dependent cleavage of pro-IL-1b and pro-IL-18 to their activated forms. While the NLRP3 inflammasome is activated by PAMPs, there is increasing evidence for a role of NLRP3 as a sensor of host metabolism via DAMPs, as shown by NLRP3 activation by a wide range of metabolites. Moreover, NLRP3 inflammasome activation is dependent on mitochondrial function. The NLRP3 inflammasome has been linked to the development of insulin resistance and other metabolic syndromes in mouse models, and has been minimally explored in both older adults and HIV-infected adults. The purpose of this proposal is to determine the effects of age and HIV infection on the NLRP3 inflammasome, and its relationship with mitochondrial function by comparing the following groups of subjects, young adults (21-35), and older adults (= 60 yrs) with and without HIV-infection. Aim 1 seeks to characterize the NLRP3 inflammasome and its relationship with mitochondrial function, in myeloid cells from peripheral blood and adipose tissue. Aim 2 seeks to characterize the metabolic pathways that are induced with activation of the NLRP3 inflammasome through RNA sequencing and CyTOF in myeloid cells from peripheral blood and adipose tissue. Data from both aims will be collected in conjunction with clinical characteristics including the components of metabolic syndrome. Our hypothesis is that increased age and HIV infection will result in dysregulated NLRP3 inflammasome function at baseline and with activation that is linked to mitochondrial dysfunction ultimately contributing to the development of metabolic syndrome in older and HIV-infected adults. The candidate, Dr. Zapata is an Infectious Disease physician at the Yale school of medicine, who has put together an interdisciplinary mentorship committee with expertise in immunology, aging, and metabolism. This training proposal is coupled with a career development plan that includes mentorship and didactic training in Immuno-metabolism, with an additional focus on learning the analysis of sequencing data, thus providing the tools that will allow the PI to apply for an R01 award.

4. **Project Title:**   **Evaluating Sleep Deficiency in Aging Populations**
Leader(s):   **MINER, BRIENNE**
YALE UNIVERSITY
NIH K76AG074905 / (2021 - 2026)

Core(s):

PROJECT SUMMARY/ABSTRACT Candidate: My career goal is to become an independent clinician-investigator focused on improving sleep- wake disturbances and preventing their adverse outcomes in older persons. My clinical training as a Geriatrics and Sleep Medicine physician and research training in Geriatric Clinical Epidemiology form the foundation on which I will build to reach this goal. My track record of success is evidenced by the publication of high-impact original reports and the receipt of 3 grants. I have distinguished myself as a national leader and received awards for my research from the Sleep Research Society, the American Academy of Sleep Medicine (AASM), and the American Geriatrics Society (AGS), including the AGS New Investigator Award and a career development award from the AASM Foundation. Mentors and Environment: I have an outstanding team of mentors and advisors, including my primary mentor, Dr. Thomas Gill (Geriatrics), an internationally recognized thought leader in aging research, and co- mentor Dr. Klar Yaggi (Sleep Medicine), an expert in conducting epidemiologic studies aimed at understanding the health outcomes of sleep disorders. I also have a team of advisors, selected based on their expertise in aging, sleep, qualitative and mixed-methods research, circadian biology and analysis, and instrument development. I have outlined a rigorous program of training that draws upon the wealth of resources across Yale University, including the Program on Aging/Claude D. Pepper Older Americans Independence Center, as well as national training opportunities in mixed methods research and leadership development. These resources, and the support of the Sections of Geriatrics and Sleep Medicine at the Yale School of Medicine, provide an ideal environment for my career development and execution of the proposed research. Mentored Research Project: Sleep-wake disturbances are associated with important adverse outcomes in older persons, including cognitive and functional decline.

Our prior work has demonstrated that these disturbances are under-diagnosed in older persons, which may be due to the poor sensitivity of existing sleep questionnaires, the frequent co-occurrence of multiple sleep-wake disturbances, and the burdensome nature of objective sleep testing. We propose to develop and test age-appropriate, comprehensive subjective and objective sleep assessment tools to facilitate identification of older persons with sleep-wake disturbances. To accomplish this, we will assess sleep-wake disturbances using a broader construct termed, sleep deficiency , which is a condition causing functional impairment as a result of a deficit in sleep quality, sleep duration, and/or sleep that is out-of-sync with the body's natural clock (i.e., non-circadian sleep). The overall objective is to develop and pilot test tools to identify sleep deficiency in older persons. Future work will validate these tools, which can be used to target interventions to improve sleep health and prevent adverse outcomes.

5. Project Title: ATTACHMENT BEHAVIORS IN PARENT CHILD DYADS COPING WITH EARLY STAGE ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

Leader(s):   **MONIN, JOAN E**
YALE UNIVERSITY
NIH R01AG058565 / (2019 - 2023)

Core(s):

