

BOSTON PEPPER CENTER

Claude D. Pepper Older Americans Independence Center

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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 Trivison, PhD TGT@hsl.harvard.edu

Leader 2: Paola Sebastiani, PhD

Leader 3: 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.

Preclinical Discovery care

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 Preclinical Discovery Core (PDC) 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
<p>Hao Zhou, MD, PhD Instructor in Surgery / Harvard Medical School <u>PESC: Donor and recipient age mismatches in organ transplantation transfer senescent cells impacting physical exercise capacity.</u> Donor and recipient age mismatches in organ transplantation transfer senescent cells impacting physical exercise capacity.</p>	2020-2022 / 5 (total) 1 (1st/Sr)
<p>Daniel Roh, MD Assistant Professor / Boston University <u>REC-3: Contribution of Cellular Senescence to Delayed Wound Healing of Aging</u> Dr. Roh is an Assistant Professor of Surgery at Boston University School of Medicine in the field of Plastic and Reconstructive Surgery whose research focus is to discover new translational therapies that can reduce the burden of wounds for the older adult⁶. His project will test the hypothesis that senescent cell accumulation in aged skin contributes to impaired wound healing, and that reduction of these cells can be a valuable tool to improve wound healing in aged individuals. Using aged mice, he will determine the contribution of senescent cell accumulation to the impaired wound healing of aging. He will evaluate topical senolytic therapy as a potential treatment and determine the effect of reducing senescent cell burden on the impaired wound healing of aging. Rejuvenating and strengthening aged skin with senolytics could be used as a preventative measure to avoid wound complications in patients at risk for acute wounds that develop into chronic wounds. In addition, this project proposes to establish potential biomarkers of senescence and wound healing status. Dr. Roh's mentors include LaDora Thompson PT PhD, Vladimir Botchkarev MD PhD, and Laura Niedernhofer, MD PhD. His project will utilize the Biostatistical Design and Analysis and the Preclinical Discovery Cores</p>	2021-2022 / 20 (total) 10 (1st/Sr)
<p>Sari Reisner, DSc. Assistant Professor / Harvard Medical School <u>PESC: Stress-driven acceleration of epigenetic age and inflammation in transgender and gender diverse adults (TransESSENCE)</u> PESC: Stress-driven acceleration of epigenetic age and inflammation in transgender and gender diverse adults (TransESSENCE)</p>	2021-2022 / 165 (total) 50 (1st/Sr)
<p>Sanjay Divakaran, MD Instructor / Harvard Medical School <u>REC-4: Skeletal Muscle Perfusion and Energetics in Patients with Symptomatic Peripheral Artery Disease. Joint Boston OAIC-Harvard Catalyst C-MERIT Awardee.</u> Dr. Divakaran 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 (PAD)⁷. 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</p>	2021-2022 / 41 (total) 12 (1st/Sr)

Cardiovascular RNA Biology at BWH. He will utilize the OAIC Functional Assessment, Preclinical Discovery, and Biostatistical Design and Analysis Cores.

Timothy Anderson, MD

Instructor / Harvard Medical School

2021-2022 /

32 (total)

REC-1: Impact of intensifying older adults' antihypertensive medication regimens at hospital discharge on home blood pressure and functional recovery.

20 (1st/Sr)

Dr. Anderson is a general internist and Instructor in Medicine at Beth Israel Deaconess Medical Center (BIDMC). His prior research has analyzed large datasets to study clinical outcomes of older adults receiving changes to their chronic disease medications at hospital discharge⁴; this work is currently supported by a NIA GEMSSTAR Award. For the OIAC REC, he proposes to conduct a prospective cohort study of 90 community dwelling older adults hospitalized at BIDMC who experience elevated inpatient blood pressure (BP). He will assess the feasibility of recruiting these older adults at hospital discharge into a 3-month study during which they will complete home BP recordings and patient reported functional questionnaires. He will compare home BPs and functional recovery in patients who did and did not receive BP medication intensifications at hospital discharge. Completion of this proposal will allow Dr. Anderson to gain experience in prospective primary data collection. He will use the OAIC Functional Assessment and Biostatistical Design and Analysis Cores. His primary mentor is Dr. Edward Marcantonio, MD, SM, Associate Director of the OAIC REC.

Clark DuMontier, MD

Geriatrician, Fellow / Harvard Medical School

2021-2022 /

20 (total)

REC-2: Integrating Feasible and Valid Functional Outcomes in Older Patients with Multiple Myeloma Undergoing Chemotherapy.

8 (1st/Sr)

Dr. DuMontier is geriatrician and research fellow in the Division of Aging, Brigham and Women's Hospital (BWH) focused on integrating geriatrics into oncology, with a focus on functional assessment⁵. Multiple myeloma is a disease of aging, with two-thirds of patients diagnosed after age 65. Improving function in older adults with cancer is a high priority for patients, yet functional outcomes in multiple myeloma remain understudied. The objective of his proposal is to compare the feasibility of several measures of function that are well-established in aging research but underutilized in myeloma practice. He will recruit 50 transplant-ineligible patients age = 75 with newly-diagnosed multiple myeloma who plan to undergo induction chemotherapy and collect several patient-reported measures of function at these patients' initial appointment and monthly thereafter for six months while undergoing induction chemotherapy. The study will determine which measures of physical function are valid and feasible to be completed by older patients in busy oncology clinics. Dr. Dumontier's primary research mentor is Dr. Jane Driver, MD, MPH, who co-directs the Older Adult Hematologic Malignancy Program at Dana-Farber. He will use the OAIC Functional Assessment and Biostatistical Design and Analysis Cores.

Past Scholars

Jason Sanders, MD, Harvard Medical School (2020-2021)

PILOT/EXPLORATORY PROJECTS (6 Pilot Projects Listed)**1. Project Title: REC-2: Integrating Feasible and Valid Functional Outcomes in Older Patients with Multiple Myeloma Undergoing Chemotherapy.****Leader: Clark DuMontier, MD**

Dr. DuMontier is geriatrician and research fellow in the Division of Aging, Brigham and Women's Hospital (BWH) focused on integrating geriatrics into oncology, with a focus on functional assessment. Multiple myeloma is a disease of aging, with two-thirds of patients diagnosed after age 65. Improving function in older adults with cancer is a high priority for patients, yet functional outcomes in multiple myeloma remain understudied. The objective of his proposal is to compare the feasibility of several measures of function that are well-established in aging research but underutilized in myeloma practice. He will recruit 50 transplant-ineligible patients age 75 with newly-diagnosed multiple myeloma who plan to undergo induction chemotherapy and collect several patient-reported measures of function at these patients' initial appointment and monthly thereafter for six months while undergoing induction chemotherapy. The study will determine which measures of physical function are valid and feasible to be completed by older patients in busy oncology clinics. Dr. Dumontier's primary research mentor is Dr. Jane Driver, MD, MPH, who co-directs the Older Adult Hematologic Malignancy Program at Dana-Farber. He will use the OAIC Functional Assessment and Biostatistical Design and Analysis Cores

2. Project Title: REC-1: Impact of intensifying older adults' antihypertensive medication regimens at hospital discharge on home blood pressure and functional recovery.**Leader: Timothy S. Anderson, MD, MAS**

Dr. Anderson is a general internist and Instructor in Medicine at Beth Israel Deaconess Medical Center (BIDMC). His prior research has analyzed large datasets to study clinical outcomes of older adults receiving changes to their chronic disease medications at hospital discharge⁴; this work is currently supported by a NIA GEMSSTAR Award. For the OIAC REC, he proposes to conduct a prospective cohort study of 90 community dwelling older adults hospitalized at BIDMC who experience elevated inpatient blood pressure (BP). He will assess the feasibility of recruiting these older adults at hospital discharge into a 3-month study during which they will complete home BP recordings and patient reported functional questionnaires. He will compare home BPs and functional recovery in patients who did and did not receive BP medication intensifications at hospital discharge. Completion of this proposal will allow Dr. Anderson to gain experience in prospective primary data collection. He will use the OAIC Functional Assessment and Biostatistical Design and Analysis Cores. His primary mentor is Dr. Edward Marcantonio, MD, SM, Associate Director of the OAIC REC.

3. 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 epigenetic age (DNA methylation score) and inflamm-aging (e.g., elevated CRP, IL-6 levels); and whether epigenetic 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.

4. Project Title: PES-1: Senescent cells from organs of older donors are transferred during transplantation and impair the physical exercise capacity of recipients.

Leader: PI: Abdala El Khal, PhD and Stefan Tullius, MD, PhD

The study will evaluate whether transplantation of younger organs into older recipients may delay aging and improve physical reserves. The study also hypothesizes that senolytics will improve organ quality, reduce the spread of senescent cells and improve physical function in older recipients.

5. Project Title: REC-3: Contribution of Cellular Senescence to Delayed Wound Healing of Aging

Leader: Daniel Roh, MD PhD

Dr. Roh is an Assistant Professor of Surgery at Boston University School of Medicine in the field of Plastic and Reconstructive Surgery whose research focus is to discover new translational therapies that can reduce the burden of wounds for the older adult⁶. His project will test the hypothesis that senescent cell accumulation in aged skin contributes to impaired wound healing, and that reduction of these cells can be a valuable tool to improve wound healing in aged individuals. Using aged mice, he will determine the contribution of senescent cell accumulation to the impaired wound healing of aging. He will evaluate topical senolytic therapy as a potential treatment and determine the effect of reducing senescent cell burden on the impaired wound healing of aging. Rejuvenating and strengthening aged skin with senolytics could be used as a preventative measure to avoid wound complications in patients at risk for acute wounds that develop into chronic wounds. In addition, this project proposes to establish potential biomarkers of senescence and wound healing status. Dr. Roh's mentors include LaDora Thompson PT PhD, Vladimir Botchkarev MD PhD, and Laura Niedernhofer, MD PhD. His project will utilize the Biostatistical Design and Analysis and the Preclinical Discovery Cores.

6. 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. Divakaran 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 (PAD)⁷. 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.

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 Trivison, 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 quantitatively 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 (4 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. Indranil Sinha. Dr. Sinha is a prior trainee of a National Institute of Aging-sponsored Postdoctoral Individual National Research Service Award (F32). He is a current awardee of a Research and Education Core Grant through the Boston Pepper Center and the National Institute of Aging. He has completed clinical training in Plastic and Reconstructive Surgery and is board-certified through the American Board of Plastic Surgery. He is now embarking 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 muscle regeneration 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 includes utilization of educational resources at Brigham and Women's Hospital, Joslin Diabetes Center, and Harvard Medical School. Career development support will also be provided by the Brigham and Women's Hospital Department of Surgery, where the principle investigator will serve as an attending physician during the period of 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 plans for the development of independent research projects and continued research funding. Dr. Sinha is interested in developing novel treatment strategies for aging-associated loss of skeletal muscle regeneration. He is investigating mechanisms by which aging alters hypoxia pathway signaling and skeletal muscle regenerative potential in a murine model. He found that two key factors in the hypoxia pathway, 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 muscle regenerative potential. Furthermore, using a genetically modified mouse model, he demonstrated that muscle-specific loss of ARNT recapitulates diminished skeletal muscle regeneration as associated with aging. Building on these intriguing preliminary data, the central goals of this project are to (1) mechanistically define the role of hypoxia pathway signaling and its impact on muscle regeneration in aging, (2) identify interventions to restore ARNT and VEGF signaling to preserve skeletal muscle myogenic potential, and (3) determine whether muscle hypertrophy in response to exercise, which is known to require skeletal muscle regeneration and hypoxia signaling, 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/ABSTRACT Cardiovascular disease (CVD) affects 70% of older adults and remains the leading cause of morbidity and mortality in the United States. Several new drugs have recently been approved for CVD, but not enough is known about their utilization, benefits and risks in frail older patients. Since conducting a clinical trial in frail older adults can be costly and impractical, there is a pressing need for innovative strategies to generate evidence on new CVD drugs in a timely manner. The objective of this application is to establish a near-real-time prospective monitoring program in Medicare data to evaluate the benefit of new CVD drugs for older adults with frailty. A prospective monitoring program seeks to find early effectiveness and safety signals of new drugs by updating the analysis at regular intervals as new Medicare data become available. The investigators will incorporate a novel claims-based frailty index into the monitoring program to generate timely evidence on disease-specific and patient-centered net benefit of new drugs by frailty status. The central hypothesis is that disease-specific benefit and net benefit are determined by a patient's degree of frailty. Disease-specific benefit will be evaluated using clinical trial endpoints of effectiveness (e.g., CVD events) and safety (e.g., bleeding), and net benefit in terms of the number of days alive and spent at home, or home time. To conduct this work, the investigators will analyze Medicare data on 6 new CVD drugs approved in 2011-2017: 3 anticoagulants vs warfarin for atrial fibrillation, 2 antiplatelets vs clopidogrel for atherosclerotic CVD, and an angiotensin receptor-neprilysin inhibitor vs enalapril for systolic heart failure. The validity and reproducibility of the results will be enhanced through the linkage of a subset 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, the investigators will accomplish 3 specific aims: 1) evaluate the temporal trends and predictors of new CVD drug use 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 with alternative therapies. This proposal's innovative approach, which combines near-real-time prospective monitoring, a claims-based frailty score, and the patient-centered outcome of home time, offers a readily scalable and feasible framework for comparative effectiveness and safety studies of newly approved medications. The impact of the proposed research is significant because timely evidence generated from real-world healthcare data can enable clinicians to optimize prescribing of new CVD drugs based on a patient's frailty and expected net benefit.

4. Project Title: ASBMR THREE YEAR SYMPOSIA
Leader(s): CAULEY, JANE ANN; CAWTHON, PEGGY MANNEN ; EDWARDS, CLAIRE ; KIEL, DOUGLAS P. ;
AMERICAN SOCIETY FOR BONE & MINERAL RES
NIH R13AR074882 / (2019 - 2022)

Core(s):

The American Society for Bone and Mineral Research (ASBMR), the largest professional, scientific and medical society established to bring together clinical and laboratory-based scientists who are involved in the study of bone, mineral and musculoskeletal science, has had a successful history of conducting annual topical meetings funded by single year NIH R13 grants since 2002. In 2015, ASBMR received a three-year R13 to cover three pre-meeting symposia for 2016-2018. This application seeks funding for a three-year R13 grant to advance the field of musculoskeletal diseases by focusing on three specific areas of scientific research in 2019, 2020 and 2021: 1) Muscle: The Path Forward to New Therapeutic Targets ; 2) The Seed and Soil: Therapeutic Targets for Cancer in Bone ; 3) Biology of the Aging Skeleton: Implications for Fracture Prevention. These three areas cover a range of topics that collectively contribute to major clinical morbidity, disability and mortality. The overall objective of this R13 is to stimulate further advances that will result in improved patient care for musculoskeletal diseases by bringing together the best researchers for each of the three symposia that will be held in conjunction with the ASBMR Annual Meetings. Each of the three symposia will review the state of the art in each topic area, exchanging ideas with attendees, and stimulating the interaction between young and established researchers. For each of the three symposia, attendees will be encouraged to attend the subsequent ASBMR Annual Meetings for additional opportunities to interact with musculoskeletal researchers. Agendas for all three years have been developed by an organizing committee with committed speakers and chairs for the first two years. The agendas include established and young investigators, women and men. Since about half of ASBMR membership is from outside the US, we also include a number of key international speakers. At the end of each meeting, a dine-around evening is planned to allow direct interaction between young investigators and more senior speakers at the meeting. In 2019, the symposium will appraise the emerging basic science of muscle (autophagy muscle, mitochondria, stem and satellite cells), translational research including development of potential therapeutic targets and to clinical research. In 2020, the symposium will focus on recent advances in the contributions of the bone microenvironment to the pathophysiology, prevention and treatment of cancer in bone. The 2021 symposium will bring together experts in geroscience and skeletal biology to enhance our understanding of biological aging that is being targeted by therapeutic interventions to increase health span and apply them to the aging skeleton.

PUBLICATIONS**2022**

1. **Virtual frailty assessment for older adults with hematologic malignancies.**
DuMontier C, Jaung T, Bahl NE, Manor B, Testa MA, Dieli-Conwright CM, Kim DH, Hshieh T, Driver JA, Abel GA
Blood Adv, 2022 May 26
[pii: bloodadvances.2022007188. https://doi.org/10.1182/bloodadvances.2022007188](https://doi.org/10.1182/bloodadvances.2022007188) | PMID: 35616435
Citations: | AltScore: NA
2. **A proinflammatory diet is associated with increased odds of frailty after 12-year follow-up in a cohort of adults.**
Millar CL, Dufour AB, Shivappa N, Habtemariam D, Murabito JM, Benjamin EJ, Hebert JR, Kiel DP, Hannan MT, Sahni S
Am J Clin Nutr, 2022 Feb 9, 115(2): 334-343
<https://doi.org/10.1093/ajcn/nqab317> | PMID: 34558613 | PMCID: PMC8827080
Citations: 1 | AltScore: 67.55
3. **Dairy food intake is not associated with spinal trabecular bone score in men and women: the Framingham Osteoporosis Study.**
Millar CL, Kiel DP, Hannan MT, Sahni S
Nutr J, 2022 May 10, 21(1): 26
<https://doi.org/10.1186/s12937-022-00781-1> | PMID: 35538577 | PMCID: PMC9092785
Citations: | AltScore: NA
4. **HIV and Aging in the Era of ART and COVID-19: Symposium Overview.**
Montano M, Landay A, Perkins M, Holstad M, Pallikkuth S, Pahwa S, HIV and Aging in the Era of ART and COVID-19 Inter-CFAR Symposium.
J Acquir Immune Defic Syndr, 2022 Feb 1, 89(Suppl 1): S3-S9
<https://doi.org/10.1097/QAI.0000000000002837> | PMID: 35015739 | PMCID: PMC8751291
Citations: | AltScore: NA
5. **Long-Term Aspirin Use and Self-Reported Walking Speed in Older Men: The Physicians' Health Study.**
Orkaby AR, Dufour AB, Yang L, Sesso HD, Gaziano JM, Djousse L, Driver JA, Trivison TG
J Frailty Aging, 2022, 11(1): 12-17
<https://doi.org/10.14283/jfa.2021.36> | PMID: 35122085 | PMCID: PMC8818085
Citations: | AltScore: 5
6. **Social Characteristics, Health, and Mortality Among Male Centenarians Using Veterans Affairs (VA) Health Care.**
Quach LT, Cho K, Driver JA, Ward R, Spiro A, Dugan E, Gaziano MJ, Djousse L, Rudolph JL, Gagnon DR
Res Aging, 2022 Feb, 44(2): 136-143
<https://doi.org/10.1177/01640275211000724> | PMID: 33779393
Citations: | AltScore: NA
7. **Elevated skin senescence in young mice causes delayed wound healing.**
Samdavid Thanapaul RJR, Shvedova M, Shin GH, Crouch J, Roh DS
Geroscience, 2022 Jun, 44(3): 1871-1878
<https://doi.org/10.1007/s11357-022-00551-1> | PMID: 35399134 | PMCID: PMC9213596
Citations: | AltScore: 1.5

8. **Relation of Testosterone, Dihydrotestosterone, and Estradiol With Changes in Outcomes Measures in the Testosterone Trials.**
Stephens-Shields AJ, Snyder PJ, Ellenberg SS, Taylor L, Bhasin S
J Clin Endocrinol Metab, 2022 Apr 19, 107(5): 1257-1269
<https://doi.org/10.1210/clinem/dgac028> | PMID: 35041751 | PMCID: PMC9016457
Citations: | AltScore: 18.05
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Citations: 3 | AltScore: 11.95
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5. **Coronary vasomotor dysfunction portends worse outcomes in patients with breast cancer.**

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Citations: | AltScore: 6.7

10. **Effects of Low Doses of L-Carnitine Tartrate and Lipid Multi-Particulate Formulated Creatine Monohydrate on Muscle Protein Synthesis in Myoblasts and Bioavailability in Humans and Rodents.**

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Harms MPM, Finucane C, P?rez-Denia L, Juraschek SP, van Wijnen VK, Lipsitz LA, van

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Auton Neurosci, 2021 Mar, 231: 102756

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Citations: 7 | AltScore: 3.7