Roughly 4 million adult children provide unpaid care to their parents with Alzheimer's disease and relateddementias (ADRD). Caring for a parent with ADRD can be stressful and negatively impact caregivers' health.While research on spousal caregiving dyads shows that emotionally supportive communication betweenspouses in the early stages of ADRD can protect caregivers' health, little is known about such interpersonalprocesses in parent-child dyads. This needs to be addressed because adult child caregivers and their parentsface different interpersonal challenges (e.g., navigating a reversal of the parent-child role) than spousal dyads.We have shown in our spousal caregiving work that mutual emotional support behaviors, defined as caregiversand care-recipients providing and receiving communication of safety, feeling comfortable expressingvulnerability and empathy, and giving and receiving tangible aid, decrease caregiving burden and protectpsychological health. Mutual emotional support behaviors are amenable to change, making them appropriatetargets for interventions. Our research is informed by attachment theory, which stipulates that the need foremotional security is a fundamental need in the parent-child dyad across the lifespan, especially in times ofcrisis. Our overarching hypothesis is that mutual emotional support behaviors can protect the health of adultchild caregivers and parents by reducing caregiver stress and negative coping strategies. We integrate ourhypotheses about mutual support into an existing dyadic caregiving stress model that shows how caregiverand care-recipient characteristics, primary and secondary stressors, caregiver appraisals and coping allinfluence both dyad members' health and relational functioning. To test our innovative model, we propose aStage 0 dyadic, longitudinal, and observational study of 200 dyads: older adults aged 60 and older with earlystage ADRD and one primary adult child caregiver. Both dyad members will be interviewed, using valid andreliable self-report measures, and have videotaped discussions about dementia-related stressors at baselineand a one-year follow-up. Mutual emotional support behaviors will be measured with an observational codingsystem created by Co-I Feeney, and blood pressure will be monitored. Dyadic analysis will be performed withmixed models and structural equation modeling. Aim 1 will examine whether mutual emotional supportbehaviors are associated with lower caregiver demand appraisals, caregiver perceived stress, and caregivernegative coping longitudinally. Aim 2 will examine whether mutual emotional support behaviors protect bothdyad members' health and relational functioning longitudinally and whether this is mediated by lower caregiverdemand appraisals, caregiver perceived stress, and caregiver negative coping. Aim 3 will examine mutualemotional support behavior differences by sex as a biological variable and contextual factors (e.g., SES,caregiver depression, relationship history). This will lead to a Stage 1 application to create an attachment-based intervention tool to protect the health of parents with ADRD and their adult child primary caregivers.

6. Project Title: PRAGMATIC TRIAL OF THE EFFECTIVENESS AND COST-EFFECTIVENESS OF DEMENTIA CARE

Leader(s):   **REUBEN, DAVID B.**
UNIVERSITY OF CALIFORNIA LOS ANGELES
NIH R01AG061078 / (2018 - 2023)

Core(s):

PROJECT SUMMARYIn the United States, an estimated 5.5 million persons are affected by Alzheimer's disease, the most commontype of dementia. The clinical manifestations of dementia are devastating and often lead to caregiver stress,burnout, and medical illnesses. Dementia is a prototype of a disorder with complex needs that span both thepatient and caregiver, medical and social domains, and health system and community-based organizations.In response, several dementia care programs have been developed to more comprehensively meet the needsof patients and their caregivers, including those based within health care systems and those based in thecommunity. These programs have been implemented at either single sites or on a relatively small scale; nonehas been replicated widely because of unanswered questions about effectiveness and cost-effectiveness.In November 2017, the Patient Centered Outcomes Research Institute (PCORI) approved a 4-site pragmaticclinical trial to compare the effectiveness of health-systems-based care (based on the UCLA Alzheimer's andDementia Care program) with community-based care (based on the Benjamin Rose Institute Care Consultationprogram) on patient- and caregiver-reported outcome measures, including behavioral symptoms and caregiverdistress (co-primary outcomes), and secondary outcomes of caregiver strain, unmet needs, and depressionover 18-months. Because of PCORI's mandate, neither intervention will be compared to usual care (thus, onlyrelative effectiveness can be determined). Nor will cost-effectiveness of either intervention be evaluated.The proposed research will add a third usual care (UC) arm and expand outcomes to include costs and healthcare utilization. This expansion will permit comparison of each of the intervention arms to current usual care,thereby providing multisite pragmatic randomized clinical trial evidence for effectiveness of the two activetreatment arms. It will also allow evaluation of whether paying for such care will offset the costs anddetermination of which intervention is more cost effective. The study will also conduct exploratory analyses oftertiary outcomes of both interventions versus usual care including mortality, time spent at home, long-termnursing home placement, physician and patient/caregiver satisfaction and comparing all three groups onseveral types of utilization and out-of-pocket expenses.The study's questions are fundamental to planning for the clinical care of persons with dementia. Theyaddress both clinical effectiveness and cost-effectiveness. By answering these questions, clinicians, healthsystems, and insurers can make decisions about which programs to promote, scale and disseminate.

7. Project Title: REHABILITATION AT HOME USING MOBILE HEALTH IN OLDER ADULTS AFTER HOSPITALIZATION FOR ISCHEMIC HEART DISEASE (RESILIENT)

Leader(s):   **DODSON, JOHN A**
   NEW YORK UNIVERSITY SCHOOL OF MEDICINE
   NIH R01AG062520 / (2019 - 2024)

Core(s):

Project SummaryParticipation in ambulatory cardiac rehabilitation (CR) by patients with ischemic heart disease (IHD) remainslow. By recent estimates, fewer than two thirds of eligible patients are referred, and fewer than half of thosereferred participate. Even among those referred, multiple barriers to participation include limited facilities,competing time demands, high out-of-pocket costs, and prolonged wait time. Barriers to CR are particularlyhigh in older adults (age =70), due to factors such as physical impairments or transportation barriers, althoughthese patients may simultaneously have the greatest potential to benefit. Mobile health-enabled CR (mHealth-CR) for IHD which involves delivery of CR via portable electronic devices has the potential to increaseengagement by reducing participation barriers, but it remains largely untested outside of small studies inrelatively healthy young persons. It is therefore unclear what proportion of older adults with IHD and barriers totraditional CR are able to engage with mHealth-CR, and whether mHealth-CR leads to better outcomes thanusual care. Therefore, we propose RESILIENT: Rehabilitation at home using mobile health in older adultsafter hospitalization for ischemic heart disease. This is a prospective, multicenter, non-blinded randomizedclinical trial (with blinded assessment of primary endpoint) to evaluate engagement and outcomes withmHealth-CR among older adults with IHD, identified at the time of acute myocardial infarction (AMI),percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG). The trial will be conductedat two academic medical centers: NYU School of Medicine and Yale School of Medicine, which collectivelyserve a diverse patient population and have a track record of successfully recruiting older adults in clinicalresearch studies. We will randomize 400 older adults with IHD to receive mHealth-CR (n=300) or usual care(n=100) for 3 months. Our intervention combines mHealth-CR software, delivered via a tablet device, withbaseline counseling and weekly phone calls by an exercise therapist over 3 months. Intervention and usualcare groups will also receive a standard referral to ambulatory CR in accordance with guidelines, as well asdynamic assessment of activities of daily living (ADLs). The primary efficacy endpoint is change in functionalcapacity, assessed by 6 minute walk distance. Secondary efficacy endpoints are goal attainment, healthstatus, ADLs, hospital readmission, and death. The engagement endpoint is defined by weekly completion ofmHealth-CR tasks. We hypothesize that mHealth-CR will improve a range of outcomes, and that distinctpatterns of engagement will be discerned. The PI for this project (Dr. Dodson) is an Early Stage Investigatorwith a focus on cardiovascular outcomes research among older adults; additional investigators have a widerange of expertise in geriatrics, biostatistics, behavioral science, cardiac rehabilitation, and computer science.The study results

could lead to new sustainable and resource-efficient CR strategies among older adults withIHD, and lay the groundwork for a subsequent large multi-center clinical trial.

8. Project Title: **Enhancing the Efficiency of Pragmatic Clinical Trials Using Administrative Data: Analysis of the STRIDE Study**

Leader(s): **ESSERMAN, DENISE ; GANZ, DAVID ; LATHAM, NANCY K;**
YALE UNIVERSITY
NIH R01AG071528 / (2022 - 2026)

Core(s):

Project Summary & Abstract Pragmatic clinical trials aim to test interventions within typical healthcare settings to produce generalizable results. Successfully implementing pragmatic trials requires overcoming a number of challenges, including acquiring data as efficiently and non-intrusively as possible, so as to encourage maximum study participation at lowest cost. Administrative data are a potential solution for some pragmatic trials. These data derive from routine activities in the healthcare system, including clinical care (e.g., billing systems; use of electronic health records). With administrative data, participants can be passively followed over long time periods, potentially with decreased participant burden, decreased loss to follow-up from inability to contact a participant and decreased cost compared to alternatives (e.g., participant interview or review of medical records). All of these features could enhance both internal and external validity and reduce the overall cost of a trial. Limited empirical work exists on the comparative value of various data sources for ascertaining outcomes in pragmatic trials. We are in a unique position to the leverage the Strategies to Reduce Injuries and Develop Confidence in Elders (STRIDE) trial, a ten-site pragmatic, cluster-randomized trial focused on serious fall injury in community- dwelling older adults, to determine whether outcome ascertainment in pragmatic clinical trials could be simplified through automated data collection, without introducing significant imprecision or bias, thus reducing costs. STRIDE has multiple sources of data including multiple reference standards (adjudicated outcomes; self-reported outcomes) and two administrative data sources (fee-for-service Medicare data; administrative data from clinical trial sites). We will be able to couple currently available administrative data with newly available Medicare Advantage data to have a complete administrative picture of this almost universally Medicare eligible population. Complete data will give us the opportunity to achieve the overall goal of this research proposal, which is to develop a framework for determining whether administrative data can be used in pragmatic clinical trials in a Medicare eligible population to efficiently and accurately ascertain the primary outcome. To achieve this goal, our project has three aims: (1) develop and validate algorithms for detecting serious fall injuries from administrative data against the reference standards of STRIDE events; (2) determine the impact of the algorithms on trial findings; and (3) assess the cost efficiency (savings) of conducting the trial using administrative data.

9. Project Title: **Circadian Rhythms and Innate Immune Response in Aging**

Leader(s): **FIKRIG, EROL ; SHAW, ALBERT C;**
YALE UNIVERSITY
NIH R01AI142624 / (2019 - 2024)

Core(s):

Circadian rhythms play crucial roles in a wide range of physiologic and behavioral processes. In mammals, variations in light intensity and other environmental cues are integrated by a master pacemaker in the suprachiasmatic nuclei of the hypothalamus, which entrains multiple peripheral circadian clocks via neuroendocrine mechanisms. The clock at the molecular level consists of a network of transcription factors organized in a series of highly conserved transcription-translation feedback loops. While circadian rhythms in mammals are typically associated with sleep-wake, body temperature, cardiovascular, and metabolic regulation, circadian periodicity has also been reported for immunologic processes as well, including daily oscillation in levels of cell populations such as CD4 and CD8 T cells and cytokine expression. We were the first to report that Toll-like Receptor (TLR)-9, one of the pattern recognition receptors of the innate immune system, shows daily variation in expression and function that is modulated by circadian clock components in mice. We found that both response to a TLR9 adjuvanted vaccine and disease severity in a TLR9-dependent sepsis model were dependent on the timing of vaccination or sepsis induction, implicating circadian control as a novel mechanism of innate immune regulation. Our preliminary data also suggests circadian variation of TLR responses in humans as well. Several lines of evidence suggest that circadian rhythms are disrupted by aging in humans and mice, and knockout mice deficient in clock genes develop phenotypes associated with premature aging. However, there remains a knowledge gap as to whether aging influences circadian variation in TLR responses in mice and humans. We hypothesize that such variation will be attenuated