13. **Effect of Protein Intake on Visceral Abdominal Fat and Metabolic Biomarkers in Older Men with Functional Limitations: Results from a Randomized Clinical Trial.**

Huang G, Pencina K, Li Z, Apovian CM, Trivison TG, Storer TW, Gagliano-Juc? T, Basaria S, Bhasin S

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Citations: 3 | AltScore: 29.35

14. **Role of Exercise Treadmill Testing in the Assessment of Coronary Microvascular Disease.**

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Marconi VC, Krishnan V, Ely EW, Montano M

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Montano M

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Citations: 2 | AltScore: 1.25

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Oh G, Lee H, Park CM, Jung HW, Lee E, Jang IY, Guralnik JM, Kim DH

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Citations: 4 | AltScore: 65.7

18. **Association Between Long-Term Aspirin Use and Frailty in Men: The Physicians' Health Study.**

Orkaby AR, Yang L, Dufour AB, Trivison TG, Sesso HD, Driver JA, Djousse L, Gaziano JM

J Gerontol A Biol Sci Med Sci, 2021 May 22, 76(6): 1077-1083

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Pencina KM, Burnett AL, Storer TW, Guo W, Li Z, Kibel AS, Huang G, Blouin M, Berry DL, Basaria S, Bhasin S

J Clin Endocrinol Metab, 2021 Jul 13, 106(8): 2171-2186

<https://doi.org/10.1210/clinem/dgab361> | PMID: 34019661 | PMCID: PMC8277210

Citations: 1 | AltScore: 0.75

20. **Novel Roles of Follistatin/Myostatin in Transforming Growth Factor- β Signaling and Adipose Browning: Potential for Therapeutic Intervention in Obesity Related Metabolic Disorders.**

Pervin S, Reddy ST, Singh R

Front Endocrinol (Lausanne), 2021, 12: 653179

<https://doi.org/10.3389/fendo.2021.653179> | PMID: 33897620 | PMCID: PMC8062757

Citations: 4 | AltScore: 0.5

21. **Restored TDCA and valine levels imitate the effects of bariatric surgery.**

Quante M, Iske J, Heinbokel T, Desai BN, Cetina Bieffer HR, Nian Y, Krenzien F, Matsunaga T, Uehara H, Maenosono R, Azuma H, Pratschke J, Falk CS, Lo T, Sheu E, Tavakkoli A, Abdi R, Perkins D, Alegre ML, Banks AS, Zhou H, Elkhali A, Tullius SG
Elife, 2021 Jun 22, 10:

[pii: e62928. https://doi.org/10.7554/eLife.62928](https://doi.org/10.7554/eLife.62928) | PMID: 34155969 | PMCID: PMC8257250

Citations: 1 | AltScore: 7.45

22. **miR-19b-3p is associated with a diametric response to resistance exercise in older adults and regulates skeletal muscle anabolism via PTEN inhibition.**

Rivas DA, Peng F, Benard T, Ramos da Silva AS, Fielding RA, Margolis LM

Am J Physiol Cell Physiol, 2021 Dec 1, 321(6): C977-C991

<https://doi.org/10.1152/ajpcell.00190.2021> | PMID: 34705586 | PMCID: PMC8714992

Citations: 1 | AltScore: 6.5

23. **Total carotenoid intake is associated with reduced loss of grip strength and gait speed over time in adults: The Framingham Offspring Study.**

Sahni S, Dufour AB, Fielding RA, Newman AB, Kiel DP, Hannan MT, Jacques PF

Am J Clin Nutr, 2021 Feb 2, 113(2): 437-445

<https://doi.org/10.1093/ajcn/nqaa288> | PMID: 33181830 | PMCID: PMC7851823

Citations: 5 | AltScore: 19.95

24. **The effects of a physical and cognitive training intervention vs. physical training alone on older adults' physical activity: A randomized controlled trial with extended follow-up during COVID-19.**

Savikangas T, Tirmakangas T, Tirkkonen A, Alen M, Fielding RA, Kivipelto M, Rantalainen T, Stigsdotter Neely A, Sipil S

PLoS One, 2021, 16(10): e0258559

<https://doi.org/10.1371/journal.pone.0258559> | PMID: 34644357 | PMCID: PMC8513828

Citations: 1 | AltScore: 14.15

25. **Trajectories of Frailty in the 5 Years Prior to Death Among U.S. Veterans Born 1927-1934.**

Ward RE, Orkaby AR, Dumontier C, Charest B, Hawley CE, Yaksic E, Quach L, Kim DH, Gagnon DR, Gaziano JM, Cho K, Djousse L, Driver JA

J Gerontol A Biol Sci Med Sci, 2021 Oct 13, 76(11): e347-e353

<https://doi.org/10.1093/gerona/glab196> | PMID: 34244759 | PMCID: PMC8825219

Citations: 1 | AltScore: 8.1

26. **Impact of coronary artery calcium testing on patient management.**

Wu WY, Biery DW, Berman AN, Hsieh G, Divakaran S, Gupta S, Steigner ML, Aghayev A, Skali H, Polk DM, Plutzky J, Cannon CP, Di Carli MF, Blankstein R

J Cardiovasc Comput Tomogr, 2021 Dec 17, 16(4): 303-308

[pii: S1934-5925\(21\)00481-0. https://doi.org/10.1016/j.jcct.2021.12.006](https://doi.org/10.1016/j.jcct.2021.12.006) | PMID: 34998708 |

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Citations: | AltScore: 37.3

27. Effects of obesity and weight-loss surgery shift the microbiome and impact alloimmune responses.

Zhou H, Tullius SG

Curr Opin Organ Transplant, 2021 Dec 1, 26(6): 603-608

<https://doi.org/10.1097/MOT.0000000000000920> | PMID: 34714789 | PMCID: PMC8562884

Citations: | AltScore: NA

EXTERNAL ADVISORY BOARD MEMBERS

Laura Niedernhofer, MD, PhD
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RECOGNITION AND AWARDS (2021-2022)

Kei Ouchi, MD (2022)

- Beeson Award

Tim Anderson, MD (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. Received a career development award in 2022

Minority Grant(s):

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

Kenneth Schmader, M.D. Principal Investigator	919-660-7500	kenneth.schmader@duke.edu
Michelle Cooley Program Administrator	919-660-7551	michelle.cooley@duke.edu

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 individual's 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 specific 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

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 Colon-Emeric, M.D. 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: S. Nicole 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: Carl F. Pieper, DPH carl.pieper@dm.duke.edu

Leader 2: Jane F. Pendergast, Ph.D. jane.pendergast@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
<p>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> 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).</p> <ul style="list-style-type: none"> • SHEA Research Scholar Award (Society for Healthcare Epidemiology of America) 	2022-2024 / 0 (total) 0 (1st/Sr)
<p>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> 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.</p>	2022-2024 / 0 (total) 0 (1st/Sr)
<p>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> 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.</p>	2022-2024 / 0 (total) 0 (1st/Sr)
<p>Brian James Andonian, MD MHSc Assistant Professor of Medicine / Department of Medicine, Division of Rheumatology and Immunology <u>Accelerated metabolic aging in rheumatoid arthritis immune cells and skeletal muscle: A pilot study</u> Rheumatoid arthritis (RA) is a model disease for studying premature aging. Persons with RA suffer from early aging-associated metabolic comorbidities, and are at risk for low resilience, a decreased ability to resist functional decline. Mitochondrial function in RA and aging is a marker of cellular reserve, and is thus important for preserving resilience. RA and aged immune cells have abnormal mitochondrial function, which coincide with immune dysregulation. Skeletal muscle in both RA and aging is also marked by altered</p>	2020-2022 / 6 (total) 4 (1st/Sr)

mitochondria. The pilot study will investigate whether dysfunction of mitochondria, the cellular metabolic “engine,” connects RA peripheral helper T-cells, macrophages and skeletal muscle abnormalities. Objectives are twofold: 1) to determine whether RA T cell, macrophage and skeletal muscle mitochondrial function abnormalities are associated, and 2) to determine associations of exercise training on RA immune cell and skeletal muscle mitochondria.

- 1R03-AG067949-02 (Andonian PI): Accelerated Metabolic Aging in Rheumatoid Arthritis Immune cells and Skeletal Muscle: A Pilot Study
- 5R21-AR076663-02 (Andonian Co-I): Weight loss and exercise to improve rheumatoid arthritis cardiovascular risk

Ming-Feng Hsueh, PhD

Medical Instructor / Department of Orthopaedic Surgery

Harness human cartilage repair capability to prevent and reverse osteoarthritis

Humans have a natural cartilage repair response which is high in the ankle, intermediate in the knee and low in hip cartilages. This repair response in humans is highly associated with the microRNAs used by salamanders and other limb regenerating animals to regenerate whole limbs. This project will evaluate the ability of microRNAs as a therapy to improve cartilage resilience to injury in vitro, and build the foundation for further evaluation in animals for microRNAs’ ability to prevent and reverse the most prevalent of age-related diseases, osteoarthritis, for which we currently have no disease-modifying treatments.

- Zimmer Biomet Company (Hsueh Post-Doctoral Associate) Development of an Early Osteoarthritis Diagnostic Panel via a Proteomic Approach

2020-2022 /

0 (total)

0 (1st/Sr)

Daniel Parker, MD

Assistant Professor of Medicine / Department of Medicine

Identification of biomarkers of cognitive resilience

Cognitive resilience is defined as preserved cognitive function in the setting of “stressors” that adversely affect cognitive function; it may explain – in part – the heterogeneity of cognitive function in older adults who otherwise appear clinically similar, especially with respect to risk factors for Alzheimer’s disease and related dementias (ADRD). Blood-based biomarkers of cognitive resilience would be useful to identify protective factors and test resilience-building interventions that preserve cognitive function in the setting of these stressors; currently, no such biomarkers exist. Building on previous work, I propose to develop a measure of cognitive resilience in a subset of community-dwelling older adults from the Duke Performance Across the LifeSpan (PALS; N=297) study with repeat cognitive testing over 3 years. Using this measure, I will identify biomarkers reflecting dysregulation in “Hallmarks of Aging” pathways that are predictive of cognitive resilience.

- 5R03-AG067897-02 (Parker PI): Healthy Skeletal Muscle, Healthy Brain: Are Kynurenine Metabolites the Link?
- 5UH3-AG056925-04 (Parker Co-I): Physical Resiliencies: Indicators and Mechanisms in the Elderly Collaborative
- 1R01-HL153497-01A1 (Parker Co-I): Skeletal Muscle Molecular Drug Targets for Exercise-induced Cardiometabolic Health
- 1R01-AG070146-01 (Parker Co-I): Extracellular Vesicle Analyses to Develop Aging and Resilience Biomarkers
- 1R33-AG070455-01 (Parker Co-I): Enhancing the CALERIE Network to advance Aging Biology
- 7R01-HL135009-04 (Parker Scientist): A Longitudinal Epigenetic Study of Atherosclerosis

2020-2022 /

4 (total)

3 (1st/Sr)

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)

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 proapoptotic 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 interventions 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 sequelae 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):** Molecular Measures Core (MMC)

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 (14 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 initiate or forgo dialysis in the context of uncertainty about their future health and physical function. Making these decisions is complicated by the course of advanced CKD which is characterized by frequent health events that further worsen function. Decisions support tools are needed that are specific to the clinical course of advanced CKD and predict outcomes that matter most to these patients, such as physical function. Characterizing how patients 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 the novel geriatric concept of physical resilience, defined as one's ability to resist or recover from functional decline following a health stressor. Objectives: To help older Veterans make informed decisions about kidney disease treatment by better characterizing physical resilience and identifying patient factors associated with physical resilience to develop a prediction tool for physical resilience in advanced CKD. This addresses the HSR&D priority of Patient-Centered Care domain. To do this, we propose Physical RESilience Prediction in Advanced RENal Disease (PREPARED), a prospective cohort study of older Veterans with advanced CKD with the 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 estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m² (excluding dialysis or transplant), and 90-day probability of hospitalization = 50% (based on the Care Assessment Needs [CAN] score). Telephone assessments will include brief validated measures of function every 8 weeks, and within 14 days following a stressor for up to 6 calls. In Aim 1, we will characterize physical resilience, first by identifying latent classes of physical resilience trajectories using general growth mixture modeling. Next, among the subset from the physical resilience latent trajectory class we will fit a piecewise linear mixed effects model to quantify resilience. In Aim 2, we will determine how the physical function trajectory is moderated by person-level health and psychosocial factors and organ system-level physiologic factors. This information will be used to identify potential candidate variables for our prediction model in Aim 3. The purpose of Aim 4 is to determine the prognostic importance of physical resilience by examining the relationship between experiencing a stressor and physical resilience with 6-month mortality. Impact: The proposed study addresses the most pressing clinical dilemma in this complex condition that disproportionately affects older Veterans. Data on physical resilience from the proposed study will be used to develop a practical tool to address a vital question that CKD patients, their families, and providers face when making treatment decisions. Limiting uncertainty about future health by predicting resilience will support individualized and patient-centered decision-making for kidney disease. Next steps: We will develop a clinical trial to test the use of our physical resilience prediction tool and work with our local and national operations partners (Durham VA Renal Service, Office of Geriatrics and Extended Care, Renal Field Advisory 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 Keys™ to Healthy Aging curriculum and the National Council on Aging's 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: 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)**

Core(s):

a. Project summary/abstract: Sarcopenia is the age-related loss in skeletal muscle mass and strength; it leads to a host of co-morbidities including loss of physical function and overall resilience. One such perturbation in persons with sarcopenia is the diminished ability to regenerate muscle after injury. Muscle stem cells, referred to as satellite cells, are required to activate, proliferate and differentiate to regenerate muscle and restore physical function. Aged satellite cells are slower to activate upon injury; susceptible to apoptosis; and less efficient in repairing injured muscle. The AMPK/ULK1/p27Kip1 pathway appears critical for successful transition from quiescence to entry into the cell cycle. Our preliminary data identify perturbations in the AMPK/ULK1/p27Kip1 pathway with advanced age. This award period will investigate the role of the AMPK/ULK1/p27Kip1 pathway in the phenotype of satellite cell aging in both human and mouse models. In Aim 1, we will test the hypothesis that activation of AMPK and its downstream targets ULK1 and p27Kip1 regulate the autophagy/apoptosis decision in aged satellite cells. We will use molecular assays to rescue the functional loss of this pathway in aged cells and return proliferative capacity. In Aim 2, we will test the hypothesis that exercise, a physiological inducer of AMPK and autophagy, stimulates the AMPK/ULK1/p27Kip1 pathway, thereby enhancing proliferation and metabolic function in aging murine and human satellite cells. Aim 3 will test the hypothesis that AMPK/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 is impaired in aging satellite cells resulting in a reduction in autophagy and susceptibility to apoptosis. Key aspects of Dr. White's career enhancement will be: to learn how to coordinate clinical exercise trials; to train in 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 toward independence. The research and career development plan detailed in this proposal will be conducted with a team of outstanding mentors. Dr. William E. Kraus, a professor at the Duke Medical School is an established expert 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 will facilitate training in aging biology, cell metabolism and aging stem cell biology, respectively. The environment at the Duke School of Medicine is ideal for the research and training activities outlined in this proposal. This award will provide Dr. White with optimal training to ensure an outstanding start to his career as an independent investigator.

**4. 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 of hospitalization. She has built her research program on investigating hazards of hospitalization, and a major threat is high-risk medication exposure. Sub-optimal CNS medication use during hospitalization is a key modifiable 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 are exposed to anxiolytics and 60% to opioids during their hospital stay. De-prescribing is a systematic process of tapering or reducing medications. Interventions to facilitate de-prescribing that target specific medication classes, like CNS medications, or specific populations, like those with existing cognitive impairment, have not been well-studied in the inpatient setting. This gap represents a key opportunity to reduce potentially inappropriate CNS medications and their debilitating side effects in vulnerable patients--in line with the National Institute of Aging's priorities to improve medication use in older adults. Dr. Pavon's K23 award proposes to develop and pilot test a de-prescribing intervention that is informed by a theoretical model of behavioral change. Aim 1 results will inform the epidemiology of the problem and identify target populations for recruitment. 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 in a 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 and patient activation strategies. This work will advance understanding of 1) which patients and CNS medication classes to target for de-prescribing interventions, 2) whether there are unique barriers to de-prescribing in the hospital 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, intervention development, health informatics, and leadership. Dr. Pavon's mentor team will provide scientific support with expertise in aging, pharmacology, hospital medicine, and research methodology. This career development plan 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 designed to facilitate de-prescribing of CNS medications for the nearly 1 in 2 older adults that will experience exposure to a CNS medication during hospitalization.

**5. 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):

ABSTRACT Among its medical complications, type 2 diabetes mellitus in older adults is associated with a two-fold increase in the risk of hip and other low-trauma bone fractures. Paradoxically, this increased risk occurs despite a higher average bone mineral density. This increased fracture risk is likely multifactorial, stemming from metabolic dysfunction that results in both increased falls risk and decreased bone strength. However, fracture risk stratification currently is limited largely to bone density testing and clinical risk tools that do not perform adequately for adults with diabetes. Because bone is both a metabolic and structural tissue, metabolomics and biomechanical analyses would be particularly useful for developing and assessing new measures of fracture risk. The objective of this application is to develop and evaluate radiographic and laboratory biomarkers of fracture risk among older adults with diabetes, utilizing biomechanical and translational measures. The proposed research has the following aims: 1) Determine the association between metabolomic profiles and incident clinical fracture among older adults with diabetes; 2) Compare geometric and biomechanical measures at the femoral neck and intertrochanteric region among older adults with diabetes, with and without hip fracture. This application builds upon the prior published work and clinical expertise of the Principle Investigator, Dr. Richard Lee, and provides him additional research skills to assist with his career development goal of understanding the interaction of chronic medical conditions on the bone health of older adults, focusing on diabetes. Dr. Lee is a dual-trained Geriatrician and Endocrinologist with expertise in metabolic bone disease. The primary training goals of this proposal include the following: 1) Develop laboratory and analytical skills in translational science that will be used in the development and evaluation of clinical biomarkers, including omic technologies; 2) Acquire principles and skills in biomechanical engineering and materials science to integrate with clinical and epidemiological analyses. By integrating biomechanical engineering and metabolomics approaches with epidemiologic research to identify new markers of fracture risk, this application addresses a significant source of morbidity and mortality among an increasing proportion of older adults.

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

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

Core(s):

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 older Americans undergo anesthesia and surgery, and up to 40% of these patients develop postoperative cognitive dysfunction (POCD), a syndrome of postoperative thinking and memory deficits. Although distinct from delirium, POCD (like delirium) is associated with decreased quality of life, long term cognitive decline, early retirement, increased mortality, and a possible increased risk 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 inflammation causes POCD, but little work has directly tested this theory in humans. Our preliminary data strongly suggest that there is significant postoperative neuro-inflammation in older adults who develop POCD. In this K76 award, we will prospectively obtain pre- and post-operative cognitive testing, fMRI imaging and CSF samples in 200 surgical patients over age 65. This will allow us to evaluate the role of specific neuro-inflammatory processes in POCD, its underlying brain connectivity changes, and postoperative changes in cerebrospinal fluid (CSF) Alzheimer's disease (AD) biomarkers, such as the microtubule-associated protein tau. This project will advance 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 National Institute of Aging's mission to understand aging and fight cognitive decline due to AD. During this K76 grant period, Dr. Berger will also complete an individually tailored MS degree in Translational Research that will include training in immunology methods, fMRI imaging, cognitive neuroscience, geroscience, and physician leadership. This career development plan will give Dr. Berger the transdisciplinary skills to pursue his longer term goal of improving postoperative cognitive function for the more than 16 million older Americans who have anesthesia and surgery each year.