by aging in both humans and mice, and have assembled in interdisciplinary group of investigators with expertise in human and mouse immunology, sleep research, chronobiology and aging research to test this hypothesis. We will focus on evaluating TLRs associated with response to viral infection (TLR3, 7, 9 in mice and TLR3, 7-9 in humans) for which our published and unpublished data in mice suggest circadian variation. We will assess circadian TLR gene expression in purified populations of B cells, monocytes, and dendritic cells, as well as in vivo and in vitro circadian variation in TLR-dependent cytokine production, costimulatory protein expression, and response to viral infection in young and aged (20-22 months of age) mice and young (21-30 years) and older (= 65 years) humans. The proposed human studies will integrate immunologic data with physiologic parameters of circadian cycling standard in chronobiology, such as polysomnography, and measurements of cortisol and core body temperature. The study of circadian innate immune function is likely to break new ground in considering temporal variation in susceptibility or outcomes of infection, or in response to treatment. These insights would have substantial impact in older adults, who are known to have increased morbidity and mortality from infectious diseases and impaired responses to vaccination.

10. Project Title: Effectiveness of Strategies to Improve Outcomes after Hospitalization for Acute Myocardial Infarction in Older Adults

Leader(s): CHAUDHRY, SARWAT I
YALE UNIVERSITY
NIH R01HL160822 / (2022 - 2025)

Core(s):

Acute myocardial infarction (AMI) is consistently ranked as one of the top five most expensive conditions billed to Medicare and has been the target of several cost containment measures, including Medicare s Hospital Readmissions Reduction Program. To improve outcomes after AMI hospitalizations, payers have implemented public reporting, financial penalties, and alternative payment models that incentivize the assumption of financial risk such as capitation. These measures have not been accompanied by evidence-based guidelines on how health systems can improve outcomes after hospitalization. An impediment to such guidance has been an incomplete understanding of patient-level factors that may influence the effectiveness of strategies to improve post-AMI hospitalization outcomes as applied in real-world settings. Notably, 30% of patients hospitalized for AMI are age = 75. These patients have lower physiologic reserve and more functional impairments, including those in cognition and physical capabilities, than younger patients. In the SILVER-AMI study, we enrolled 3041 patients age = 75 hospitalized for AMI at 94 hospitals. The primary objective was to evaluate the contribution of functional impairments and geriatric conditions to improving risk prediction for mortality within 6 months of hospital discharge. The premise of the SILVER-AMI study was that risk prediction at the time of discharge could identify high-risk patients who might benefit from more intensive post-hospital care. Findings from SILVER-AMI have demonstrated that functional impairments substantially improve risk prediction for important outcomes. We did not obtain Medicare data in this study so could not examine strategies being deployed in an effort to improve post-AMI outcomes. The overall objective of this proposal is to refine our understanding of the impacts of home health care (HHC) (Aim 1), early outpatient care (Aim 2), and Medicare Advantage (MA) (Aim 3) after AMI hospitalization by examining their effects in the context of functional impairments and illness severity. We will focus on outcomes of primary importance to older patients, including home days (days alive out of the hospital and other inpatient facilities) and health status, as well as disease-specific outcomes of relevance post-AMI. We will merge data from the SILVER-AMI study with Medicare data to achieve our aims. Combining these data sources will afford us the unique opportunity of accounting for an array of rigorously assessed covariates that are not generally available in studies using only administrative data and to identify patients who may benefit most from post-discharge services. In addition to accounting for a rich array of measured confounders, we will employ advanced statistical techniques to address bias from unmeasured confounding. We have assembled a team with a track record of collaboration and expertise in cardiovascular outcomes, home health care, outpatient care delivery, epidemiology, and biostatistics. This hypothesis-driven research will leverage the most comprehensive set of data on functional impairments and geriatric conditions collected during AMI hospitalization on a large, national cohort to inform strategies to improve outcomes of importance to older patients.

11. Project Title: A Multifactorial Approach to Evaluating Disparities in Outcomes after Major Surgery in Disadvantaged Older Persons

Leader(s): GILL, THOMAS MICHAEL; BECHER, ROBERT DAVID;
YALE UNIVERSITY
NIH R01MD017298 / (2022 - 2026)

Core(s):