7. 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 goal is to become a leader in geriatric nephrology and develop effective interventions targeting geriatric conditions in older dialysis patients. Compared to older adults without kidney disease, older dialysis patients are more likely to 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 older dialysis patients are highly susceptible to adverse effects of potentially inappropriate medications because of altered 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 for improving quality of care for these vulnerable patients. The objective of Dr. Hall's proposed research is to develop an evidence-based strategy to reduce inappropriate prescribing in older dialysis patients. The research aims are to: 1) identify the prevalence of specific potentially inappropriate medications and the extent to which there is an association with hospitalization risk in prevalent older dialysis patients, 2) identify elements of a deprescribing intervention that are acceptable to nephrologists, primary care providers, and patients, and 3) determine the feasibility of a deprescribing intervention tailored for older dialysis patients. This work will provide evidence to support a definitive clinical trial of deprescribing in dialysis units. Effective deprescribing interventions have the potential to reduce hospitalizations and ameliorate geriatric syndromes in dialysis patients which is consistent with NIA's mission. Complementary to this research, this career development award will solidify Dr. Hall's transition to research independence through coursework and mentoring to: a) fill knowledge gaps in directing a team of statisticians, interpretation of pharmacoepidemiologic data, advanced methods in handling bias in observational data, timely qualitative analyses, execution of a pilot study, and clinical trial design; b) enhance her leadership skills; and c) successfully compete for a R01. Duke University is the ideal environment for Dr. Hall to pursue this research career development because of the strong aging research expertise housed in its Center for Aging and affiliated Pepper Center, as well as, rich resources available through Duke's Clinical and Translational Institute.

8. 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 mediate a broad spectrum of biological processes through regulation of gene expression. Our experimental evidence indicates that serum levels of miRNAs (one form of sRNA) change considerably, the vast majority increasing with age. The ability of circulating sRNAs to 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 inside different types of extracellular vesicles. Consequently, in contrast to messenger RNA, sRNAs are protected from extracellular RNases and are measurable and stable in samples stored for decades. Despite numerous recent developments, we are far from understanding the role of sRNAs in aging. An understanding of their role in aging mammals, and in humans in particular, is still very limited due to the increased complexity and longer life-spans of mammals compared with invertebrates. This project leverages existing human sample resources from three completed NIH-funded studies (EPESE, STRRIDE and CALERIE), to discover and validate longevity-associated miRNAs in humans. Our preliminary analysis of 175 circulating microRNAs 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 < 0.05) compared with age, sex and race matched but short-term survivors (

9. 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 health priority. 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 geroprotective therapies to humans faces the barrier that human clinical trials of midlife geroprotective therapy would require decades of follow-up to measure healthspan extension. An alternative is a short-term accelerated geroprotector trial that tests if geroprotective intervention can slow the rate of biological aging. Biological aging is the gradual and progressive decline in system integrity that occurs with advancing chronological age. This process is thought to be the root cause of increases in morbidity and disability in later life. New research shows that biological aging can be measured in humans and that measures of biological aging predict human healthspan. Geroprotective therapies that target basic biological processes of aging are hypothesized 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 biological aging 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 of biological 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-month follow-ups. We will use this 3-time-point repeated-measures multi-omics dataset to test (i) Does CR slow the rate of biological aging as measured from DNA methylation (ii) Does CR cause changes to gene expression in the pathways known to mediate healthspan-extending effects of CR in animals, e.g. the mTOR pathway (iii) Do changes to DNA methylation and gene expression mediate effects of CR on organ system 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 new knowledge about effects of caloric restriction on biological aging in humans and test proof of concept for an accelerated geroprotector trial design that can speed translation of new age-delaying therapies from animals to humans. Open data sharing through the CALERIE Biorepository will enable research beyond the scope of this project to improve understanding of caloric restriction and advance the field of geroscience.

10. 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.

11. 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 the United States and nearly twice as many worldwide. Meniscal tears in the avascular inner zone of the tissue do not 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. These cellular activities are controlled not only by biochemical factors in the joint but also by physical factors associated with 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. Our overall goal is to identify critical meniscus mechanotransduction pathways and modulate these pathways to promote meniscus repair and prevent OA development. Our work has shown that transient receptor potential vanilloid 4 (TRPV4) is a critical component in cartilage mechanotransduction and metabolism. The activation of TRPV4 can block IL-1 induced catabolic responses and also increases cell migration and proliferation, which are important processes to enhance tissue repair. While we have found that TRPV4 is expressed in the meniscus, the function of this mediator in meniscus health and disease is currently unknown. In this proposal, we will determine how mechanotransduction occurs through TRPV4 in meniscus and identify modulators of this pathway that will be used to enhance tissue repair and prevent OA development. We hypothesize that mechanotransduction by TRPV4 plays a key role in meniscus metabolism and can be modulated to enhance meniscus repair and prevent the development of OA. In this proposal, we will determine 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 of mechanotransduction pathways. In this proposal, we will identify the key signaling pathways downstream of TRPV4 that may function as novel drug targets to 1) treat patients with immobilized joints to simulate exercise and 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 this proposal can subsequently be developed into drugs to enhance meniscus repair and prevent the development of OA.

12. 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)**

Core(s):

ABSTRACT Exercise is a powerful physiological stimulus contributing to disease prevention and intervention. The protective and preventive effects of exercise are well-documented for metabolic, neurodegenerative, and cardiovascular diseases, and certain cancers. While scientists acknowledge the extensive benefits of exercise, there is still insufficient understanding about the underlying mechanisms by which exercise prevents disease and improves health across diverse organ systems. The NIH Common Fund has developed a forward-looking funding mechanism six tethered RFA's tied to creating a research consortium, the Molecular Transducers of Physical Activity Consortium (MoTrPAC) to create resources and critical information for exercise and health investigators well into the future. Two products of the MoTrPAC collective efforts will be a publically available data resource that will enhance and accelerate subsequent mechanistic research on diseases and conditions affected by physical activity; and a biorepository of clinical and animal model samples to be used in studying exercise biology. Based on prior collaborative efforts, our group believes that we are ideally positioned to propose a protocol that will respond directly to the RFA, while at the same time execute the 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 Clinical Site Consortium (NCCSC). The NCCSC consists of the

experienced research teams Duke University School of Medicine; East Carolina University (ECU); and Wake Forest School of Medicine (WFSM). As described in the study plan, the NCCSC weighed a number of alternatives for training regimens, timing, and type of tissue sampling, sample sizes for the four obligated study groups, and other factors, while staying within budget constraints. The following Aims will maximize the value of the data and sample repositories; this will be accomplished 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.

13. 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, 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 (PRagmaticEValuation 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.

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

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

Core(s):

ABSTRACTThe overarching objectives of the PRIME Collaborative (Physical Resilience: Indicators and Mechanisms in the Elderly) are to characterize specific resilience phenotypes, elucidate biological mechanisms, and validate clinically valuable predictive tools and measures of physical resilience. The application focuses on resilience in three systems that are central to older adults' overall health: musculoskeletal, cognitive, and immune. The central hypothesis of this application is that resilience to physical stressors is influenced by biological mechanisms at the molecular level. We will examine whether mechanisms associated with one or more of these seven Pillars of Aging, which have been described by the trans-NIH Geroscience Interest Group, underlie a more 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 team represents expertise from six NIA-funded Older American Independence Centers (OAICs) and leverages other existing resources. The PRIME Collaborative team will use a two-phased approach. In Phase 1, workgroups will define specific resilience phenotypes in existing datasets using latent class trajectory analysis of sequential outcome measures following a stressor. The three resilience phenotypes, selected for their over-arching relevance to late life health as well as our team's expertise, are: musculoskeletal recovery after orthopedic surgery, immune recovery after infection, and cognitive recovery after surgery/anesthesia. We will conduct pilot studies to identify novel clinical tests and biomarkers associated with each of these resiliencies. Feasibility and response data from pilot studies will inform the design of a larger cohort study in Phase 2. In the final 6 months of Phase 1, the most promising predictive tests and markers will be selected and will inform two parallel activities in Phase 2. First, a longitudinal cohort study of older patients undergoing elective surgery will be conducted to validate predictors in a more diverse population. The Phase 2 cohort study will also allow us to assess synergy and interactions between different types of predictors (provocative tests, physiologic output measures, biomarkers) and different types of resilience (musculoskeletal, cognitive, immune). Second, biological mechanisms underpinning resilience will be identified using newly developed mouse resilience models, and in vitro human and mouse myotubule systems. These model systems are suitable for intervention studies. The Phase 2 biological studies will be designed to identify pathways related to one or more Pillars of Aging so that they are likely to underpin multiple types of resilience, and suggest therapeutic targets and novel, resilience-bolstering interventions.

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Citations: 1 | AltScore: 0.75

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Citations: 2 | AltScore: 5

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Citations: 6 | AltScore: 7.3

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Citations: 3 | AltScore: 210.246

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Citations: 3 | AltScore: NA

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RECOGNITION AND AWARDS (2021-2022)**Ashley Poole, PT, DPT, CCS (2021)**

- American Physical Therapy Association Centennial Scholar

Harvey J. Cohen, MD (2022)

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Heather Whitson, MD, MHS (2021)

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

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Kenneth Schmader, MD (2022)

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

Kenneth Schmader, MD (2021)

- Appointed to CDC Advisory Committee on Immunization Practices (ACIP) COVID-19 Vaccine Effectiveness Work Group
- American Geriatrics Society Annual Scientific Meeting Plenary Symposium Presenter on COVID-19 Vaccines

Virginia Byers Kraus, MD, PhD (2021)

- Appointed the Mary Bernheim Distinguished Professor of Medicine

MINORITY RESEARCH

General Brief Description of Minority Activities:

Determinants of maintenance and recovery of function in a representative older community-resident biracial sample

Gerda Fillenbaum, PhD, co-investigator, Katherine Hall, PhD, Carl Pieper, DPh, Heather Whitson, MD, MHS, Cathleen Colón-Emeric, MD, MHS, Core leaders

Focus on decline in performance of activities of daily living (ADL) has not been matched by studies of recovery of function. Advised by a broad conceptual model of physical resilience, we ascertain characteristics that identify (1) maintenance, (2) decline, and (3) recovery of personal self-maintenance activities over six years in an older (age 65-105 years), community representative sample (n = 3187; African American: 54%, White: 45%). All were participants in the Duke Established Populations for Epidemiologic Studies of the Elderly, and were unimpaired at baseline.

Over six years, ~75% remained unimpaired, of whom 30% were unimpaired when they dropped out or died. Of ~25% who became impaired, just over half recovered. Analyses, which took into account demographic characteristics, health conditions, health service use, social services provided and received, neighborhood safety, and survival status, indicated that those who became impaired were in poorer health, were younger, and more likely to be African American. Characteristics of recovery included younger age, not hospitalized in the previous year, and increased social support.

Our analyses indicate that maintenance of health status facilitated continued unimpaired basic activities of daily living. While decline was associated with poorer health, younger age, and being African American, recovery was also associated with younger age, and in addition social support, and no further deterioration in health as measured here.

Following decline in functioning, increased effort is needed to improve health and avoid further decline, and effort that takes into account not only physical but also personal social conditions.

Fillenbaum GG, Sloane R, Burchett BM, Hall K, Pieper CF, Whitson HE, Colón-Emeric CS. Determinants of maintenance and recovery of function in a representative older community- resident biracial sample. *J Am Med Dir Assoc.* 2020 Feb 6:S1525-8610(19)30891-6. doi: 10.1016/j.jamda.2019.12.021. Online ahead of print. PMID: 32037299 NIHMS 1569426 <https://doi.org/10.1016/j.jamda.2019.12.021>

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 proapoptotic 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 proapoptotic 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 of IL-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 funded 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):

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

Jeremy Walston, M.D. Principal Investigator	410-550-1003	jwalston@jhmi.edu
Karen Bandeen-Roche, Ph.D. Principal Investigator	410-955-3067	kbandeel@jhu.edu
Brian Buta, MHS Program Administrator	410-502-3412	bbuta@jhu.edu

CENTER DESCRIPTION

Since its inception in 2003, the **Johns Hopkins University (JHU) Older Americans Independence Center (OAIC)** has pursued a rigorous and distinctive scientific approach considering physical frailty as a biologically-rooted state of decreased resiliency and reserve, which induces a syndromic phenotype and specific etiological mechanisms. As evidenced by peer-reviewed publications and associated NIH grant funding, this specific conceptualization of frailty has provided a highly productive framework for population-based, clinical, and biological discovery, for the development of potential prevention and treatment strategies, and for the training of junior investigators for academic careers in frailty and aging research.

This center's mission remains, in many respects, as it has been throughout the life of our OAIC: To make fundamental etiological discoveries related to 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 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. Given the rapidly growing interest in frailty, its detection, its management, and the critical mass of frailty-related knowledge that this OAIC has generated, we have launched an Information Dissemination Core (IDC) to enable our OAIC to more comprehensively disseminate frailty-related findings so as to better impact clinical and public health practice.

We pursue our mission through the following specific aims:

1. To stimulate, lead and develop effective frailty-focused interdisciplinary research programs that promote the maintenance of independence. This has helped to create a vibrant and growing center with scientific vigor and a rich interdisciplinary milieu of experienced faculty and successful trainees focused on frailty research.
2. To translate the new knowledge generated in this OAIC into targeted prevention and treatment strategies that help older adults maintain independence. An existing clinical translational resource core, an IDC, and the national OAIC network facilitate this effort.
3. To provide the highest quality expertise, support, infrastructure and technology in biological, data analytic and clinical research methodologies to OAIC 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, and Clinical Translational cores.
5. To provide tailored training and mentorship to junior investigators interested in developing careers focused on frailty in older adults. We continue with a leadership team that has

- demonstrated expertise and commitment to training the next generation of investigators.
6. To attract outstanding investigators and trainees to frailty research from across the Johns Hopkins University and beyond. We augment our successful local approach to this by providing highly visible educational and training activities on a local and national level, and through the IDC.

CORES

Leadership and Administrative Core (LAC)

Leader 1: Karen Bandeen-Roche, PhD kbandee1@jhu.edu

Leader 2: Jeremy Walston, MD jwalston@jhmi.edu

The Leadership/Administrative Core (LAC) spearheads the vision for the Johns Hopkins Older Americans Independence Center (JHU OAIC), sets goals through which to implement it, and assures energy and quality in accomplishing goals. It leads in identifying the next generation of research on frailty that should be created, supports research planning and recruitment of investigators, and sets and monitors progress benchmarks. It is the OAIC base for recruiting and nurturing a critical mass of investigators dedicated to the creation of high impact, innovative research essential to the prevention and treatment of frailty in older adults. It administrates the OAIC and its Cores for soundness of operations and accomplishes required reporting. It promotes a stimulating intellectual environment around scholarship on frailty so as to attract outstanding researchers and knit them into an interdisciplinary community. It creates visibility for the accomplishments of the OAIC locally and globally: In the current cycle it leverages a new Information Dissemination Core (IDC) to amplify these efforts. The LAC is led by OAIC Co-Principal Investigators with broad interdisciplinary scientific expertise and institutional reach. They work closely with the other OAIC Cores Directors, and with a diverse Leadership Council and Internal Advisory Committee to develop and promote a frailty-focused agenda across the Johns Hopkins University. An experienced External Advisory Board reviews this OAIC annually, and provides crucial feedback and additional scientific vision. The LAC provides essential leadership in planning, integrating, sustaining, implementing and monitoring OAIC operations. Its goals are to envision and then support research leading to new strategies to enhance independence in older Americans and to create a new generation of research leaders in the field.

Research Education Component (REC)

Leader 1: Gary Gerstenblith, MD gblith@jhmi.edu

The purpose of the Research Education Core (REC) is to foster the career development of junior faculty from multiple disciplines into academic scientists in gerontology and geriatrics, focusing on the theme of exercise and activity rehabilitation and recovery research. The REC supports mentor-based research training and education to promote the career development of REC Scholars as well as other junior faculty, fellows, and students pursuing research careers in aging. The UM-OAIC has a successful history of mentored training that crosses traditional disciplinary boundaries to develop novel research for improving function and independence in older persons. This has enriched the cadre of scientists at UM and elsewhere conducting aging research in exercise and rehabilitation science.

Pilot and Exploratory Studies Core (PESC)

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

The major goal of Pilot and Exploratory Studies Core (PESC) is to cultivate and support innovative pilot and exploratory studies that are needed to develop crucial larger scale and confirmatory studies to advance the development of effective prevention and/or therapies for frailty, and hence facilitate independence in older adults. The PESC provides funding, access to biostatistical, biological, and clinical research core resources, and mentoring and oversight pilot and exploratory

studies. Because of the importance of these studies to the development of new scientific priorities, additional resources are provided to this core to help maximize flexibility, efficiency, and rapid development of areas of focus for this OAIC. The PESC Core, in close collaboration with the OAIC Leadership Council, sets ideas the next stages of research most essential to advancing science on frailty, and then works to identify investigators whose expertise and career goals are applicable to furthering knowledge in these target areas. The leadership and resources of these cores are then focused on the development, conduct and eventual translation of high impact pilot studies. The proposed studies must be novel and either hypothesis-driven or focused on development of methods needed to validly address hypotheses: they ideally address potential mechanisms, etiologies, or screening approaches for frailty, or lay groundwork for evaluating potential therapies to prevent or treat the frailty and its consequences and hence maintain independence. It is expected that PESC-supported studies establish preliminary data that will lead to substantive, long term external funding that can bring the research initiated to completion. Given our roadmap goals of accelerating translation of frailty to increase healthspan in clinical and public health settings, elucidating the biological underpinnings and role of multisystem dysregulation in frailty and resilience, and improving ascertainment of frailty measurement in settings that challenge measurement, special focus was given to these areas for the PESC studies funded by our OAIC.

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

Leader 1: Qian-Li Xue, PhD qxuel@jhu.edu

Leader 2: Karen Bandeen-Roche, PhD kbandeel@jhu.edu

The Johns Hopkins Older Americans Independence Center (OAIC) has empowered by many-fold the creation of significant research, training and practice paradigms for addressing frailty in older adults. The functions supplied by this Biostatistics Core have been central in this. They include: our key roles in the mentorship and training of junior colleagues in the statistics of frailty and aging; our development and dissemination of emerging resources and technologies for data management and analysis; our provision of database and statistical expertise and support to scholarship on frailty and aging, needed methodological innovation, and collaborative intellectual leadership for the creation and translation of research on frailty. Outcomes of this Core, in collaboration in this OAIC and beyond, include advancement of knowledge on the ascertainment, biological and etiological underpinnings, health consequences, and treatment of frailty, research surmounting significant methodological challenges to the study of frailty, and the creation of intellectual capital and infrastructure for further advances. These have laid crucial groundwork for intervening on frailty. For nearly 20 years our Biostatistics Core has dedicated a critical mass of leadership from gerontologically informed biostatisticians toward the amelioration of frailty in older adults through our OAIC, and its leadership has dedicated the same to research on aging for 30+ years. Our leadership and our external advisory committee consider it crucial that this Core continue to contribute to the OAIC's overarching aims through the intellectual innovation, collaboration and support it provides.

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

Advances in understanding of molecular and physiological processes that influence aging phenotypes, and in methodologies that help to measure these changes, have greatly improved our ability to identify biological pathways that are potentially relevant to the etiology of frailty. The major goal of this core is to promote molecular and biological studies of aging and frailty-relevant pathways, and to translate these findings into relevant diagnostic, preventive and treatment strategies. Building on our prior cycles, mitochondrial biology, chronic inflammation, renin angiotensin system, and genetics continue to be a core expertise content offered to investigators from within the core. We have also gained expertise and collaborators at Johns Hopkins who have considerable “omics” and in computational biology expertise. These technologies have provided a logical basis for searching and identifying specific biomarkers associated with human phenotypes and diseases; they can not only provide markers for human disease that are useful for nosology in heterogeneous clinical phenotypes but, more importantly, provide deep insight into pathophysiology and disease mechanisms that will form the bases for future diagnostics and treatments. Consequently, the rationale for RC-2 is to provide the expertise, technology access and infrastructure, mentoring, and training necessary to facilitate the highest quality etiologic research in frailty.