Major surgery is a common event in the lives of community-living older persons, with a 5-year cumulative inci- dence of 13.8%, representing nearly 5 million persons aged 65 years or older in the US. This value will in- crease substantially in the coming years based on the projected doubling of this age group to 98 million by 2060. As our society ages, it is also becoming increasingly diverse, with growing proportions of racial/ethnic minorities and other disadvantaged groups. Yet, despite the public health imperative, disparities in outcomes after major surgery in disadvantaged older persons are poorly understood. Prior research has generally relied on large administrative datasets and, hence, has usually been restricted to disadvantaged populations defined only by individual-level demographic characteristics, a small number of short-term outcomes, and a limited set of explanatory variables. To address current gaps in knowledge, and build the evidence for action, a more ro- bust approach is needed that focuses on multiple disadvantaged populations of older persons, emphasizes the importance of social contextual factors in defining the scope and complexity of disadvantage, includes a larger array of geriatric-specific outcomes that are clinically meaningful, evaluates a comprehensive set of explana- tory variables that include modifiable patient-centered variables, and assesses the use of post-surgical pallia- tive treatments such as hospice. The overarching objective of this proposal is to identify and elucidate sources of potential disparities in outcomes after major surgery in disadvantaged older populations, defined on the ba- sis of individual-level and social contextual factors. Building on our prior work, we will use high-quality data from the National Health and Aging and Trends Study (NHATS), an ongoing nationally representative longitudi- nal study that includes 7,600+ community-living persons aged 65+ years with oversampling of Blacks, compre- hensive annual assessments with patient-centered phenotypic data that are not available in administrative da- tasets, cohort replenishment at 5-year intervals, and linkages to Medicare and geographic data. This unique resource will permit a series of innovative longitudinal analyses at the patient level that will complement sys- tems-based research on the quality of surgical care. We will rigorously test three distinct but related hypothe- ses: (1) disparities after major surgery in older persons will be observed consistently for multiple outcomes across multiple disadvantaged populations; (2) for each disadvantaged population, these disparities in out- comes will be largely attributable to a set of patient-centered variables, including several that are potentially modifiable; and (3) similar disparities will be observed in the use of hospice but will not be as easily explained. By taking a comprehensive, multifactorial, and multilevel approach that emphasizes the importance of social contextual factors, the proposed research will build the evidence that is essential to understanding the mecha- nisms of potential disparities in outcomes after major surgery. These actionable results will inform novel inter- ventions, collaborations, and policies designed to improve these outcomes in disadvantaged older persons.

12. Project Title: Evaluating Sleep Deficiency in Older Persons
Leader(s):   MINER, BRIENNE
YALE UNIVERSITY
NIH R03AG073991 / (2021 - 2023)

Core(s):

PROJECT SUMMARY Sleep complaints occur in nearly half of older persons and are associated with cognitive decline, disability, and many other adverse outcomes. Accurate and feasible evaluation is needed to identify persons at risk for these adverse outcomes. However, the traditional approach to evaluating sleep complaints in older persons is limited for several reasons. First, because the underlying etiology is likely to be multifactorial in older persons, a comprehensive strategy that considers the multiple domains contributing to sleep complaints is needed. Second, reliance on self-report alone may miss severe sleep problems or specific sleep disorders in older persons. Third, polysomnography is the gold standard for evaluation of sleep apnea and sleep architecture (i.e., arousals from sleep and deeper, more restorative sleep stages), but it is costly, burdensome, and may not be feasible or reflect habitual sleep patterns. To address these limitations, we propose to evaluate sleep deficiency, a comprehensive construct aimed at identifying factors contributing to sleep complaints in three domains: 1) poor sleep quality, including sleep disorders; 2) insufficient sleep duration; and 3) non-circadian sleep (abnormalities of sleep timing, sleep regularity, and daytime alertness). Novel, home-based measures from sleep headbands and actigraphy will objectively evaluate sleep architecture and duration, detect sleep apnea, and assess non- circadian sleep. Measures of sleep quality, duration, and non-circadian sleep from the headbands and actigraphy can be performed over multiple nights in the home. They may be more feasible than laboratory- based measures and more reliable than self-reported measures. We will enroll 50 community dwelling persons 65 years with sleep complaints (insomnia or daytime sleepiness) to undergo evaluation of sleep deficiency using validated self-reported measures, single-night home-based polysomnography, 7 nights of the headband, and 7 days and nights of actigraphy. The aims of this study are to compare self-reported versus objective measures of sleep deficiency. We hypothesize that the headband measures will have stronger concordance with polysomnography than self-report and that concordance between self-reported and actigraphy measures of non-circadian sleep will be low. Collectively, such results would suggest the need for objective measures of sleep deficiency in older persons. The proposed work will develop robust objective

measures of sleep deficiency that are feasible in this vulnerable and understudied population. These measures may advance the management of sleep deficiency in future work through enhanced identification of underlying sleep problems, improved targeting and monitoring of future interventions, and reduction of the risk of adverse health outcomes.

13. Project Title: Generating novel predictive models to estimate the risk of future ASCVD & Dementia in older adults

Leader(s):　　　**NANNA, MICHAEL**
YALE UNIVERSITY
NIH R03AG074067 / (2021 - 2023)

Core(s):