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

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

In order to more effectively meet JHU OAIC’s goal of translating frailty-related etiological discoveries into clinical studies that help maintain independence in older adults, and to overcome the substantial barriers to success in clinical investigation for junior investigators, the leadership of this OAIC made a strategic decision to develop this resource core. RC-3 provides to supported OAIC investigators: 1) comprehensive training and mentorship in clinical research that spans from study design through implementation through outcome interpretation, 2) clinical research space and assistance with all aspects of forms and protocol development, data collection, and recruitment of human subjects, 3) an active registry of more than 650 older adults who have consented to be contacted for aging and frailty related studies, and 4) synergy with other cores in order to optimize all aspects of frailty-related study design, data collection, and biological measurement and junior faculty training. This synergy is greatly augmented by our core leader, Dr. Todd Brown, an endocrinologist with considerable human subjects research expertise and leader in the ICTR at Johns Hopkins, who leads RC-3. The daily operations are led by a highly skilled and experienced research program manager with expertise in the measurement of frailty, mobility, and cognition, as well as expertise in protocol development and implementation and in subject recruitment and retention, in coordination with our OAIC administrator and Drs. Brown and Walston. This initiative, which is closely aligned with the JHU Division of Geriatric Medicine and Gerontology's goals of better integrating clinical practice with clinical research, is funded in part by philanthropic resources.

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.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time

Years /
Publications

Melissa deCardi Hladek PhD, CRNP, FNP-BC

Assistant Professor / Johns Hopkins School of Nursing

Using Human-Centered Design to Adapt CAPABLE as a Prehabilitation

Intervention for Adults with Frailty Awaiting Kidney Transplant

Over 700,000 Americans live with end-stage renal disease (ESRD), disproportionately 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.

2021-2023 /

1 (total)

1 (1st/Sr)

Gizem Keceli, PhD

Postdoctoral Fellow / Johns Hopkins School of Medicine, Division of Cardiology

Dissecting the Mechanisms Whereby Tryptophan Metabolites Alter Myocardial

Function

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

2021-2023 /

1 (total)

1 (1st/Sr)

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.

Assistant Professor / Johns Hopkins University School of Medicine

Identifying mechanisms by which circulating-cell free DNA contribute to increased TNFR1 in frailty

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.

2021-2023 /

4 (total)

1 (1st/Sr)

Nicholas R. Rowan, MD

Assistant Professor / Johns Hopkins Department of Otolaryngology-Head and Neck Surgery

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.

2021-2023 /

2 (total)

0 (1st/Sr)

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, Neurology (2019-2019)

Sabra Lewsey, MD, Division of Cardiology (2020-2021)

Jude Phillip, PhD, Department of Biomedical Engineering (2020-2021)

PILOT/EXPLORATORY PROJECTS (11 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 mortality². 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 indoleamine 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.

DEVELOPMENT PROJECTS (4 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-hydroxyanthranilic 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 α -methyltryptophan (α -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⁺ (α -MT+NAM or α -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.

RESEARCH (25 Projects Listed)**1. Project Title: VISION LOSS AND COGNITION: TESTING THE SENSORY CONSEQUENCE HYPOTHESIS**

Leader(s): SWENOR, BONNIELIN
THE JOHNS HOPKINS UNIVERSITY
NIH K01AG052640 / (2017 - 2022)

Core(s):

ABSTRACTThis is an application for a K01 Research Career Development Award. The goal of the proposed project is to provide the candidate with advanced skills needed to establish an independent research program examining the relationship between vision loss and cognitive decline in older individuals. To facilitate this long-term goal the candidate will: (1) characterize the longitudinal relationship between objective measures of visual function and cognition in older adults, (2) determine the relationship between vision loss and brain volume and cortical thickness in older adults, and the role brain volume and thickness may play in the vision-cognition relationship, and (3) assess the association between vision loss and participation in cognitively stimulating activities, exploring this participation as a mediator of the vision-cognition relationship. The candidate proposes a comprehensive training plan, combining formal coursework, meetings and tutorials overseen by her mentors, participation in applied training experiences, and involvement in seminars and workshops. Specific training goals include: (1) receive training in the neuropsychological and clinical assessment of older individuals, (2) develop neuroimaging analyses skills, (3) receive training in the neuroscience of vision, (4) gain advanced knowledge of mediation and experimental study design and analyses, and (5) continued training in the responsible conduct of research. The training plan will be executed in coordination with the set of research activities, mentioned above, that are based on preliminary data collected by the applicant. The preliminary data show that reduced visual functioning is associated cross-sectionally with: (1) lower executive function, memory, and language test scores, and (2) reduced gray and white matter volumes, in the visual cortex and frontal lobes. The candidate will expand on these findings, using longitudinal data from participants in the Baltimore Longitudinal Study on Aging (BLSA) who are 60 years and older. The aim of the project is to test the 'sensory loss consequence hypothesis', using a multi-domain approach to examine the vision-cognition relationship. The primary hypotheses to be examined are that: (1) reduced visual function is associated with greater declines in executive function, memory, and language test scores, and an increased risk of incident dementia, (2) reduced visual function is associated with reduced brain volume and thickness in regions of interest within the frontal cortex and visual pathways, which mediate the vision-cognition relationship, and (3) age-related vision loss is associated with a reduction in the frequency and variety of participation in cognitively stimulating activities, which also influences the vision-cognition relationship in older adults. Results from this research will be used to develop a subsequent R01 research proposal that will facilitate the candidate's transition to an independent researcher.

2. 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.

3. 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/ABSTRACT (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.

4. 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 sequelae. 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.

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 understanding the underlying mechanism of age-related decline of skeletal muscle function. This study uniquely focuses on the intersection between kynurenine metabolic pathway, motor neuron, neuromuscular junction (NMJ), and skeletal muscle function. Kynurenine pathway is a major route to the synthesis of Nicotinamide adenine dinucleotide (NAD), a critical coenzyme that balances redox status of all living cells. Many intermediate metabolites of kynurenine pathway are known to be potent neurotoxins, and involved in various age-related neurodegenerative diseases. The preliminary studies of this project showed alterations of kynurenine pathway in aging peripheral neuromuscular system. Herein, it is hypothesized that age-related alterations in kynurenine pathway contributes to neurodegeneration in spinal motor neurons, eventually causing age-associated muscle weakness. Aim 1 propose to identify key alterations in the kynurenine pathway in the aging spinal motor neurons, using mass spectrometry, PCR, and Western blot techniques. Aim 2 propose to determine the neurotoxicity of kynurenine pathway in aging neuromuscular system both in vitro and in vivo models. Finally, Aim 3 tests the effects of pharmacological inhibition of kynurenine 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 Jeremy Walston, MD, Ahmet Hoke, MD, PhD, and Robert Schwarcz, PhD. An integrated career development and mentoring plan has been also proposed to ensure Dr. Chung's successful transition to independence. The training goals are focused on development of Dr. Chung's expertise in kynurenine neurobiology, various molecular techniques in neuroscience research, and translational gerontology. The strength of the proposal comes 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: ASSOCIATION OF FRAILITY WITH POST THYROIDECTOMY ALTERATIONS IN VOICE, SWALLOWING, AND QUALITY OF LIFE

**Leader(s): MATHUR, AARTI
THE JOHNS HOPKINS UNIVERSITY
NIH K23AG053429 / (2017 - 2022)**

Core(s):

Project SummaryThis project aims to evaluate the association of frailty with post-operative changes in voice, swallowing, and quality of life following thyroidectomy in older adults. Specifically, Aim 1 is to evaluate the effect of thyroidectomy on voice, swallowing, and quality of life in older adults. The literature suggests that these alterations occur at a relatively high frequency in younger patients. We aim to quantify frequency and magnitude of changes in voice, swallowing, and QOL using subjective assessment with surveys and semi-structured patient interviews. Additionally we aim to correlate this with objective data obtained from speech-language pathology evaluations using videostroboscopy and videofluoroscopy. In Aim 2, we will explore the associations between a frailty phenotype with pre-operative findings, thyroid-specific markers, and post-thyroidectomy alterations in voice, swallowing or decline in QOL. In addition to exploring the role of frailty to predict these alterations and identify a high-risk group, we will also explore the utility of thyroid or laryngeal specific markers to augment the predictive power of frailty. In Aim 3, we hope to investigate the role of pre-operative interventions including tracheal traction exercises and voice therapy to reduce the incidence of impact of post-operative alterations. We will randomize patients to intervention or usual care and evaluate the frequency of alterations after thyroidectomy. This work represents an interdisciplinary approach to establish alterations in voice and swallowing that occur after thyroidectomy in older individuals, the impact of these changes on quality of life, and an attempt to reduce post-surgical disability. Findings from this study will inform the design of 2 future clinical trials aimed at 1) evaluating pre-operative interventions to reduce surgical disability after thyroidectomy and 2) creating a patient-reported outcome measurement tool specifically for older adults undergoing thyroidectomy.

7. 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 heterogeneous 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. Aim 1 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.

8. Project Title: PATIENT-CENTERED CARE FOR OLDER ADULTS WITH MULTIPLE CHRONIC CONDITIONS: RESEARCH AND MENTORING PROGRAM

**Leader(s): BOYD, CYNTHIA MELINDA
THE JOHNS HOPKINS UNIVERSITY
NIH K24AG056578 / (2017 - 2022)**

Core(s):

Project SummaryThe aims of this proposal are to 1) develop the candidate's capacity for research, leadership, and mentorshipthrough career development in clinical trials, building and leading national collaborations, and mentoring, 2) toexpand her mentorship of promising junior investigators in patient-oriented aging research, and 3) to pursue aninnovative research direction to develop and evaluate person-centered interventions to optimize medicationuse in older people with multiple chronic conditions that will serve as a platform to engage an expanding groupof mentees. The candidate, a geriatrician who practices in a primary care clinic, has established a nationally-and internationally-recognized, high impact, well-funded independent clinical research program with anoutstanding publication record. In the 14 years since completing her geriatrics fellowship, she has establishedherself as a successful mentor of trainees from all levels who have published high-impact research, obtainedfunding and necessary research skills, and continue to conduct patient-oriented research. The candidate hasdeveloped a robust research portfolio focused on patient-centered care for older adults, particularly those withmultiple chronic conditions. The candidate's work to date has been transformative both within aging and inother fields by shifting attention from a disease-specific approach to care to one that recognizes that most olderadults live with multiple chronic conditions. The candidate has a strong track record of research funding fromAHRQ, PCORI and the NIA to improve the generation and synthesis of evidence to better inform the care ofpeople with multiple chronic conditions, and to develop patient- and family-centered approaches to care ofolder adults with multiple chronic conditions. This proposal will provide the candidate with protected time toincrease her expertise, expand her mentoring program, and develop new research focused on optimalmedication prescribing to improve patient-centered outcomes for this population. The candidate will furtherdevelop a formal mentoring program for the engagement and development of high-caliber mentees who willserve as the next generation of leaders in patient-oriented research for aging populations. She will work witheach mentee to implement a focused career development plan in which they complete research projects anddevelop skills including grant and scientific writing, study design, and presentation skills necessary to besuccessful independent patient-oriented investigators. The outstanding environment for aging research andclinical research training at Johns Hopkins is fundamental to this proposal.

9. Project Title: IMPROVING CANCER SCREENING IN OLDER ADULTS WITH LIMITED LIFE EXPECTANCY

**Leader(s): SCHOENBORN, NANCY
THE JOHNS HOPKINS UNIVERSITY
NIH K76AG059984 / (2018 - 2022)**

Core(s):

PROJECT SUMMARYBackground: Cancer screening can lower cancer-related mortality and morbidity but may be associated with significant harms and burdens in older adults. There is often a lag-time of 10 years before patients screened for breast, colorectal, or prostate cancers actually benefit. On the other hand, multiple harms from screening can occur in the short-term. Older adults with limited life expectancy continue to receive cancer screening at high rates even though it exposes them to the harms of screening with little chance of benefit. Clinicians are a major driver of over-screening but why they often continue to recommend cancer screening in older adults with limited life expectancy is unknown. This proposal aims to improve the cancer screening of older adults by 1) identifying the factors that facilitate or hinder clinician recommendations to stop routine screening in older adults with limited life expectancy, and 2) better supporting clinicians to appropriately incorporate life expectancy in their screening recommendations. Research proposal: Aim 1 will use qualitative methods to understand the range of factors that facilitate or hinder clinicians from recommending screening cessation in older adults with limited life expectancy. Aim 2 will test these factors in a national physician survey to determine and quantify their effects on physicians' screening recommendations in older adults with limited life expectancy. Aim 3 will then develop and pilot test a novel multi-modal intervention to target the factors that significantly contribute to over-screening. The intervention will be developed with input from clinicians and older adults and will use multiple, overlapping strategies that may include decision support, communication coaching, and clinician feedback. Career development plan: The candidate is a geriatrician who has already demonstrated national and institutional leadership in research and a strong track record of academic scholarship with numerous high impact publications and early investigator grants. Her long-term career goal is to be a research leader focused on incorporating life expectancy to inform patient-centered, individualized preventive care decisions for older adults. She has laid out a comprehensive, feasible career development plan that will enable her to transition into an independent investigator and research leader. She proposes to learn new skills in decision support, clinical trial design, and implementation science, in addition to continued development of leadership skills. She has assembled an exemplary mentoring team with expertise in the subject area and the relevant research methods and works in a rich research environment with tremendous resources to support her development. Summary: The proposal addresses an important research gap and produces a novel intervention that may have major impact to improve the cancer screening of older adults. The results from this proposal will support a subsequent large-scale clinical trial to test the intervention. This proposal will also further foster the career development of the candidate into a research leader focused on individualized preventive care in older adults.

10. 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 are proposing 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 disparities research, with a focus on Alzheimer's disease and related disorders (ADRD), using a life course perspective encompassing biological, behavioral, and community factors contributing to cognitive impairment and dementia in older minority adults; (2) conduct epidemiological, preventive, and intervention research that addresses ADRD in later life within a multi-level framework that encompasses individuals, families, social networks, and communities; and (3) engage communities and health care providers especially family caregivers, primary care practices, communities of faith, and community organizations as our partners in recognizing dementia and developing interventions with the potential to prevent cognitive decline and reduce 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 an administrative structure, to support research, to foster interactions between Cores and other Centers, and to ensure RCMAR Scientists develop mentoring relationships across the affiliated departments, schools, the intramural program at NIA in Baltimore, and nationally; (2) a Research Education Component to foster diverse junior investigators and mid-career investigators transitioning into ADRD-relevant research through support for individual pilot projects, 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 increase knowledge of engagement of community members in the research enterprise with the creation of a Community Resource Institute as a venue for community-investigator interaction; and (4) an Analysis Core as a foundation for methodological and statistical mentoring, including education and mentoring in mixed-methods research. An Executive Committee includes community representatives and a Scientific Advisory Panel consists of distinguished investigators with relevant expertise in minority aging, disparities, and ADRD. A pilot project program supported by all Cores to facilitate the development of RCMAR Scientists includes three initial pilot projects focusing on recruitment of

minority populations for ADRD research, early diagnoses of dementia, and intervention development related to ADRD-related driving disparities.

11. 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.

12. Project Title: NEIGHBORHOODS, COGNITIVE AGING AND MODIFIABLE RISK FACTORS

**Leader(s): CARLSON, MICHELLE C
THE JOHNS HOPKINS UNIVERSITY
NIH R01AG055404 / (2018 - 2022)**

Core(s):

The role of modifiable risk factors (RF), like physical activity (PA), sleep quality, social engagement, and cardiovascular (CV) risk is receiving greater attention to promote the cognitive health of an aging population and reduce risk of Alzheimer's disease. Each of these risk factors is known to be influenced by environmental sources, such as neighborhood walkability, safety, noise, and access to low-cost transportation, retail, and healthy food sources. However, little is known about the role of neighborhood factors as drivers of cognitive aging and risk for Alzheimer's disease. If neighborhood matters, adaptations in the use of available infrastructures have the potential to impact thousands at a time. Those neighborhood factors that most impact individual RF and cognitive health to reduce Alzheimer's disease risk may further

differ by race and sex. Evaluating the role of neighborhood characteristics on cognitive health is difficult to interpret from more widely used cross-sectional data due to residual confounding. Therefore, investigating how residentially stable older adults are affected by their local stable and changing contexts and how older adults who relocate to a new neighborhood may respond to their new context by changing health behaviors requires long-term study during the last 1/3 of life years prior to the onset of Alzheimer's disease. The Cardiovascular Health Study (CHS) represents an ideal cohort for studying interactions between individual health and neighborhood risk factors for various reasons. First, participants were well characterized for key modifiable RF, above, as well as cognition, and mobility. Second, the cohort is nationally representative, bi-racial and spans socioeconomically diverse, urban and rural neighborhoods, allowing us to examine the relation between individual risk and variability in neighborhood factors. Third, our proposal seeks to address the research challenges and opportunities articulated in the NIA Health Disparities Research Framework by examining interactions between environment, biology and behavior. We hypothesize that long-term exposure to neighborhood disadvantage may serve as a common cause of individual risk factors and neurocognitive and functional health, particularly in socio-demographically at-risk groups. Specific aims are to characterize associations between long-term neighborhood exposures and: 1) individual rates of decline and impairment in cognition and physical function; 2) individual risk factors (PA, sleep quality, social engagement and CV burden) for Alzheimer's disease, which may mediate neighborhood differences in cognitive and functional risk, and; 3) whether specific neighborhood exposures account for racial and sex differences in cognitive and functional risk. Addressing these questions in the CHS provides an unmatched opportunity to examine the influence of a range of neighborhood factors on long-term trajectories of cognitive and functional aging prior to the onset of Alzheimer's disease. This work will inform future design of multi-level approaches to target those neighborhood factors impacting multiple RF to optimize healthful activity, reduce health disparities, and help adults remain active and age in place. 1

13. Project Title: AGING, COGNITION, AND HEARING EVALUATION IN ELDER (ACHIEVE) RANDOMIZED TRIAL

**Leader(s): LIN, FRANK R; CORESH, JOSEF ;
THE JOHNS HOPKINS UNIVERSITY
NIH R01AG055426 / (2017 - 2022)**

Core(s):

Novel approaches to reduce the risk of age-related cognitive decline, Alzheimer's disease (AD), and other dementias in older adults are urgently needed given the aging of the population. Epidemiologic studies demonstrate that peripheral hearing loss in older adults is strongly and independently associated with accelerated cognitive decline and incident dementia. Hypothesized mechanistic pathways underlying this observed association include the effects of poor hearing and distorted peripheral encoding of sound on cognitive load, brain structure/function, and/or reduced social engagement. Importantly, these pathways may be modifiable with comprehensive hearing loss treatment consisting of the use of hearing technologies (hearing aids, other integrated hearing assistive devices) and rehabilitative training. To date, however, there has never been a randomized trial that has investigated whether such therapies could reduce cognitive decline and the risk of Alzheimer's disease and other dementias in older adults. Over the past two years, we have developed the Aging, Cognition, and Hearing Evaluation in Elders (ACHIEVE) randomized trial. The ACHIEVE trial will recruit 750 70-84 year-old cognitively-normal older adults with hearing loss who will be randomized 1:1 to the hearing intervention (hearing needs assessment, fitting of hearing devices, education/counseling) or control intervention (individualized successful aging education sessions with a health educator covering healthy aging topics). The trial will be powered to detect a minimum of a 0.30 standard deviation (SD) difference in the annual rate of cognitive decline between the hearing intervention and the successful aging intervention arms over a 3-year follow-up period. The ACHIEVE study brings together a multidisciplinary group of investigators and leverages the existing research infrastructure, scientific expertise, and well-characterized participant cohort of the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). The ACHIEVE trial has the following aims: Aim 1 To determine the effect of hearing rehabilitative intervention versus a successful aging control intervention on rates of cognitive decline (primary outcome measure) in 70-84 year-old cognitively-normal older adults with hearing loss. Aim 2 To determine the effect of hearing rehabilitative intervention versus a successful aging control intervention on secondary outcome measures of adjudicated incident dementia, physical and social functioning, health-related quality of life, and physical activity. Secondary Aims: 1) To investigate whether hearing rehabilitative intervention alters established trajectories of cognitive decline in participants recruited from ARIC-NCS. 2) To investigate the effect of hearing rehabilitative intervention on rates of cognitive decline in persons with Alzheimer's disease risk factors and biomarkers. Given that nearly two-thirds of all adults 70 years and older have a clinically-significant hearing loss, conducting the ACHIEVE study to determine if existing hearing rehabilitative interventions can reduce the rate of cognitive decline in older adults is of substantial public health importance.

14. Project Title: ESRD-SPECIFIC PHYSIOLOGIC RESERVE: IMPROVING GERIATRIC TRANSPLANT PROGNOSTICATION - DIVERSITY SUPPLEMENT

**Leader(s): MCADAMS DEMARCO, MARA A.
THE JOHNS HOPKINS UNIVERSITY
NIH R01AG055781 / (2017 - 2022)**

Core(s):

Older adults with end stage renal disease (ESRD) who receive kidney transplantation (KT) double their life expectancy. The new kidney allocation system, designed to better match longevity of recipients and allografts, has been in effect for 2 years. During this time, access to KT among older adults has plummeted; with rates declining 10% for candidates aged 61-70 and 24% for those aged >70. The core problem is that the United Network for Organ Sharing (UNOS) decided that longevity matching for the new allocation system would be based on Estimated Post-Transplant Survival (EPTS), a simple model that only includes chronologic age, diabetes, time on dialysis, and prior transplant. EPTS has poor predictive power among older recipients; the c-statistic of EPTS for older recipients is 0.59, which is lower than the c-statistic of 0.67 for younger recipients. We hypothesize that a measure of physiologic reserve will more accurately stratify risk among older KT recipients than chronologic age. Our preliminary work suggests that the Fried frailty phenotype, is associated with poor post-KT outcomes. While our findings are encouraging, it is unlikely that this construct captures all the dimensions of physiologic reserve associated with ESRD. It is likely that some attributes of the Fried frailty phenotype are not even relevant for this population. We believe an ESRD-specific measure of physiologic reserve, beyond frailty and/or other conventional measures, would greatly improve risk stratification. UNOS and the transplant community might be reluctant to add a new variable to the purposefully parsimonious EPTS score, which was debated for 15 years. Our novel approach, supported by the upcoming UNOS president, is to replace chronologic age with physiologic age in the model. The overarching goal of our research will be to develop a physiologic age calculator and test whether replacing chronologic age with physiologic age improves prognostication for older adults with ESRD. To achieve these goals, we will leverage existing data and collect new data within an ongoing longitudinal cohort study of 5,500 ESRD patients. We will abstract new data on components of physiologic reserve from the parent study and enroll an additional 2,342 new ESRD patients in an ancillary study which will directly measure the physiologic reserve components that cannot be abstracted. We will test the following aims: 1) To elicit and evaluate novel constructs that might quantify physiologic reserve in older ESRD patients; 2) To create a valid, reliable, and generalizable measure of physiologic reserve for ESRD patients; 3) To test if replacing chronologic age with physiologic age improves prognostication in older recipients. This work would improve prognostication for older adults with ESRD, which would benefit patient selection, informed consent, and case-mix adjusted transplant center report cards. Our novel approach to replacing chronologic age with physiologic age has the support of UNOS leadership and could have an immediate impact on organ allocation and prioritization, possibly improving access for older KT candidates.

15. 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 summary This 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 association between baseline vestibular function and 2-year incidence of falls. We will also explore whether vestibular function is associated with balance and gait function, as well as spatial cognitive function, as potential mechanisms by which vestibular function contributes to fall risk. Specifically, Aim 1 is to determine whether vestibular loss predicts falls in patients with mild-moderate AD. We hypothesize that poorer vestibular function at baseline predicts a higher 2-year incidence of falls. Additionally, we hypothesize that the attributable risk of falls associated with vestibular loss will be substantial enough (>~10%) to warrant further investigation of vestibular therapy as a clinically significant modifier of fall risk. Aim 2 is to evaluate whether vestibular loss in AD predicts impaired static and dynamic balance, measured using the Berg Balance Scale (BBS) and the Timed-Up-and-Go (TUG) test. We hypothesize that greater reduction in vestibular 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 will administer cognitive tests of spatial cognition (including the Money Road Map test, the Card Rotation test, the Visual Form Discrimination test and the Clock Drawing test), and we will also query participants and caregivers about difficulty with driving, losing objects, getting lost and wandering behaviors as functional manifestations of impaired spatial cognition in AD patients. We hypothesize that greater reduction in vestibular function over the 2-year follow-up period predicts greater decline in spatial cognitive test scores, and a higher incidence of functional spatial cognitive impairment. Moreover, we hypothesize that impaired balance measures (from Aim 2) and impaired spatial cognitive skills will both be independent mediators of the association between vestibular loss and incident falls. To accomplish these aims, we will leverage well-established resources at Johns Hopkins including the Johns Hopkins Alzheimer's Disease Research Center and the Memory and Alzheimer's Treatment Center. Falls are a major source of morbidity in AD and current interventions are not uniformly effective. If our observational studies demonstrate 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.

16. 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/ABSTRACT With effective antiretroviral therapy (ART), life expectancy for HIV-infected persons has markedly improved, yet marked deficits in survival remain for HIV-infected persons with a history of injecting drugs (PWID). Disparities among PWID have been attributed in part to a shifting spectrum of disease to aging-associated conditions driven by persistent inflammation even with ART. Frailty is an important aging-related state of vulnerability to stress, with an increased burden in HIV infection, strongly associated with heightened inflammation, and predictive of premature mortality and aging-related morbidity among PWID. Injecting drugs itself can increase the severity of inflammation in HIV. The human gut microbial ecosystem (gut microbiome) critically regulates inflammation and immunity. Alterations in the gut microbiome (gut dysbiosis) together with associated disruptions of gut structure and immune integrity constitute an inflammatory-microbiome signature (gut dysbiosis, increased gut permeability, translocation of microbial products, immune activation, heightened inflammation) linked to adverse aging-associated inflammatory conditions and disease. Proposed is a systematic 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 of the 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 and active IDU alter microbiome composition and function and the relationship of these changes to inflammation and frailty progression over time. Using a germ free murine model, we will further define the frail human microbial communities and gene products that precipitate inflammation. These studies will facilitate elucidation of gut microbial determinants of frailty among HIV-infected PWID and could significantly inform microbiota modulation strategies to reduce frailty-associated inflammation beyond ART. Understanding the role of the gut microbiome in relation to HIV, injection drug use, and frailty remains a critical next step to reducing the marked disparities in clinical outcomes among HIV-infected PWID.

17. 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 SUMMARY Alzheimer's disease (AD) is the most common cause of dementia. Underlying pathological and physiological changes related to the onset and progression of AD are believed to emerge several years prior to clinical manifestations. Sensory impairments, gait abnormalities, and motor slowing may precede the diagnosis of AD by a decade or more, presenting the exciting possibility that changes in sensorimotor functioning may act as early noninvasive biomarkers for AD. Previous work by our group has identified links between cognitive performance and sensory impairment and gait speed and variability, making them potential preclinical markers of early AD pathology. We propose to use up to 10 years of existing longitudinal data, and ongoing/new data collection in approximately 1,000 older adults in the Baltimore Longitudinal Study of Aging (BLSA), to examine the 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 and biomarkers of AD pathology, including A deposition using [¹¹C]-Pittsburgh compound B positron emission tomography, brain atrophy using structural magnetic resonance imaging (MRI), Tau and pTau from cerebrospinal fluid, and cognitive performance. We will further utilize the rich data resources of the BLSA to develop a parsimonious prediction model for risk of progression to MCI/AD, and validate its performance in the Atherosclerosis Risk in Communities (ARIC) study. A better understanding of the associations among sensorimotor changes, subclinical AD pathology, and cognitive performance may elucidate a high-risk phenotype that is associated with increased risk of poor cognitive outcomes over time and increase our understanding of the 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 phenotype reflective 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 by identifying critical threshold(s) for implementation of assistive and rehabilitative technologies such as hearing aids, 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 to correct gait abnormalities.

18. 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 experience accelerated functional decline (decreased strength, slowed gait, reduced exercise tolerance) and increased frailty, as compared to non-infected individuals. The syndromes of functional decline and frailty are associated with impaired quality of life, increased vulnerability to superimposed stresses, and the likelihood of premature morbidity and mortality. The mechanisms underlying this accelerated dysfunction and disability, however, are poorly 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 pilot clinical 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 decreased performance in older PLWH individuals. However the extent, underlying responsible factors, and functional significance of altered SM mitochondrial bioenergetics in this population have not been characterized. In addition, two potential mechanisms responsible for altered SM high energy phosphate metabolism in other populations, increased inflammation and SM lipid accumulation, have not been examined and related to muscle energetics in PLWH and so these too will be examined. The central hypothesis is that impaired SM mitochondrial energy metabolism, initiated by aging and accelerated in the setting of contemporary HIV, is a central contributor to the geriatric syndromes of fatigue, exercise intolerance, and frailty in older PLWH. We propose to use state-of-the art ³¹P MRS exercise testing, detailed muscle and whole body composition measures, functional assessments during observed and free-living conditions, and biomarkers of inflammation and immune activation in 200 older (age ≥ 60) women and men derived from four local NIH-sponsored cohorts to address these questions. The specific aims are 1) to define the scope of SM metabolic changes in older women and men living with HIV, 2) to probe whether inflammation, skeletal fat and other underlying factors are related to the energetic abnormalities in older PLWH and 3) to determine the functional significance of SM energetic changes in older PLWH by examining the relationships between the energetic changes and exercise tolerance and other functional assessments as well as the frailty phenotype. Fatigue, exercise intolerance, and frailty 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 or reverse mitochondrial and bioenergetic decline and thereby reduce the personal and societal toll of these geriatric conditions in older women and men living with HIV.

19. Project Title: HEMODIALYSIS-BASED INTERVENTIONS TO PRESERVE COGNITIVE FUNCTION

**Leader(s): MCADAMS DEMARCO, MARA A.
THE JOHNS HOPKINS UNIVERSITY
NIH R01DK114074 / (2018 - 2022)**

Core(s):

ABSTRACT Over 640,000 US adults suffer from ESRD, >95% of whom receive hemodialysis (HD) for the rest of their life until transplantation. Kidney disease and HD significantly impact cognitive function, especially higher-order executive function. Only 13% of HD patients have normal cognition; HD patients experience executive function impairment at a rate 3-fold higher than the general population, leading to hospitalization, disability, and death. Studies of older adults suggest that the only effective interventions for preserving executive function are cognitive training (CT) and/or exercise training (ET). These modalities have not been tested for executive function preservation in HD patients; even younger HD patients suffer substantial executive function impairment and could benefit from these interventions. HD frequency (3 sessions a week) and duration (4-6 hours/session) makes HD patients a captive audience for intradialytic CT and/or ET to mitigate executive function decline. In preliminary studies, HD patients reported spending most of their time watching TV; intradialytic CT and/or ET could replace these passive activities. In preliminary studies, 87% of nephrology providers believed that their patients would be interested in intradialytic CT and 83% believed that their patients would be interested in intradialytic ET. Among HD patients, 67% wanted to improve their cognition through CT and 71% wanted to improve their strength and cognition through ET while undergoing HD. To test the feasibility of intradialytic interventions, we conducted a pilot RCT of 20 HD patients, comparing standard of care to CT or ET; even in this pilot, we found that intradialytic CT and ET preserved executive function. As expected, executive function in patients receiving standard of care declined substantially by 3 months (difference=47.4 seconds, P=0.006); however, this decline was not seen among those receiving CT or ET. Compared with standard of care, the difference in mean change was -46.72 seconds (95% CI: -91.12, -2.31; P=0.04) for CT and -56.21 seconds (95% CI: -105.86, -6.56; P=0.03) for ET. In just 3 months, CT and ET preserved executive function compared to a striking decline with standard of care. To properly test the impact of intradialytic CT and/or ET, on the executive function decline associated with HD, we propose the following aims: 1) To conduct an RCT to evaluate executive function decline in the setting of intradialytic CT and/or ET, 2) To quantify the effects of intradialytic CT and/or ET on ESRD-specific clinical outcomes, 3) To quantify the effects of intradialytic CT and/or ET, on patient-centered outcomes. Through this RCT, we will learn the impact of two potential non-pharmacological interventions, cognitive and exercise training, in preserving executive function during HD. If successful, this will improve HD outcomes of >640,000 adults with ESRD. For the first time, we will have validated, beneficial activities replace the typical passive activities of HD patients. Our findings will be implementable in dialysis centers across the country to help reduce the decline in executive function.

20. Project Title: DEVELOPING PERSONALIZED IMMUNOSUPPRESSION FOR OLDER KIDNEY TRANSPLANT RECIPIENTS

**Leader(s): MCADAMS DEMARCO, MARA A.
THE JOHNS HOPKINS UNIVERSITY
NIH R01DK120518 / (2018 - 2022)**

Core(s):

ABSTRACT >400,000 older adults (age =55) suffer from end-stage renal disease (ESRD). There has been a 5-fold increase in the number of kidney transplants (KT) in this age group. Older recipients are a distinct group due to impaired homeostasis, higher comorbidity burden, and immune system attenuation. These physiologic factors influence older KT recipients response to immunosuppression (IS) medications, a lifelong treatment. The balance between short-term benefits and long-term adverse outcomes of IS can be challenging in older KT recipients. Excellent short-term outcomes (1-year allograft survival >95% and acute rejection [AR] 78,800 older KT recipients KT recipients (2005-2019): (1) national data from the Scientific Registry of Transplant Recipients (SRTR); (2) Medicare claims to identify post-KT outcomes and costs; (3) pharmacy claims to identify not only IS agents used but also novel lab data of metabolized IS levels (for 14,000 older recipients). Using this integrated data, we will: 1) compare the effects of IS regimens on efficacy, morbidity, and mortality for older KT recipients; 2) develop Markov models and calculate cost-effectiveness for IS regimens for older KT recipients; and 3) generate individualized reports of predicted efficacy, morbidity, and mortality along with IS regimen cost

for practitioners to use for the clinical counseling of older KT recipients. Our goal is to provide evidence and communication tools to help move the field of transplantation away from center-based protocols for IS to personalized IS for older KT recipients. The ability to predict trade-offs in AR and graft survival against long-term adverse outcomes for specific IS regimens in older KT recipients will allow patients and physicians to customize IS choices in a cost-effective and more informed manner.!

**21. Project Title: REPRODUCTIVE RISK FACTORS FOR ALZHEIMER'S DISEASE
DEMENTIA AND PATHOLOGY**

**Leader(s): MIELKE, MICHELLE M
MAYO CLINIC
NIH RF1AG055151 / (2017 - 2022)**

Core(s):

PROJECT SUMMARY/ABSTRACT Recent estimates suggest that almost two-thirds of the individuals diagnosed with Alzheimer's disease [AD] are women. The National Institutes of Health and the Alzheimer's Association have highlighted the critical need to understand sex differences in the risk factors and clinical progression of AD. Reproductive and hormonal factors may be particularly important for women. Hypertensive pregnancy disorders [HPD] have been associated with subjective cognitive complaints or white matter lesions five to ten years after the HPD, but the long-term effects of HPD on brain structure and cognitive function are unknown. Population-based studies are needed to assess the contribution of HPD and subtype (i.e., preeclampsia) to the risk of cognitive decline, AD, and neuroimaging measures of amyloid-beta [A β], neurodegeneration, and cerebrovascular pathologies. Further, observational studies and clinical trials have examined the effects of early menopause (natural or surgically-induced) and hormonal therapy [HT] on the risk of AD and other dementias. However, it is not currently known whether the effects of early menopause, HT use, and their interactions with APOE genotype, are associated with specific type(s) of brain pathology (i.e., A β , neurodegeneration, cerebrovascular) because multi-modal imaging studies have not been conducted. The overall aims of this proposal are to elucidate the impact of two hormonally-related sex-specific factors for women, pregnancy (e.g., number of pregnancies, HPD) and menopause (surgically-induced or natural), on the risk of cognitive decline, AD, and neuroimaging measures of A β , neurodegeneration, and cerebrovascular pathologies. Because the literature and our preliminary data suggest that risk scores for cardiovascular disease and dementia are less predictive in women compared to men, we also propose to incorporate these sex-specific factors to develop a more predictive risk score of mild cognitive impairment and AD for women. To accomplish our goals, we will utilize two existing infrastructures at the Mayo Clinic: the Mayo Clinic Study of Aging (MCSA; U01 AG006786) and the Rochester Epidemiology Project medical records-linkage system (REP; R01 AG034676). Using the REP, we will newly abstract information on pregnancy and menopause for 2,370 women enrolled in the MCSA. Because few studies assessing pregnancy and menopause have also adjusted for putative confounding variables, we will also abstract this data using the REP to determine whether these sex-specific conditions are independent predictors of cognitive decline, AD, and neuroimaging measures of specific brain pathologies. Successful completion of these aims will be a key step towards understanding whether these sex-specific factors are associated with the risk of AD in women, to understanding whether these factors are related to a specific type of brain pathology (i.e., A β , neurodegeneration, cerebrovascular), and to developing a better risk score for predicting cognitive impairment, dementia, and specific brain changes in women.

**22. Project Title: ENERGY RESERVES, PHYSICAL ACTIVITY, AND ALZHEIMER'S
DISEASE IN THE BALTIMORE LONGITUDINAL STUDY OF
AGING**

**Leader(s): SCHRACK, JENNIFER ANN
THE JOHNS HOPKINS UNIVERSITY
NIH U01AG057545 / (2017 - 2022)**

Core(s):

PROJECT SUMMARY Alzheimer's disease (AD) is the most common cause of dementia. Underlying pathological and physiological changes related to the onset and progression of AD are believed to emerge several years prior to clinical manifestations. Gait abnormalities and motor slowing typically precede the diagnosis of AD by a decade or more, presenting the exciting possibility that changes in gait may act as early noninvasive biomarkers for AD. Previous work by our group has identified key markers of impending and/or accelerated gait speed decline based on physiological measures of the energy cost of slow walking, peak energy capacity, and quantities and patterns of objectively measured free-living physical activity (PA), making them potential preclinical markers of early AD pathology. We propose to use 8 years of existing longitudinal data, and ongoing/new data collection in nearly 1,000 older adults in the Baltimore Longitudinal Study of Aging (BLSA), to examine the roles of altered energy reserves, and reduced and fragmented daily PA as precursors to clinical markers of Alzheimer's disease and neuronal injury, which include A β deposition using [^{11}C]-Pittsburgh compound B positron emission tomography, brain atrophy using structural magnetic resonance imaging (MRI), and cognitive performance. We will also explore potential vascular mechanisms linking energy reserves and PA to these outcomes, including cerebral blood flow, ankle brachial index, and pulse wave velocity, as well as the role of mediating or modifying factors such as inflammation and the apolipoprotein E genotype. The BLSA is a continuously enrolled cohort study of aging that already contains repeated measures of cognition and adjudication of cognitive status, in which a subset completes repeated MRI and PiB PET scans. Importantly, our preliminary cross-sectional data from the BLSA indicate strong associations among energy reserves, cognitive performance, b-amyloid burden, and diurnal patterns of daily PA. We propose to investigate the longitudinal associations among these variables to identify physiological thresholds of poor energy reserve and reduced and fragmented patterns of diurnal PA as early precursors to the onset and progression of AD pathology. A better understanding of the association between energy reserves/PA, subclinical AD pathology, and cognitive performance may elucidate a physiological threshold of diminished energy reserve that is associated with increased risk of poor cognitive outcomes over time, and increase our understanding of the complex association between declines in physical and cognitive functioning with age. Moreover, uncovering patterns of daily free-living PA most commonly associated with this threshold will help define a phenotype of reduced and/or fragmented PA that signifies impending emergence and progression of AD. Given the proliferation of wearable devices to monitor PA in the consumer and research markets, identifying changes in PA consistent with the development of AD pathology could provide evidence for future wide-scale screening for early detection of persons at high risk of AD.