Response to Grants for Early Medical/Surgical Specialists' Transition to Aging Research (GEMSSTAR) Competition Title: Generating novel predictive models to estimate the risk of future ASCVD & Dementia in older adults Project Summary/Abstract: A person s baseline risk determines to a large extent their anticipated benefit from many preventive treatments. Older patients desire to live longer while maintaining cognitive function and freedom from dementia, including Alzheimer s disease, the #1 cause of morbidity and disability in older adults. Older adults also prioritize avoiding atherosclerotic cardiovascular disease (ASCVD), the #1 killer of older adults. Importantly, many risk factors for Alzheimer s disease and dementia also increase risk for ASCVD. Alzheimer s disease is the most common etiologic basis for incident mild cognitive impairment and dementia in older adults and can be identified as the cause in 70-75% of cases. Thus, providing older patients with personalized risk estimates for both dementia, including Alzheimer s disease, and ASCVD could facilitate a comprehensive, evidence-based and patient-centered approach to therapeutic decision making in older adults. Unfortunately, current risk models were derived in younger adults, and fail to accurately predict risk in older adults. Second it remains unclear whether existing ASCVD risk models can also predict dementia risk and vice versa. Finally, to date, no one has evaluated whether these risk estimates help stratify therapeutic benefits of intervention in older adults. Leveraging a mentorship team of world experts in geriatrics, cardiology, and epidemiology, I will utilize data from subjects =75 years old from the National Heart, Lung, and Blood Institute (NHLBI) Pooled Cohorts in order to develop a clinical risk model to estimate risk of dementia, including Alzheimer s disease, at 5 years from the selected baseline visit (Aim 1). In parallel, we will develop a clinical risk model to estimate the risk of ASCVD over the same time period in the same population of individuals =75 years old. In addition to traditional risk factors, we will derive these models using a novel set of candidate predictors not previously included in prior risk models including baseline cognition, functional status, depression, and mobility. Both models will then be externally validated using data from the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort (Aim 2). Finally, we will apply our model to patients =75 years old from the Systolic Blood Pressure Intervention Trial (SPRINT) in order to determine whether therapeutic benefit from intensive vs. conservative anti-hypertensive therapy in older adults differs across levels of predicted risk (Aim 3). Once developed and validated, we will develop an electronic health record-based version of the model for widespread dissemination and use in clinical care. The training I will receive through this work will give me expertise in model building and deployment and broaden my research interest in dementia including Alzheimer s disease. It will also lay the groundwork for a future application for the Paul B. Beeson Emerging Leaders Career Development Award and other independent funding, with the ultimate goal of becoming an independent clinician-researcher focused on the care of older adults.

14. Project Title: Linked Lives, Linked Health: Health Trajectories of Persons with Cognitive Impairment and Their Caregivers' Health

Leader(s):　　　**ZANG, EMMA XIAOLU**
YALE UNIVERSITY
NIH R21AG074238 / (2021 - 2023)

Core(s):

Project Summary More than 20% of people =65 years old living in the US are cognitively impaired, with diagnoses ranging from mild cognitive impairment (MCI) to dementia. Because of its progressive nature, as persons with cognitive impairment (hereafter PCIs) experience decline in cognitive function and other health outcomes, the health of their caregivers or care partners (CG) may also be negatively impacted due to factors such as increased caregiving burden and stress. Determining how the health trajectories of all PCIs affect CG health outcomes over the course of cognitive decline will build a scientific foundation to design effective policies to reduce caregiving cost and improve care quality. The proposed study will investigate the health trajectory patterns of PCIs and their relationships with CG health in the US. Data will be drawn from the annual National Health and Aging Trends Study in 2011 2019 coupled with data from the National Study of Caregiving in 2011, 2015, 2017, and potentially 2021 if available. We will consider general health status, physical health, and psychological well-being for both PCIs and CGs. Our unique contribution to the field of dementia research is threefold: 1) our proposed study is the first to examine both PCI and CG health using a trajectory approach; 2) we will use high-quality population data; 3) we will study the full spectrum of cognitive impairment, rather than only the most severe scenarios. We will first describe health trajectories among PCIs and examine how their trajectories predict CG health across time. For each health outcome, we will apply the single-trajectory Bayesian group-based trajectory model (BGBTM) to identify distinct trajectory groups for PCIs and apply linear regression models to predict CG health. We will also determine how PCI health trajectories are related to CG health trajectories. Applying the dual-trajectory BGBTM, we will visually demonstrate how PCI and CG health trajectories are parallel in time and estimate the probability of one trajectory pattern among CGs conditional upon one pattern among PCIs. Second, we will determine how the relationships examined above are moderated by caregiving and sociodemographic characteristics of CGs. We hypothesize that a distant relationship with PCIs, high-intensity caregiving, a heavy caregiving burden, and social disadvantage are associated with adverse health outcomes and trajectories among CGs, and that these characteristics moderate the association between PCI health trajectories and CG health outcomes and trajectories. Finally, we will determine joint trajectories in PCI cognition and other health outcomes, as well as the impact of PCI cognitive trajectories on CG health. Findings of this study will assist policymakers in understanding the health consequences of caregiving for PCIs, which will build a scientific foundation for the development of effective interventions to improve the quality of care and reduce long-term care cost. Further, understanding the prognosis for various types of PCI and CG health trajectories may enable better preparation of caregiving and ultimately higher quality care.

15. Project Title: Priorities Aligned Deprescribing for Persons Living with Dementia and their Caregivers

Leader(s): **STEINMAN, MICHAEL A.; BOYD, CYNTHIA MELINDA; NORTHERN CALIFORNIA INSTITUTE/RES/EDU NIH R24AG064025 / (2019 - 2024)**

Core(s):