23. 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):

Abstract Alterations in the nuclear protein lamin and associated structures in the nucleus have been identified as a source of nuclear morphology changes that markedly impact overall cellular function. These changes in nuclear morphology are thought to drive molecular changes that influence a wide range of aging-related phenotypes and chronic disease states. Importantly, we have recently used high-throughput measurements of nuclear morphology to identify outstanding biomarkers of chronological age. We hypothesize that these age-related changes in nuclear morphology are highly correlated with chronological age in healthy individuals, and that a specific age-related biological change in lamin underlies this phenomenon. Building on our prior development of these high-throughput and accurate measures of nuclear morphology, we propose here to further develop this biological discovery and technology as a valid and reliable biomarker of aging-related biological mechanisms. We hypothesize that changes in nuclear morphology can be rapidly measured and that age-related alterations correlate with aging-related phenotypes and disease states independently of chronological age, consistent with a measure of cellular biological age. To test these hypotheses and move results toward clinical utility, we have assembled a highly synergistic, interdisciplinary team propose the following specific aims: Aim 1. Using our validated single-cell technologies, we will develop a mechanistic understanding of how descriptors of nuclear morphology in human dermal fibroblasts and B-lymphocytes are robust biomarkers of aging in healthy individuals. Aim 2. Establish the accuracy and precision with which our proposed biomarkers identify chronological age for individuals with varying demographic, behavioral, and health characteristics. Aim 3. We will examine the strength with which morphological biomarkers discriminate individuals with adverse phenotypes and outcomes of aging, and at risk for the development of these, from healthy older adults, above and beyond chronological age.

24. 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.

25. Project Title: CHARACTERIZING RESILIENCIES TO PHYSICAL STRESSORS IN OLDER ADULTS: A DYNAMICAL PHYSIOLOGICAL SYSTEMS APPROACH

**Leader(s): WALSTON, JEREMY DAVID; BANDEEN-ROCHE, KAREN J. ;
VARADHAN, RAVI ;
THE JOHNS HOPKINS UNIVERSITY
NIH UH3AG056933 / (2019 - 2022)**

Core(s):

Project SummaryWhen confronted with a major physical stressor, some older adults are able to recover, with minimal decline,their physical and cognitive function, while others suffer precipitous, irreversible declines in function. This is thecentral notion behind resiliency. Little is known about the intrinsic (e.g., physiologic and molecular processes)and extrinsic (e.g., health behaviors) factors that impact resiliency. A two-phase study is proposed here toaddress this gap in our understanding. In phase 1, data will be generated to characterize age-related changesin physical resiliencies, their determinants, and their outcomes. Phase 2 will involve construction and validationof measures of resiliency; assessment of their predictive and clinical value; and investigation of age-relatedbiological mechanisms determining specific resiliencies.Phase 1 Specific Aims:1. To define, develop and refine phenotypic measures of resiliency responses to three pre-defined physical stressors: hip replacement surgery, initiation of hemodialysis, and bone marrow transplantation for hematologic malignancy.2. To develop and pilot test candidate indicators of physical resiliency to include static and dynamic, as well as global and stressor-specific, measures.3. To identify pre-stressor determinants of resilience, including measures of disease states, psychosocial factors, and molecular measures, and to characterize their measurement and statistical properties.4. To synthesize data developed in Aims 1-3 to inform the design of Phase 2 studies.Phase 2 Specific

Aims:1. For each of clinical stressor to be studied: To build and evaluate assessments of resiliency incorporating measures identified in phase 1. Promising candidate measures will be cross-validated and their accuracy in predicting short- and long-term resilient stressor response rigorously characterized. The relative predictive value of global vs. specific, static vs. dynamic, and solely EHR-based versus broader resiliency measures will be assessed.2. To characterize and assess age-related biological mechanisms that contribute to resilience or lack thereof that are specific to each clinical stressor, as well as mechanisms that are common across three specific physical stressors in older adults.3. In preparation for the conduct of intervention studies: to cross-validate measures of resiliency at an external institution and to design pilot studies of strategies to bolster resiliencies based on clinical findings and biological mechanisms identified in Phase 1.

PUBLICATIONS

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1. **Telomere shortening and the transition to family caregiving in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study.**
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<https://doi.org/10.1371/journal.pone.0268689> | PMID: 35657918 | PMCID: PMC9165822
Citations: | AltScore: NA
2. **The effects of vitamin D supplementation on frailty in older adults at risk for falls.**
Cai Y, Wanigatunga AA, Mitchell CM, Urbanek JK, Miller ER 3rd, Juraschek SP, Michos ED, Kalyani RR, Roth DL, Appel LJ, Schrack JA
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3. **Moving toward clinical implementation of the physical frailty phenotype in kidney transplantation.**
Chen X, Shafaat O, Liu Y, King EA, Weiss CR, Xue QL, Walston JD, Segev DL, DeMarco MA
Am J Transplant, 2022 Apr 29
<https://doi.org/10.1111/ajt.17080> | PMID: 35486021
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4. **Revision of frailty assessment in kidney transplant recipients: Replacing unintentional weight loss with CT-assessed sarcopenia in the physical frailty phenotype.**
Chen X, Shafaat O, Liu Y, King EA, Weiss CR, Xue QL, Walston JD, Segev DL, McAdams-DeMarco MA
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5. **Long-term Trajectories of Frailty and its Components after Kidney Transplantation.**
Chu NM, Ruck J, Chen X, Xue QL, Norman SP, Segev DL, McAdams-DeMarco MA
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[pii: glac051. https://doi.org/10.1093/gerona/glac051](https://doi.org/10.1093/gerona/glac051) | PMID: 35184167
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6. **New horizons in evidence-based care for older people: individual participant data meta-analysis.**
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7. **Higher Angiotensin II Type 1 Receptor Levels and Activity in the Postmortem Brains of Older Persons with Alzheimer's Dementia.**
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Salib J, Oh ES, Ferrucci L, Dincer P, Bennett DA, Walston JD, Abadir PM
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8. **The Influence of Frailty on Cardiovascular Disease: The Time for a Frailty Academic Research Consortium Is Now!**

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11. **Genome-Wide Analysis in *Drosophila* Reveals the Genetic Basis of Variation in Age-Specific Physical Performance and Response to ACE Inhibition.**

Gabrawy MM, Khosravian N, Morcos GS, Morozova TV, Jezek M, Walston JD, Huang W, Abadir PM, Leips J
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13. **Interventions for Frailty Among Older Adults With Cardiovascular Disease: JACC?State-of-the-Art Review.**

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15. **Serum concentrations of losartan metabolites correlate with improved physical function in a pilot study of prefrail older adults.**

Lee JL, Zhang C, Westbrook R, Gabrawy MM, Nidadavolu L, Yang H, Marx R, Wu Y, Anders NM, Ma L, Bichara MD, Kwak MJ, Buta B, Khadeer M, Yenokyan G, Tian J, Xue QL, Siragy HM, Carey RM, de Cabo R, Ferrucci L, Moaddel R, Rudek MA, Le A, Walston JD, Abadir PM

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21. **Cardiogenic Shock From Heart Failure Versus Acute Myocardial Infarction: Clinical Characteristics, Hospital Course, and 1-Year Outcomes.**

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, Psocka MA, Raja A, Shah P, Sherwood MW, Singh R, Tang D, Young KD, Welch T, O'Connor CM, Batchelor WB

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Tehrani BN, Damluji AA, Batchelor WB

Curr Cardiol Rev, 2022, 18(2): 15-30

<https://doi.org/10.2174/1573403X1766621125090929> | PMID: 34823461

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23. **Association of Frailty Status and Dietary Patterns in a Nationally Representative Sample of United States Adults with Olfactory Dysfunction.**

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3. **Visual Impairment and Objectively Measured Physical Activity in Middle-Aged and Older Adults.**

Cai Y, Schrack JA, Wang H, E JY, Wanigatunga AA, Agrawal Y, Urbanek JK, Simonsick EM, Ferrucci L, Swenor BK

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<https://doi.org/10.1161/CIRCULATIONAHA.121.055891> | PMID: 34133885 | PMCID:

PMC8340723

Citations: 88 | AltScore: 731.22

30. **Abernethy Malformation with Massively Dilated Main Pulmonary Artery Manifesting as Acute Myocardial Infarction.**

Rout A, Chongthammakun V, Siegel YJ, Mendoza D, Damluji AA

J Cardiovasc Imaging, 2021 Oct, 29(4): 379-381

<https://doi.org/10.4250/jcvi.2021.0011> | PMID: 34080337 | PMCID: PMC8592679

Citations: | AltScore: NA

31. **Understanding surgical decision-making in older adults with differentiated thyroid cancer: A discrete choice experiment.**

Sutton W, Genberg B, Prescott JD, Segev DL, Zeiger MA, Bandeen-Roche K, Mathur A

Surgery, 2021 Jan, 169(1): 14-21

<https://doi.org/10.1016/j.surg.2020.03.022> | PMID: 32475718 | PMCID: PMC7704531

Citations: 1 | AltScore: 16.35

32. **Transradial access in acute myocardial infarction complicated by cardiogenic shock: Stratified analysis by shock severity.**

Tehrani BN, Damluji AA, Sherwood MW, Rosner C, Truesdell AG, Epps KC, Howard E, Barnett SD, Raja A, deFilippi CR, Murphy CE, O'Connor CM, Batchelor WB

Catheter Cardiovasc Interv, 2021 Jun 1, 97(7): 1354-1366

<https://doi.org/10.1002/ccd.29098> | PMID: 32744434 | PMCID: PMC8165635

Citations: 1 | AltScore: 1.5

33. **Objectively measured patterns of daily physical activity and phenotypic frailty.**

Wanigatunga AA, Cai Y, Urbanek JK, Mitchell CM, Roth DL, Miller ER, Michos ED, Juraschek SP, Walston J, Xue QL, Appel LJ, Schrack JA

J Gerontol A Biol Sci Med Sci, 2021 Sep 25

[pii: glab278. https://doi.org/10.1093/gerona/glab278](https://doi.org/10.1093/gerona/glab278) | PMID: 34562073

Citations: | AltScore: 12.55

34. **The effects of vitamin D supplementation on types of falls.**

Wanigatunga AA, Sternberg AL, Blackford AL, Cai Y, Mitchell CM, Roth DL, Miller ER 3rd, Szanton SL, Juraschek SP, Michos ED, Schrack JA, Appel LJ, STURDY Collaborative Research Group.

J Am Geriatr Soc, 2021 Jun 12, 69(10): 2851-2864

<https://doi.org/10.1111/jgs.17290> | PMID: 34118059 | PMCID: PMC8497407

Citations: 2 | AltScore: 49.9

35. Association Between Brain Volumes and Patterns of Physical Activity in Community-Dwelling Older Adults.

Wanigatunga AA, Wang H, An Y, Simonsick EM, Tian Q, Davatzikos C, Urbanek JK, Zipunnikov V, Spira AP, Ferrucci L, Resnick SM, Schrack JA

J Gerontol A Biol Sci Med Sci, 2021 Jul 13, 76(8): 1504-1511

<https://doi.org/10.1093/gerona/glaa294> | PMID: 33230557 | PMCID: PMC8495900

Citations: 2 | AltScore: 11.2

36. Plasma metabolites associated with chronic kidney disease and renal function in adults from the Baltimore Longitudinal Study of Aging.

Yamaguchi Y, Zampino M, Moaddel R, Chen TK, Tian Q, Ferrucci L, Semba RD

Metabolomics, 2021 Jan 11, 17(1): 9

<https://doi.org/10.1007/s11306-020-01762-3> | PMID: 33428023 | PMCID: PMC9220986

Citations: 4 | AltScore: 1.5

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 (19 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 (19 years)

Joan E. Bailey-Wilson, Ph.D.

Head, Statistical Genetics Section; Co-Branch Chief, Inherited Disease Research Branch; National Human Genome Research Institute; National Institutes of Health
Serving since 2008 (14 years)

Gerald Beck, Ph.D.

Section Head, Clinical Trials; Design and Analysis, Department of Quantitative Health Sciences, Cleveland Clinic Foundation
Serving since 2013 (9 years)

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 (9 years)

RECOGNITION AND AWARDS (2021-2022)

Recognition and Awards not specified.

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 healthy ageing.
- 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

Minority Grant(s):

UNIVERSITY OF MARYLAND
Claude D. Pepper Older Americans Independence Center

Jay Magaziner, Ph.D., M.S.Hyg MPI	410-706-3553	jmagazin@som.umaryland.edu
Alice Ryan, Ph.D. MPI	410-605-7851	aryan@som.umaryland.edu
Les Katzel, M.D., Ph.D. MPI	410-605-7248	lkatzel@som.umaryland.edu
Anne Sullens, M.A Program Administrator	410-706-1695	asullens@som.umaryland.edu

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)

Leader 1: Jay Magaziner, PhD, MS Hyg. jmagazin@som.umaryland.edu

Leader 2: Leslie I. Katzel, MD lkatzel@som.umaryland.edu

Leader 3: 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)

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

Leader 2: 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)

Leader 1: Stephen Seliger, MD, MS sseliger@som.umaryland.edu

Leader 2: 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

Leader 1: Alice Ryan, PhD aryan@som.umaryland.edu

Leader 2: Leslie I. Katzel, MD lkatzel@som.umaryland.edu

Leader 3: 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

Leader 1: John D. Sorkin, MD, PhD jsorkin@som.umaryland.edu

Leader 2: 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.

Neuromotor Mechanisms and Rehabilitation

Leader 1: Richard Macko, MD rmacko@som.umaryland.edu

Leader 2: Li-Qun (Larry) Zhang, PhD l-zhang@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. The aims of RC-3 are as follows: 1) develop and support mechanistic investigations of physical activity and exercise-mediated central and peripheral neuromuscular adaptations that underlie the neuroplastic mediated improvements in functional performance produced by rehabilitative interventions and enabling technologies; 2) mentor and support REC Scholars and UM-OAIC researchers in the design, development and implementation of motor learning-based rehabilitation studies and enabling technologies and the underlying neuromuscular mechanisms to improve functional outcomes in older persons with functional limitations and 3) facilitate translation of UM-OAIC discoveries across the mechanistic, rehabilitation engineering, applied clinical testing, and technology transfer phases in order to catalyze transition of discoveries into evidence-based services, products, and tools for precision rehabilitation.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time

**Years /
Publications**

Jeanine Ursitti, PhD

Assistant Professor / Department of Orthopaedics

Cell Mechanics as a Biomarker of Osteosarcopenia”

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

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

Andrea Levine, MD

Assistant Professor / Department of Medicine

The Longevity of ARDS Inflammatory Subphenotypes and Their Role in Predicting Functional Recovery in Older Adults

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.

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

Sarasijhaa Desikan, MD

Assistant Professor / Department of Surgery, University of Maryland School of Medicine

2020-2023 /

10 (total)

2 (1st/Sr)

Asymptomatic Carotid Stenosis: Cognitive and Mobility Function after Exercise (ACCOF-Ex)

The purpose of her study is to determine the effect of a challenging aerobic and balance exercise intervention on cognitive and mobility function in patients with moderate (50-69%) asymptomatic carotid artery stenosis. In addition, the study evaluates functional near-infrared spectroscopy (fNIRS) as a novel modality to assess cerebral oxygenation during cognitive and mobility tasks.

- Asymptomatic Carotid Stenosis: Cognitive Function and Plaque Correlates- Exercise Intervention. University of Maryland Institute for Clinical and Translational Research Voucher Support Grant, Desikan (PI). 1/2020-1/2021. \$5,000
- Asymptomatic Carotid Stenosis and Mobility Function with Exercise Intervention. RR&D CDA-2. Desikan (PI). 10/2022-09/2027. \$2,029,681

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)

Jason Falvey, PT, DPT, PhD, Department of Physical Therapy and Rehabilitation Science (2021-2021)

PILOT/EXPLORATORY PROJECTS (10 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: Immune mechanisms responsible for the impaired B cell responses to new antigens in the elderly**Leader: Franklin Toapanta, PhD**

Abstract: Development of humoral responses to new antigens are impaired in older adults (>65 years). Alterations at multiple levels of the immune system are likely implicated and, to date, there is little information about the intrinsic B cell factors responsible for the poor antibody responses in older adults. We have used Hepatitis B virus vaccination as a model to study potential alterations on B cell responses. We hypothesized that older adults, compared to young adults, have a reduced pool of circulating antigen-specific B cells to novel antigens. Furthermore, we hypothesized that in older adults, antigen-specific B memory cells induced by vaccination will have reduced antibody production capacity due to higher activation thresholds. These studies were proposed to be carried out in cryopreserved specimens (PBMC) of volunteers vaccinated with Recombivax-HB (HBV vaccine).

3. 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.

4. 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.

5. 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.

6. 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).

7. Project Title: Engaging Community and Municipal Stakeholders to Improve High-Quality Aging in Place for Community Dwelling Older Hip Fracture Survivors with Alzheimer's Disease or Related Dementias

Leader: Jason Falvey, PT, DPT, PhD

Abstract: This project will assess factors that most strongly impact the number of healthy days spent at home after hip fracture for patients with dementia, using Medicare claims data linked with social vulnerability data. Hypothesis/Aims: 1) Assess how socioeconomic disadvantage at individual and neighborhood level impacts healthy days at home for persons with dementia; 2) Assess high-quality aging in place phenotypes among older adults with dementia and determine pre and peri-operative factors associated with these phenotypes

8. 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.

9. 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.

10. 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.

DEVELOPMENT PROJECTS (0 Development Projects Listed)

No development projects.

RESEARCH (23 Projects Listed)**1. Project Title: Resistive Training and Functional Genetic Mechanisms of Skeletal Muscle Recovery Post-stroke**

Leader(s): XU, HUICHIN
UNIVERSITY OF MARYLAND BALTIMORE
American Heart Association (AHA) 19CDA34760258 / (2019 - 2022)

Core(s):

Stroke is the leading cause of long term disability in US with motor dysfunction being one of the most common deficit post-stroke. The purpose of this career award application is to facilitate my successful transition into an independent investigator in the field of molecular mechanisms of post-stroke muscle recovery as well as the development of therapy targets to promote post-stroke motor function recovery. The proposed research plan leverages the strengths of the mentee's expertise in functional genomics, and a mentor team's long-standing research program in muscle biology and exercise training for stroke participants to optimize skeletal muscle adaptation and recovery. Having already established a highly effective resistive exercise training (RT) protocol for stroke disability by my mentors, I am now well positioned to elucidate the molecular-genetic underpinnings of RT-hypertrophy in stroke survivors. A better understanding of the molecular mechanisms underlying the benefit of exercise intervention for post-stroke muscle atrophy and adaptation is central to developing pharmacological targets for prevention and treatment of post-stroke muscle atrophy and strength decline. This proposal uses a systems biology approach combined with candidate hypothesis to address the gap in knowledge by testing whether exercise-induced changes in muscle are mediated by functional genomics regulation of myoplasticity pathways. This career development award proposal will use banked muscle biopsy samples obtained from existing resistive exercise intervention trials led by my mentors to identify myoplasticity related gene expression and DNA methylation changes underlying the beneficial effect of RT. This project will enable me to have a deep understanding of muscle biology, clinical rehabilitation intervention and assessment. The results of this project and the skills acquired through the proposed training plan will set a solid foundation for me to launch a career delineating the signaling cascades and developing therapy targets to promote post-stroke muscle recovery and health.

2. 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.

3. 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 to chlorhexidine than the placebo group and b) the chlorhexidine group will not be colonized with ESKAPE [and diabetic 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 prevent recurrent foot ulcers in Veterans with diabetes, and 2) an understanding of the risk of antimicrobial resistance with long term chlorhexidine use. Our long term goal is to test whether interventions which manipulate the skin microbiota prevent foot ulcers in a larger (adequately powered for a clinically relevant endpoint) clinical trial in order to reduce the risk of amputation associated with diabetic foot ulcers.

4. 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 history of Diabetes Mellitus (DM); and as for 2012, \$125 billion dollars were costs associated with hospitalization of diabetics in the United States (US). Up to 30% of the hospitalized diabetics develop hypoglycemia, a condition that 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 prevention policies; policies which are however limited by the infrequent Point of Care (POC) capillary blood glucose testing in the general wards. Continuous Glucose Monitoring (CGM) devices represent additional ways to monitor blood glucose levels. Only a limited number of studies have examined the use of CGM devices in the non-ICU setting. 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 the participants, interventions to prevent hypoglycemia were not performed. Additionally, one major limitation of CGM technology is that CGM receiver/monitor needs to be located in the patient's room, due to Bluetooth Technology signal-strength restrictions, necessitating nurses to enter frequently the patient's room in order to check CGM glucose values.