Project Summary Title: Priorities Aligned Deprescribing for Persons Living with Dementia and their Caregivers Persons living with dementia (PlwD) have a significant burden from multiple chronic conditions and overmedication, and particularly benefit from deprescribing to reduce polypharmacy. Deprescribing is a systematic process to reduce medications with unacceptable harms or lack ofbenefit in the context of a patient s overall status and goals and preferences for care. Patient Priorities Care (PPC) is an evidence- based approach to identify outcome goals and care preferences (health priorities) and align care to meet those priorities. Deprescribing is targeted towards therapies that are misaligned with priorities. Less is known about how PPC works in thecontext of clinician, caregiver, and persons living with dementia (PlwD). Aligning all three goals could be crucial for successful, safe deprescribing in the setting of dementia. To facilitate the adaptation of the PPC approach to the context of deprescribing for PlwD, we will address the following research questions: Q1) How does the identification of patient priorities facilitate deprescribing for PlwD and their caregivers Q2) How are blended (PlwD and caregiver) outcome goals and caregivers care preferences interpreted and used by clinicians Q3) How do clinicians make treatment decisions to reduce or stop medications based on the misalignment of drugs with priorities that include blended outcome goals and caregiver preferences Q4) What are the adverse drug withdrawal events (ADWEs) that occur from deprescribing medications based on patient priorities aligned care decisions To answer these questions, we propose the following study aims: Aim 1: Conduct a pilot randomized clinical trialwith 50 PlwD and caregiver dyads and their clinicians to compare the PPC approach and usual care to identify differences in post-encounter medication changes, treatment burden, and shared decision making. We will also compare differences in medication changes based on documentation of care preferences and goals by patients, caregivers, or both. (Q1) Aim 2: For PPC participants, we will conduct cognitive-task-analyses with primary providers to understandtheir sense-making and communication approaches related to deprescribing decisions in relation to the identified health priorities. (Q2, Q3) Aim 3: For all participants, we will conduct a post-encounter follow up televisit to identify and categorize ADWEs. (Q4) The study results willinform the processes of how clinicians make decisions about medication misalignment with priorities and

the extent to which those decisions result in ADWE. Findings will also provide feasibility and effect size data to inform a larger clinical trial of Patient Priorities Care, testing itseffectiveness and safety for deprescribing for PlwD and their caregivers.

16. Project Title: **UNINTENDED PROLONGED OPIOID USE**
Leader(s):   **HOOTEN, W. MICHAEL**
MAYO CLINIC
NIH U01TR002743 / (2019 - 2023)

Core(s):

PROJECT SUMMARYMisuse of prescription opioids remains a public health crisis. Appropriate short-term use of these medicationsin opioid-na ve patients is indicated in select health care settings, but intentional short-term use is emerging asa previously under-recognized segue to unintended prolonged opioid use (UPOU). Clinical strategies aimed atpreventing UPOU in health care settings are lacking due, in part, to absence of information about how thispoorly-understood clinical phenomenon develops.Investigators at Mayo Clinic recently organized a group of thought leaders to develop a conceptual frameworkto explain UPOU. Such a framework is essential both to guide the study of this problem and to identify potentialtargets for interventions to reduce UPOU. The framework is comprised of three domains, including (1) patientcharacteristics; (2) practice environment characteristics; and (3) opioid prescriber characteristics that interact toeither facilitate or impede UPOU. Within each domain, potential factors, drawn from the relevant literature,moderate or mediate the influence of each domain. However, much of the information needed to evaluate thisframework does not currently exist. The widespread adoption of electronic health records (EHR) providesunique potential opportunities for translational research, including identifying subjects eligible for studyparticipation and serving as a data sources for retrospective or prospective studies. However, interoperabilitybetween EHRs poses a considerable challenge to taking advantage of these opportunities.Researchers at the Yale School of Medicine recently launched Hugo, a secure mobile personal health(mHealth) platform that enables patients to access their information from multiple EHRs and other healthcareinformation sources, including commercial pharmacy records. The Hugo platform has tremendous potential tofacilitate clinical research, especially research conducted across multiple centers as information from diversesource systems at each institution can be easily integrated into a common dataset.In this application, four CTSA hubs (Mayo Clinic, University of Minnesota, University of Michigan, and Yale) willexplore the Hugo platform's potential to facilitate clinical research, with the UPOU study as a use case. We willuse the Hugo platform to identify incident cases of UPOU and prospectively recruit patients and opioidprescribers for assessments, as well as to evaluate the proposed conceptual framework using structuralequation models. At this study's conclusion, we will have successfully deployed a highly innovative mHealthplatform across multiple centers and this platform will be immediately available for widespread disseminationacross the entire CTSA consortium and other clinical research sites. The information gained about UPOU willsignificantly advance core knowledge about this poorly understood clinical phenomenon. This newly acquiredinformation will be used design, test, and deploy prevention strategies aimed at mitigating the risks of UPOU.

17. Project Title: **PAIN MANAGEMENT COLLABORATORY COORDINATING CENTER (PMC3)**
Leader(s):   **KERNS, ROBERT D; BRANDT, CYNTHIA A. ; PEDUZZI, PETER NATALE ;**
YALE UNIVERSITY
NIH U24AT009769 / (2017 - 2023)

Core(s):

Project Summary / AbstractThe Pain Management Collaboratory Coordinating Center (PMC3) will (1) provide national leadership andtechnical expertise in all aspects of research supporting the design and execution of high impactDemonstration Projects that conduct cost-effective, large-scale, pragmatic clinical trials on non-pharmacological approaches for pain management and other comorbid conditions in veteran or military healthcare systems, and (2) make data, tools, best practices, and resources from these and other projects availableto facilitate research partnerships in VA and DoD health systems. The PMC3 will leverage the expertise of thePain Research, Informatics, Multimorbidities and Education (PRIME) Center of Innovation based at the VAConnecticut Healthcare System (VACHS) and its partners at VACHS and Yale, including the VA CooperativeStudies Program Coordinating Center/Clinical Epidemiology Research Center and the Yale Center forAnalytical Sciences and Yale Center for Medical Informatics, enhanced by a strong

partnership with colleaguesat the Uniformed Services University for the Health Sciences Center for Rehabilitation Sciences Research anda novel Military Treatment Facility Engagement Committee comprised of collaborating DoD and universityaffiliated investigators, clinicians and educators devoted to facilitating successful pragmatic trials in DoDsettings. We will use our expertise in pain management, electronic health records (EHR), data systems and thedesign and coordination of multi-site pragmatic trials to accomplish these objectives in collaboration with ourVA, DoD and Yale partners. To achieve these objectives, three specific sims will be addressed: Aim 1: Todevelop, adapt and adopt technical policy guidelines and best practices for the effective design and conduct ofpragmatic trials; Aim 2: To work collaboratively with and provide operational, technical, design and othersupport to Demonstration Project teams to develop, initiate and implement a research protocol; and Aim 3:Towidely disseminate NIH-DoD-VA Pain Management Collaboratory endorsed policies and best practices andlessons learned within military and veteran health care systems. Achievement of these objectives and SpecificAims promise to significantly accelerate the integration of evidence-based non-pharmacological approaches forthe management of pain into routine clinical care in military and veteran health care systems consistent withkey recommendations from the National Pain Strategy.

18. Project Title: NIA AD/ADRD HEALTH CARE SYSTEMS RESEARCH COLLABORATORY

Leader(s): **MOR, VINCENT; MITCHELL, SUSAN L ;**
BROWN UNIVERSITY
NIH U54AG063546 / (2019 - 2024)

Core(s):

PROJECT SUMMARYOver five million Americans have Alzheimer's disease (AD) or an AD-related dementia (AD/ADRD). These high-need, high-cost patients are vulnerable to receiving poor quality, uncoordinated care, ultimately leading toadverse health outcomes, poor quality of life, and misuse of resources. As recently concluded by the federally-funded Research Summit on Dementia Care, improving the care of PWD and their CGs is an urgent public healthchallenge that must be met and informed by high quality evidence. While prior research has elucidatedopportunities to improve the care of PWD and their CGs, the adoption of promising interventions has beenstymied by the lack of research evaluating their effectiveness when implemented under real-world conditions.Pragmatic clinical trials embedded (ePCTs) in healthcare systems (HCS) have the potential to accelerate thetranslation of evidence-based interventions into clinical practice. Since its inception in 2012, the NIH CommonFund HCS Research Collaboratory has made pivotal contributions towards advancing the conduct of ePCTs.However, as concluded in a 2017 NIA-sponsored conference, ePCTs conducted with PWD and their CGs haveunique considerations that merit specific focus. Thus, the overarching objective of this proposal is to build on themodel of the NIH Collaboratory to establish the National Institute on Aging (NIA) AD/ADRD ResearchCollaboratory, co-led by the multiple principal investigators (MPIs), Drs. Vince Mor (Brown University) and SusanMitchell (Hebrew SeniorLife (HSL)) and co-administered by their respective institutions. The Aims are: 1. Toestablish the infrastructure of the AD/ADRD Collaboratory, 2. To develop and disseminate guidelines for theconduct of all aspects of ePCTs among PWD and their CGs in partnership with HCS, 3. Enhance researchdevelopment and investigator capacity to conduct ePCTs in PWD and their CGs within HCS, and 4. Todisseminate knowledge and best practices to engage stakeholders in this research. Accomplished investigatorsfrom across the nation will lead the following Working Group Cores: 1. Technical and Data (B), J. Bynum, MD,MPH; 2. Regulation and Ethics (C), J. Karlawish, MD; 3. Design and Statistics (D), H. Allore, PhD; 4. Pilot Studies(E), A. Brody, PhD, RN; 5. Patient and CG Reported Outcomes (F), L. Hanson, MD, MPH; 6. Dissemination andImplementation (G), L. Gitlin, PhD/J. Gaugler, PhD; 7. HCS (H): E. Larson, MD, MPH, and Training (I): C.Callahan MD/A. Torke MD. An Administration Core (A) will integrate all critical functions across the Collaboratory.IMPACT: There is an urgent need to improve care provided by HCS for PWD and their CGs. ePCTs conductedare ideally-suited to test the effectiveness of interventions aimed at improving their health outcomes but requirespecific expertise, methodology, data sources, and industry partnerships. The knowledge, investigativeexperience, collaborations, and evidence generated by an AD/ADRD Collaboratory has the potential to transformthe delivery, quality, and outcomes of care for Americans from all backgrounds with AD/ADRD and their CGs.

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RECOGNITION AND AWARDS (2022-2023)

<u>Edward Manning</u> (2022)

- Submission of 2022 GEMSSTAR (priority score: 14)

<u>Lauren Ferrante</u> (2022)

- American Society for Clinical Investigation (ASCI) Young Physician-Scientist Award, 2022

<u>Snigdha Jain</u> (2022)

- Receipt of 2022 Parker B. Francis

MINORITY RESEARCH

General Brief Description of Minority Activities:
Not defined.

Minority Trainee(s):

- Lauren Ferrante, Assistant Professor of Medicine (Pulmonary); Director, Operations Core, Yale Claude D. Pepper Older Americans Independence Center
  Lauren Ferrante, MD, MHS, assistant professor of medicine (pulmonary, critical care, & sleep medicine), is the Director of the Operations Core and serves as a member of the Yale OAIC Executive Committee, which meets bimonthly.

No minority grant information specified.