In the current award application, we describe the development of an innovative system that allows CGM glucose values to be transmitted from the patients' bedside to a monitoring device that is 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 combined with a hypoglycemia prevention protocol, can decrease hypoglycemia in the medical wards without resulting in hyperglycemia- resulting to better clinical outcomes. Specifically we hypothesize that: (1) Veterans who will be randomized 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 of the frequent application of the hypoglycemia prevention protocol, compared to Veterans randomized to the control group; and (3) GTS use will reduce the frequency of hypoglycemia induced seizures during their hospitalization decreasing length of stay and inpatient mortality. We will study 244 Veterans with DM2 who are at a higher risk for hypoglycemia. Consenting Veterans will be stratified in two groups based on the number of risk factors of hypoglycemia (=2 risk factors, =3 risk factors); and then further randomized in a 1:1 randomization 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 be used in order to compare glycemic outcomes between the two groups. Our primary outcome is difference in hypoglycemic 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 to hypoglycemia and inpatient mortality. Discovering novel ways to monitor glucose values in the hospital setting could have a significant impact in preventing 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 hospitalized patients with DM who are at a higher risk for hypoglycemia, similar to the way that we use cardiac telemetry for patients who are at an increased risk for developing arrhythmias.

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

**Leader(s): RYAN, ALICE S.; ORTMAYER, 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.

6. 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.

7. 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.

8. 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, and depressive symptoms are common, estimated to be prevalent in one-fifth of these patients. Depressive symptoms worsen knee OA disease severity and are a barrier to pain management and engagement in physical activity. Clinical care guidelines recommend depression treatment in older adults with knee OA but provide no direction on how to simultaneously manage both conditions, and patients are often not treated for their depressive symptoms and receive interventions only for their chronic physical illness. This issue is exacerbated by the routine exclusion of individuals with chronic physical diseases and comorbid depression from clinical trials and lack of protocols designed for these patients. Recent research advocates the use of treatments that benefit both conditions simultaneously, or combined treatment using two interventions in parallel that are designed to work together, such that approaches enhance efficacy beyond that of an individual therapy with a single disease target. Treatment guidelines advise exercise programs to manage pain and disability and improve psychosocial health in those with knee OA, but compliance to physical activity protocols is low in persons with chronic pain and disability and is only made worse by comorbid depression. Adherence is critical to the efficacy of depression treatments using exercise training, and no such exercise program has ever been designed for and tested in OA patients with co-occurring depressive symptoms in a way to enhance compliance. Duloxetine is the only antidepressant medication indicated for pain management in knee OA patients 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 treatments using 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 medical practitioners. Thus, the research goal of this K01 application is to evaluate the feasibility of and then pilot test a protocol comprised of aerobic exercise training plus duloxetine for the treatment of symptomatic knee OA and comorbid depression. The proposed research will be implemented with a period of close mentoring and career development activities focused on learning 1) methods for qualitative data collection and analysis that can be used to understand patients' perspectives and experiences and 2) strategies for the implementation and evaluation of interventions in clinical research. This proposal is aligned with the NIA Strategic Directions for Research on Aging emphasizing older adults with multiple chronic conditions that complicate clinical care

and is intended to lead to a research program that uses observational epidemiology evaluating the relationships and mechanisms between musculoskeletal disorders and comorbid depression in older adults to inform the development of protocols that are designed to manage symptoms of both the primary condition and sequelae.

9. 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.

10. 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.

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

**Leader(s): NEUMAN, MARK
UNIVERSITY OF PENNSYLVANIA
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.

12. Project Title: LONG-TERM OUTCOMES OF KNEE OA IN THE OAI COHORT

Leader(s): NEVITT, MICHAEL C; JACKSON, REBECCA D ;

**UNIVERSITY OF CALIFORNIA SAN FRANCISCO
NIH R01AG050469 / (2017 - 2022)**

Core(s):

DESCRIPTION (provided by applicant): Knee osteoarthritis (OA) is a major cause of pain, functional limitation and disability and among the most costly musculoskeletal conditions. A burgeoning population with knee OA and poor clinical outcomes in the absence of effective treatments are key drivers of the soaring rates and costs of knee replacement. Knee OA pathology and clinical outcomes typically unfold over decades and have a highly varied time course. It is a priority to understand the range of factors that contribute to poor and good outcomes in knee OA, but there are critical gaps in knowledge about the long-term course of the disease and its determinants. It is sensible to target prevention and treatment on those most at risk for poor outcomes. However, there is a paucity of longitudinal studies long enough (=10 years) with frequent assessment using standardized measures to capture the full trajectory, range and variability of outcomes and investigate their determinants. In addition, investigation of these questions is hampered by baseline heterogeneity in knee OA severity and impact, which can be a source of imprecision and bias in observational studies of disease prognosis. Started in 2002, the OAI is a unique cohort study of 4796 persons with or at risk for knee OA that has uniform, rich clinical and imaging data from annual assessments and has been followed comprehensively for up to 8 years with good retention. We now propose to continue assessment of outcomes of knee OA for up to 15 years after baseline, primarily by phone and mail, an efficient and less burdensome approach that will yield more complete follow-up than clinic visits alone in this aging cohort. A brief clinic visit in a subset of participants will enable us to study performance measures of function as a long-term outcome. Our goal is to take advantage of this unprecedented opportunity for long-term follow-up to describe the full trajectory and probability of outcomes at different stages of disease, to identify vulnerable and protected phenotypes in its long-term course and investigate potentially modifiable predictors of these outcomes. Outcomes will span a range of health domains, including: knee-OA related (pain, functional limitation and performance, OA global impact, knee replacement), disability/participation and general health. The extended follow-up provides the opportunity for an analysis design that reduces the risk of common sources of bias and imprecision in studies of disease prognosis by allowing the use of changes from baseline to year 4 to define 'inception events,' such as the transition to more advanced stages of knee pain or structural OA or the development of favorable and unfavorable trajectories of risk factors (knee OA-related, physical performance, general health and psychosocial variables). These changes will then be evaluated for their association with subsequent outcomes occurring from year 5 to year 15 in analyses conditioned on a range of baseline knee OA-related and other covariates with a minimal risk of collider stratification bias. Using this approach we will investigate questions that can inform emerging strategies for prevention and treatment that are focused on improving outcomes in persons with knee OA. These include describing the probabilities of both poor and good long-term outcomes at different stages of knee pain and structural OA, comparing outcomes in those with recent transitions to more advanced stages with those whose course has been stable, and identifying the modifiable determinants of long-term outcomes at different stages of disease and whether these differ by stage, thus suggesting the need for tailored interventions to improve outcomes.

13. Project Title: COMBINING TESTOSTERONE THERAPY AND EXERCISE TO IMPROVE FUNCTION POST HIP FRACTURE

**Leader(s): BINDER, ELLEN F; KIEL, DOUGLAS P. ; MAGAZINER, JAY ; ORWIG, DENISE L ; SCHECHTMAN, KENNETH B. ; SCHWARTZ, ROBERT S ; VOLPI, ELENA ; WASHINGTON UNIVERSITY
NIH R01AG051647 / (2017 - 2022)**

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.

14. 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 muscle power, 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 risk for falls have particular difficulties with successfully stepping sideways as a protective response to loss of balance in the lateral direction. We propose that age-related declines in lateral balance function through impaired weight transfer and protective stepping linked with falls, result from neuromuscular and biomechanical limitations in hip abductor-adductor (AB-AD) muscle power generation. Moreover, we hypothesize that these functional and neuromotor impairments can be improved with high velocity muscle resistance power training. The specific aims are: Aim 1. To determine the age-associated changes in neuromuscular and biomechanical performance of the hip joint AB-AD musculature by evaluating the isolated maximum torque and power production and neuromuscular activation patterns. Aim 2. To determine the aging changes in neuromotor performance 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 that hypothesized aging deficits in sidestepping caused by neuromotor impairments in hip AB-AD muscle power production may be reversible, we will determine the effects of velocity dependent muscle resistance power training (3 x/week x 10 weeks) compared with strength training on neuromuscular, biomechanical, and functional performance outcomes. Overall, the studies will identify age-related neuromotor mechanisms of abnormal hip AB-AD muscle power production that impair lateral weight transfer, balance stability, and mobility function. Establishing a first line of support for the superiority of velocity dependent power training over strength training on muscle performance and protective balance and functional mobility outcomes, will lead to a future comparative intervention trial to enhance these functions and prevent falls in older adults.

15. 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 SUMMARY Osteoporosis and other diseases of skeletal fragility affect more than 200 million people worldwide and contributes to ~9 million fractures annually. Preventing bone loss and/or restoring lost bone mass in patients is of vital importance to limiting the personal and economic impact of diseases of skeletal fragility. A key target in the stimulation of new bone formation is the protein sclerostin, an antagonist of the Wnt/beta-catenin signaling cascade, which is produced by bone embedded osteocytes. Numerous osteoanabolic cues, including mechanical load, reduce expression of the sclerostin leading to de-repression of osteoblastogenesis and stimulation of de novo bone formation. However, key mechanistic details of how osteocytes sense mechanical load, transduce these load signals to biologic effectors, the identity of these biological effectors and how sclerostin bioavailability is regulated are unclear. Our preliminary data have uncovered a number of novel mediators 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 TRPV4 as a major mechano-dependent Ca²⁺ influx pathway that drives Ca²⁺ dependent activation of calcium/calmodulin-dependent kinase II (CamKII) to reduce sclerostin bioavailability in the osteocyte. In the present grant, we will use in vitro, ex vivo and in vivo models to determine the contribution of MT density and cytoskeletal crosslinking to osteocyte mechanosensing, define the contribution and mechanisms of osteocyte TRPV4 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 more fully explain the biological regulation of sclerostin, will mechanistically link several gaps in the knowledge of how osteocytes sense and respond to mechanical load, and will reveal novel targets to improve or preserve bone mass in aging and disease.

16. Project Title: CHEMO-MECHANICAL SIGNALING IN ATRIAL MYOCYTES
Leader(s): LEDERER, WILLIAM JONATHAN; WARD, CHRISTOPHER WILLIAM ;
UNIVERSITY OF MARYLAND BALTIMORE
NIH R01HL142290 / (2019 - 2022)

Core(s):

Atrial myocyte cell biology will be examined in isolated single cells in vitro and mice in vivo to characterize quantitatively how chemo-mechanical signaling works in health and disease. This signaling pathway is activated by changes in myocyte shape as happens when the atria fill with blood, and myocytes stretch, during diastolic filling. Using extremely high temporal and spatial resolution imaging the PIs will examine how chemo-mechanical signaling contributes to subcellular changes in Ca²⁺, excitation-contraction coupling to influence both electrical and Ca²⁺ instability. Preliminary results suggest that newly identified large axial tubules in atrial myocytes (discovered by the PIs) along with Ca²⁺ release 'super-hubs' play a role in a unique Ca²⁺ signaling system found in atrial myocytes. Furthermore, the mechano-chemo X-ROS pathway discovered by the PIs in ventricular myocytes is likely to have a special role to play in atrial myocytes. This signaling pathway links the mechanics of cellular stretch, transmitted through microtubules, to the generation of local subcellular reactive oxygen species (ROS) that likely target multiple Ca²⁺ signaling proteins such as CaMKII and RyR2. Preliminary results suggest this X-ROS signaling is very active in atrial myocytes and maybe linked to the novel structures described by the PIs. The proposed work will identify quantitatively the contributions of the special structures, X-ROS signaling and chemo-mechanical signaling to the normal physiology of atrial myocytes and the contributions to the development of atrial fibrillation (AF). Two very different mouse models of AF will be used along with specific transgenic mice to quantitatively characterize Ca²⁺ signaling and cellular electrophysiology in atrial myocytes and determine how chemo-mechanical signaling contributes to cellular physiology and pathophysiology. This investigation will provide critically important new information on how atrial myocytes work and fail in health and disease. The likely new discoveries produced by the proposed work will broaden our understanding of atrial cell biology and lay the foundation for innovative, effective and novel therapies for atrial dysfunction and AF.

17. Project Title: SHOULDER PAIN, ROTATOR CUFF TEAR, COORDINATION, AND MOBILITY IN AGING
Leader(s): DAVIS, DERIK L
UNIVERSITY OF MARYLAND BALTIMORE
NIH R03AG067927 / (2020 - 2022)

Core(s):

Mobility limitation is a major burden to public health, affecting one-third of adults 65 years and older. Mobility limitation is predictive of disability, hospitalization, falls and mortality in older populations. The contribution of lower limb dysfunction to mobility limitation is well established. The influence of upper-limb dysfunction on mobility performance is less well understood. Shoulder pain and rotator cuff tear are common in adults 65 years and older. Well-known manifestations of shoulder pain or rotator cuff tear include lower performance on subjective measures of activities of daily living and lower performance on objective measures of shoulder strength and range of motion. Recent studies suggest that impaired rhythmic interlimb coordination variability between shoulders is associated with mobility limitation in healthy older adult populations. We hypothesize that the presence of shoulder pain or rotator cuff tear alters the rhythmic interlimb coordination variability between shoulders in community-dwelling older adults. The first aim of the proposal investigates the association of rhythmic interlimb coordination variability between shoulders during overground walking with mobility performance in a population which includes community-dwelling older adults with shoulder pain or rotator cuff tear. The second aim of the proposal investigates the association of shoulder pain or rotator cuff tear with rhythmic interlimb coordination variability during overground walking. The knowledge gained from this proposal will inform future studies designed (1) to test novel strategies for identifying community-dwelling older adults who are vulnerable to develop mobility limitation and (2) to test novel interventions designed to slow functional declines in community-dwelling older adults with mobility limitation.

18. Project Title: BUILDING TRUST TO ENHANCE DIVERSITY IN AGING RESEARCH

**Leader(s): MULLINS, C. DANIEL; MAGAZINER, JAY ;
UNIVERSITY OF MARYLAND BALTIMORE
NIH R24AG063728 / (2019 - 2022)**

Core(s):

PROJECT SUMMARY/ABSTRACT Aging Research focuses on aging processes, age-related diseases, and special problems and needs of older adults. Aging Research helps us to understand the nature of aging and how best to extend the healthy, active years of life. Greater diversity among the populations engaged in Aging Research studies is essential in order to understand the complex relationships among health status and age, race, physical functioning (and physical impairment), culture, and socioeconomic status. The proposed project will foster a community-academic Aging Research collaborative that promotes trust and develops recruitment and retention methods to increase the diversity of older adult participants in clinical studies of aging. Achieving greater diversity in clinical research study populations involving older adults is desirable and feasible, yet comes at a cost. Our proposed study of recruitment methods will help answer the question, Can we identify evidenced-based recruitment methods that are both effective (successfully recruit populations underrepresented in clinical research) and efficient (provide a reasonable return on investment) in recruiting and retaining underrepresented populations in clinical studies of aging. We will accomplish this by building the infrastructure necessary to support methodological research in partnership with community organizations with whom we have worked on prior multiyear federal grants, including an R24 from the U.S. Department of Health and Human Services' Agency for Healthcare Research and Quality (AHRQ). The project aims are: Aim 1: Foster a community-academic Aging Research collaborative that promotes trust and develops recruitment and retention methods to increase the diversity of older adult participants in clinical studies of aging. Aim 2: Engage diverse older adults, their community-based health care providers, and investigators in a manner that facilitates bi-directional learning for future Aging Research studies. Aim 2a: Move older adults along the willingness to participate in research continuum. Aim 2b: Enhance the cultural competence of investigators studying aging and by doing so promote trustworthiness of Aging Research studies by community members. Aim 3: Guided by co-developed ethical principles, facilitate the enrollment of three difficult-to-recruit subpopulations: older African Americans, older adults with impairments (hearing, vision, mobility), and those who are homebound into a Registry.

19. 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 grant mechanism (R24 AG045050), was initiated in 2014 to foster collaborations between HCSRN and OAIC (aka Pepper Centers) investigators in order to advance an interdisciplinary research agenda focused on advancing the 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, embedded within healthcare delivery systems caring for nearly 2 million persons aged 65 and older, in partnership with investigators from 15 premier, university-based centers established by the National Institute on Aging (the OAICs). Under the R24, efforts relevant to advancing MCCs science have centered around: (1) characterizing and sharing unique data resources; (2) supporting innovative, collaborative pilot projects; (3) mentoring new and early-stage investigators; and (4) disseminating research methods and findings. This collaboration has identified several understudied, high priority research domains, as well as an urgent need for formal career development 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 R33 program, conceived and developed by the R24 HCSRN-OAICs AGING Initiative Steering Committee, and its Workgroups and External Advisory Committee, is to elaborate on the successful programs and infrastructure of the R24, while taking our AGING Initiative in new, more ambitious directions. We will create new core resources, career development opportunities, and funding opportunities, aligning patients' interests with those of scientists. Our specific aims are: (1) to expand on and further develop innovative methods related to measurement and analytics, observational research, and pragmatic clinical trial design and implementation, to inform the development and testing of novel interventions that improve the care and outcomes of older persons with MCCs; (2) to foster the career development and success of new and early-stage investigators, including underrepresented minorities, and create a nation-wide cohort of MCCs scholars, who are prepared to establish productive collaborations early in their careers to catalyze an expansion of interdisciplinary research relevant to the science of MCCs; (3) to create a new core function as part of an elaborated infrastructure that promotes patient-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 relevant to the science of MCCs. The P-2-R grants will serve to promote the development and implementation of larger, multi-disciplinary, multi-site studies laying a foundation upon which to continue to grow the AGING Initiative.

20. Project Title: Elderly Oral Health: The relationship between oral health problems, dental care use, medical conditions, and provided medical care

Leader(s): MANSKI, RICHARD J
UNIVERSITY OF MARYLAND BALTIMORE
NIH R56AG064782 / (2019 - 2022)

Core(s):

The goal of this project is to focus on the relationship between dental use, overall health, comorbidity, and medical services use. The central hypothesis guiding this study is that dental care use is highly correlated with better-than-average general health and lower levels of comorbidity and utilization of medical services. We will test the hypothesis and conduct this study using secondary data available from the Medicare Beneficiary Survey (MCBS) and Chronic Conditions Warehouse (CCW), Area Health Resources File (AHRF) and the University of Michigan Institute for Social Research (ISR) Health and Retirement Study (HSR). We will also take advantage of a HRS dental specific module co-developed by members of this research team and the survey staff at the ISR. This proposed project builds upon and is an extension of several collaborative studies previously conducted by this research team. Results obtained from this study will have a high impact on the health and welfare of the Medicare eligible community population by describing which co-morbid states are associated with the presence of oral diseases, whether or not preventive treatments are associated with lower levels of those co-morbid states, and whether or not the use of corrective treatments are associated with amelioration of those co-morbid states in comparison to the frequency and severity of those co-morbid states among individuals whose oral diseases are not treated. Specifically we will: Aim 1. Estimate the relationship between utilization of dental care services by elderly persons and co- morbidities over time. The working hypothesis is that elderly persons not using dental care service are more likely to experience specific co-morbidities compared to those using dental services on a regular basis. Aim 2. Estimate the relationship between preventive dental care service use, oral health problems, and co- morbidities over time by elderly persons. The working hypothesis is that elderly persons with regular use of preventive dental care or without oral health care problems are less likely to experience specific co-morbidities over time than elderly persons not regularly using preventive dental care or with oral health care issues. Aim 3. Estimate the relationship between oral disease and co-morbidities over time for elderly persons. The working hypothesis is that elderly persons with oral disease are more likely over time to experience specific co- morbidities compared to elderly persons without oral disease.

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

Core(s):

The aging of the United States population highlights the need for increased interdisciplinary research on diseases and disabilities that affect older persons. The objective of years 21-25 of this successful program is to continue training 5 pre- and 2 postdoctoral fellows to conduct independent and original research in the epidemiology of aging, with an emphasis on the prevention of late life disability and functional decline and the maximization of function in those with existing disabilities and disabling conditions. The program emphasizes four broad substantive areas in which program faculty have gerontologic research experience and are conducting ongoing projects: musculoskeletal epidemiology; neuroepidemiology; genetic epidemiology; and pharmacoepidemiology. The program prepares trainees to: 1) contribute to an interdisciplinary research team under the supervision of a primary mentor expert in the epidemiology of aging and secondary mentors expert in epidemiology methods and/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 expert in at least one substantive area relevant to functional decline and the maximization of function in those with disabilities 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 of responsible 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 of Maryland School of Medicine. Major program strengths include: 1) availability of core epidemiology of aging faculty, and faculty expert in gerontology, epidemiology, biostatistics, and substantive areas that are focus of program; 2) interdisciplinary training and research opportunities in aging and related areas; 3) graduate training opportunities including advanced coursework through the Doctoral Programs in Epidemiology and Human Genetics, Gerontology, and Pharmaceutical Health Services Research; and 4) ability to capitalize on Baltimore/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 trainees in launching successful careers as leaders in the epidemiology of aging. The program director is recognized for his leadership nationally and within the University of Maryland; as such, he is in an excellent position to foster the 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 program associate directors.

22. 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.

23. 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.

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Cells, 2021 Dec 10, 10(12):pii: [3490](https://doi.org/10.3390/cells10123490). <https://doi.org/10.3390/cells10123490> | PMID: 34943997 | PMCID: PMC8700073

Citations: | AltScore: 2.25

47. Bone Mineral Density Changes during Weight Regain following Weight Loss with and without Exercise.

Serra MC, Ryan AS

Nutrients, 2021 Aug 19, 13(8):pii: [2848](https://doi.org/10.3390/nu13082848). <https://doi.org/10.3390/nu13082848> | PMID: 34445008 | PMCID: PMC8400683

Citations: | AltScore: 5.9

48. Sex-specific 25-hydroxyvitamin D threshold concentrations for functional outcomes in older adults: PProject on Optimal Vitamin D in Older adults (PROVIDO).

Shardell M, Cappola AR, Guralnik JM, Hicks GE, Kritchevsky SB, Simonsick EM, Ferrucci

L, Semba RD, Shaffer NC, Harris T, Eiriksdottir G, Gudnason V, Cotch MF, Orwoll E,

Ensrud KE, Cawthon PM

Am J Clin Nutr, 2021 Jul 1, 114(1): 16-28<https://doi.org/10.1093/ajcn/nqab025> | PMID: 33826696 | PMCID: PMC8246604

Citations: | AltScore: 6.5

49. Association of Vaginal Microbiota With Signs and Symptoms of the Genitourinary Syndrome of Menopause Across Reproductive Stages.

Shardell M, Gravitt PE, Burke AE, Ravel J, Brotman RM

J Gerontol A Biol Sci Med Sci, 2021 Aug 13, 76(9): 1542-1550<https://doi.org/10.1093/gerona/rlab120> | PMID: 33903897 | PMCID: PMC8361365

Citations: 3 | AltScore: NA

50. A guide for authors and readers of the American Society for Nutrition Journals on the proper use of P values and strategies that promote transparency and improve research

reproducibility.

Sorkin JD, Manary M, Smeets PAM, MacFarlane AJ, Astrup A, Pigeon RL, Hogans BB, Odle J, Davis TA, Tucker KL, Duggan CP, Tobias DK

Am J Clin Nutr, 2021 Oct 4, 114(4): 1280-1285

<https://doi.org/10.1093/ajcn/nqab223> | PMID: 34258613 | PMCID: PMC8488872

Citations: 4 | AltScore: 61.75

51. Excess Mortality in COVID-19-Positive Versus COVID-19-Negative Inpatients With Diabetes: A Nationwide Study.

Spanakis EK, Yoo A, Ajayi ON, Siddiqui T, Khan MM, Seliger SL, Klonoff DC, Feng Z, Sorkin JD

Diabetes Care, 2021 Sep, 44(9): e169-e170

<https://doi.org/10.2337/dc20-2350> | PMID: 34233926 | PMCID: PMC8740932

Citations: 3 | AltScore: 1.5

52. Augmented exercise pressor response during maximal treadmill exercise is not related to systemic inflammation in stroke survivors.

Sprick JD, Serra MC, Ryan AS, Li Y, Park J

Top Stroke Rehabil, 2021 May, 28(4): 251-257

<https://doi.org/10.1080/10749357.2020.1806436> | PMID: 32783602 | PMCID: PMC7878569

Citations: | AltScore: 1.5

53. Evaluating Test-Retest Reliability of Fatigability in Chronic Stroke.

Stookey AD, Macko RF, Ivey FM, Katzel LI

J Stroke Cerebrovasc Dis, 2021 Sep, 30(9): 105895

<https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.105895> | PMID: 34242857 | PMCID: PMC8767492

Citations: | AltScore: NA

54. The Effect of High Protein and Mobility-Based Rehabilitation on Clinical Outcomes in Survivors of Critical Illness.

Wappel S, Tran DH, Wells CL, Verceles AC

Respir Care, 2021 Jan, 66(1): 73-78

<https://doi.org/10.4187/respcare.07840> | PMID: 32817444 | PMCID: PMC8208101

Citations: 1 | AltScore: 25.15

55. Effects of transcranial direct current stimulation (tDCS) on posture, movement planning, and execution during standing voluntary reach following stroke.

Yang CL, Gad A, Creath RA, Magder L, Rogers MW, Waller SM

J Neuroeng Rehabil, 2021 Jan 7, 18(1): 5

<https://doi.org/10.1186/s12984-020-00799-8> | PMID: 33413441 | PMCID: PMC7791870

Citations: 2 | AltScore: NA

56. Predictors of the start of declining eGFR in patients with systemic lupus erythematosus.

Yip TC, Saria S, Petri M, Magder LS

Lupus, 2021 Jan, 30(1): 15-24

<https://doi.org/10.1177/0961203320966393> | PMID: 33115373 | PMCID: PMC7770013

Citations: | AltScore: 0.5

57. Intensive In-Bed Sensorimotor Rehabilitation of Early Subacute Stroke Survivors With Severe Hemiplegia Using a Wearable Robot.

Zhang C, Huang MZ, Kehs GJ, Braun RG, Cole JW, Zhang LQ

IEEE Trans Neural Syst Rehabil Eng, 2021, 29: 2252-2259

<https://doi.org/10.1109/TNSRE.2021.3121204> | PMID: 34665733 | PMCID: PMC8843010

Citations: 1 | AltScore: NA

EXTERNAL ADVISORY BOARD MEMBERS

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Julius Dewald, PT, PhD
Northwestern University
Serving since 2022 (0 years)

RECOGNITION AND AWARDS (2021-2022)

Alice Ryan, PhD (2022)

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

Alice Ryan, PhD (2021)

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

Andrea Levine, MD (2022)

- Dean's Alumni Award for Diversity and Inclusion

Barbara Resnick, PhD, RN, CRNP, FAAN, FAANP (2021)

- Ada Sue Hinshaw Award from the National Institute of Nursing Research

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

Jennifer Albrecht, PhD (2021)

- University of Maryland School of Medicine, Department of Epidemiology and Public Health: Faculty Mentoring Award

Michelle Shardell, PhD (2021)

- Elected Program Chair, American Statistical Association Statistics in Epidemiology Section
- Elected to Board of Directors, American Statistical
- Elected to Council of Sections Governing Board, American Statistical Association

MINORITY RESEARCH

General Brief Description of Minority Activities:

Not defined.

Minority Trainee(s):

- 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.
- 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.
- Doyinsola Bailey, PhD, Post-Doctoral student, Department of Epidemiology and Public Health, University of Maryland School of Medicine
Her research focus is long term outcomes of traumatic brain injury among older adults. In

addition to her dissertation work, she worked on projects that used Medicare administrative claims data to assess the effects of adherence to continuous positive airway pressure therapy on cardiovascular (CV) and healthcare utilization outcomes among older adults with obstructive sleep apnea (OSA). She was awarded a diversity supplement from the American Association of Sleep Medicine Foundation to conduct additional work specifically related to older adults with comorbid OSA and CVD. Dr. Jennifer Albrecht served as the chair of her dissertation committee and her mentor.

- Eduardo Alsina, PhD Candidate, PhD Student, Psychology Department, University of Maryland Baltimore County
Mr. Alsina's interests include disparities in the relations of cardiovascular risk factors to cognitive function and magnetic resonance imaging assessed subclinical brain pathology as a function of self-identified race and socioeconomic status. His master's thesis examined interactive relations of left ventricular mass and sociodemographic factors on cognitive outcomes in urban-dwelling African American and White adults. His dissertation project examines whether interactive relations between the APOE polymorphism and race to memory function are mediated by brain atrophy patterns indicative of early risk for Alzheimer's dementia. Dr. Shari Waldstein currently serves as his mentor and dissertation chair.
- 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.
- Jason Ashe, PhD Candidate, PhD Student, Psychology Department, University of Maryland, Baltimore County
Mr. Ashe's interests include how religious participation protects against risk for cardiovascular disease and accelerated aging in the context of racial health disparities. His master's thesis project examined the interactive relations of religious coping, self-identified race, and sex to telomere length in urban dwelling African American adults. His dissertation will determine whether religious coping buffers the negative relation of discrimination to cardiovascular risk profiles in African American women and men. Dr. Shari Waldstein currently serves as his mentor and dissertation chair.
- 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. Dr. Jennifer Albrecht served as the chair of her dissertation committee and her 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.
- 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.
- Von Homer, PhD, Assistant Professor of Biomechanics at Delaware State University
Dr. Homer completed a post-doctoral award this past year. Dr. Homer is studies computational neuroscience and biomechanics-based methods to evaluate neuromuscular performance and fatigue within footwear to assess whether its construction is ergonomically fit to safeguard people from injury while helping footwear companies create superior products focused on comfort, fit, and performance biomechanics and neuroscience and developed, a method for predicting Injury Risk. Drs. Macko and Charlene Hafer-Macko served as his mentors.

Minority Grant(s):

UNIVERSITY OF MICHIGAN
Claude D. Pepper Older Americans Independence Center

Raymond Yung, M.D.
Principal Investigator

734-647-9746

ryung@umich.edu

Stephanie Gatica, B.A.
Program Administrator

734-763-1118

sgatica@umich.edu

CENTER DESCRIPTION

Funded by the NIA as the nation's 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)

Leader 1: Raymond Yung, MD ryung@med.umich.edu

Leader 2: 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)

Leader 1: Neil B. Alexander, MD nalexand@med.umich.edu

Leader 2: Lillian Min, MD, MSHS lmin@umich.edu

Leader 3: Carrie Karvonen-Gutierrez ckarvone@umich.edu

The REC is a component of the Claude D. Pepper Older Americans Independence Center, funded by the National Institute on Aging. The primary goal of the Research Education Core 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. The REC focuses on stimulating the translation between basic and clinical research across the spectrum of its training activities, including the annual research education core retreat(link is external). To this end it serves a critical function in supporting the overall OAIC focus by training the next generation of investigators whose research will lead to an improved understanding of the predictors and modulators of the aging phenotype.

Pilot and Exploratory Studies Core (PESC)

Leader 1: Lona Mody, MD lonamody@med.umich.edu

Leader 2: Donovan Maust, MD maustd@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

Leader 1: James Ashton-Miller, PhD jaam@umich.edu

Leader 2: 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)

Leader 1: Raymond Yung, MD ryung@med.umich.edu

Leader 2: 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
Emily Briceno, Ph.D. Clinical Assistant Professor / Department of Physical Medicine & Rehabilitation <u>Measurement of cognition across language and education among Mexican American and non-Hispanic white older adults</u>	2021-2023 / 4 (total) 2 (1st/Sr)
Joseph Endicott, M.D. Research Investigator / Department of Pathology <u>Metabolic reprogramming by chaperone-mediated autophagy downstream of the lifespan-extending PTEN transgene</u>	2022-2023 / 3 (total) 3 (1st/Sr)
David Flood, M.D., M.Sc. Clinical Instructor / Department of Internal Medicine <u>Cross-national comparisons of disability among older adults with diabetes in 23 countries</u>	2022-2023 / 4 (total) 2 (1st/Sr)
Victoria Powell, M.D. Clinical Instructor / Division of Geriatric and Palliative Medicine <u>Recruiting Older Adult Research Participants: Considerations, Sources, and Methods</u>	2022-2023 / 31 (total) 17 (1st/Sr)
Michael Smith, PharmD Clinical Associate Professor / Department of Pharmacy <u>Understanding medication use in older adult cancer survivors with centralized pain, focusing on practice patterns</u>	2021-2022 / 9 (total) 5 (1st/Sr)
Matthew Pianko, M.D. Clinical Assistant Professor / Department of Internal Medicine <u>Evaluating the impact of immunosenescence and inflammaging on vaccine-induced immunity in older adults with plasma cell neoplasms</u>	2021-2022 / 4 (total) 3 (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)

PILOT/EXPLORATORY PROJECTS (14 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. The 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 specific 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 objective 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 herpesviruses 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: Aging and tryptophan immune metabolism in CKD associated cardiovascular disease**Leader: Anna Mathew, M.B.B.S.**

PESC Year 17 (7/1/21-6/30/22) Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in chronic kidney disease (CKD), reducing CKD patients' life expectancy. However, the accelerated CVD pathogenesis in CKD is not yet clearly understood, and no specific therapeutic strategies are currently available to attenuate this phenomenon. Our long-term goal is to understand the role of aging and immune-metabolic mechanisms underlying accelerated atherosclerosis to improve CKD patients' lifespan. Our overall objective is to define the role of aging and tryptophan catabolism via the kynurenine pathway (KP) in the pathophysiology of CKD atherosclerosis. Our central hypothesis is that the macrophage-derived tryptophan catabolite kynurenic acid (KA) causes CKD atherosclerosis in older CKD patients, whereas 3-hydroxy anthranilic acid (3-HAA) ameliorates this problem. Our rationale is that if KP metabolites play a causal role in CKD atherosclerosis in older adults, then we can develop new therapeutic strategies and biomarkers to attenuate the CVD burden in the CKD population. We will test our central hypothesis by pursuing the following specific aims: 1) demonstrating the role of aging and macrophage-derived KP metabolites in the pathophysiology of CKD related CVD, and 2) delineating the mechanisms downstream of KP

metabolites (namely KA and 3-HM) in the pathogenesis of CKD atherosclerosis. Under Aim 1, we will delineate the role of aging and peripheral blood mononuclear cell KP metabolism on CVD in CKD patients. Regarding Aim 2, we plan to demonstrate that KA causes CKD atherosclerosis by acting on macrophage cytosolic aryl hydrocarbon and cell-membrane G protein-coupled receptor 35 receptors, whereas 3-HM ameliorates CKD atherosclerosis by acting on the macrophage inflammasome using primary macrophage cultures.

3. Project Title: Aging Associated Transcriptional Changes of Metabolic Pathways in the Kidney

Leader: Jennifer Schaub, M.D.

PESC Year 16 (7/1/20-6/30/21) Chronic Kidney Disease (CKD) is a global health epidemic, particularly among the elderly. Pathologic analysis of the aging kidney shows nephrosclerosis, which includes global glomerulosclerosis, interstitial fibrosis, tubular atrophy and atherosclerosis. Vascular changes are an integral part of nephrosclerosis and may be linked to tubular injury and atrophy, but this is understudied because it is difficult to assess the vasculature, which is often not sampled in kidney biopsy specimens. While interstitial fibrosis and tubular atrophy are the strongest known pathologic predictors of progression of CKD, we have limited understanding of how vascular disease and aging contributes to tubular cell atrophy and transcriptional changes in glycolysis and oxidative metabolism pathways. It is critical to better understand how transcriptional regulation of these metabolic pathways in tubular cells are altered with aging and vascular disease, as Prolyl Hydroxylase Inhibitors (PHI), novel therapeutic agents that increase the activity of Hypoxia Inducible Factors, are effective treatments for anemia of CKD. Mechanistic data shows that PHI may alter transcriptional regulation of metabolic pathways within the kidney and could alter the progression of kidney disease. The PRECISE cohort, a cohort of nephrectomy specimens, has abundant sampling of vasculature and is a unique opportunity to evaluate the relationship between aging, vascular disease, tubular atrophy and transcriptional regulation of metabolism. The proposed studies will assess a) the relationship between tubular atrophy, vascular disease and aging from a morphometric perspective and b) the changes in the tubular cell specific expression of genes involved in glycolysis and oxidative metabolism in those with vascular disease and aging kidneys. We will then generate the transcriptional data from kidneys that have already been harvested from the Glenn Mouse Aging Study and align these results with the human data. In addition, we will use publically available gene expression data from animal models treated with PHI to assess how these agents impact transcriptional expression of metabolic pathways. Results from these studies can be used for potential future collaborations with the Core Facility for Slow Aging Mice.

4. Project Title: Supporting older adults with cognitive impairment before elective surgery; Developing a measure of preoperative preparedness of patient-caregiver dyads

Leader: Alexandra Norcott, M.D., M.Sc.

PESC Year 17 (7/1/21-6/30/22) The proposed study has two specific aims: 1. Identify the core domains of transitional preparedness to address in the preoperative period: We will conduct pre and postoperative qualitative interviews of patients with cognitive impairment and their designated caregivers to identify core domains of transitional preparedness. We will also measure caregivers' perceived locus of control and caregiving contributions. 2. Develop a

PESC Year 16 (7/1/20-6/30/21) The global pandemic infectious disease COVID-19 caused by severe acute respiratory coronavirus 2 (SARS-CoV-2) has caused worldwide devastation, and a strikingly high mortality rate of 30-55% in multiple myeloma (MM) patients aged 65 years or more. While the advent of effective and safe vaccines against SARS-CoV-2 provides hope, both MM patients and elderly adults are known to have suboptimal antibody responses to vaccines and the effectiveness of these novel vaccines in this population is unknown because immunocompromised persons were excluded from the phase III trials of SARS-CoV-2 vaccines. The long-term goal of this project is to gain deeper insight into the impacts of frailty and age-related immune dysfunction on immune response to vaccination in aged adults with plasma cell disorders in order to optimize vaccination strategies for these patients. The central hypothesis is that frailty can predict suboptimal immune responses to SARS-CoV-2 vaccinations in patients with plasma cell neoplasms. The rationale for this project is that frailty is predictive of clinical outcomes in MM and the aged immune system affects vaccine responses in frail and non-frail persons. The central hypothesis will be tested by pursuing two Specific Aims: 1) To estimate the impact of frailty on immunogenicity of SARS-CoV-2 vaccines in older adults with plasma cell neoplasms in a prospective pilot-phase observational cohort study; and 2) Determine the impact of B cell immunosenescence on SARS-CoV-2 vaccination outcomes in older adults with plasma cell neoplasms. Under the first Aim, a validated geriatric assessment will be performed, SARS-CoV-2 Spike antibodies will be quantified at 4-6 weeks after vaccination, and rates of suboptimal immune responses will be compared in frail and non-frail individuals stratified by clinical factors. Under the second Aim, functional assessment of antibody-binding affinity will be evaluated using a pseudo-typed virus neutralization assay. The research proposed in this application is innovative because it seeks to evaluate the impact of frailty on the immunogenicity of a novel vaccine type in a population at great need of protection from morbidity and mortality from severe COVID19. The proposed research is significant because it is expected to provide justification and preliminary data to prospectively evaluate methods to improve vaccination outcomes for individuals at high risk of lethal infectious diseases. This work will provide key support for career development and will fund generation of preliminary data to obtain external funding support.

8. 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.

9. 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.

10. Project Title: Mechanisms of Tumor Resistance in Slow-Aging Mice

Leader: Scott Maynard, Ph.D.

PESC Year 18 (7/1/22-6/30/23) Two major forces in the multistage cancer process are the inactivation of tumor suppressor genes and alterations in the activation state of cell receptor-mediated pathways that promote neoplasia. Studies in mice have shown that caloric restriction (CR) and certain single-gene mutations enhance lifespan and deter several age-related health changes (including cancer) by disrupting the receptor mediated pathway known as the growth hormone (GH)/insulin growth factor-1 (IGF-1) axis. However, the exact mechanisms are not known; studies suggest that the CR mice and long-lived mutant mice have both independent and shared underlying mechanisms. A shared mechanism appears to be reduced mTOR signaling, a pathway important in protein synthesis, DNA repair, autophagy and cell proliferation. This pilot grant is designed to measure skin tumor formation in mouse models that have longevity-promoting GH/IGF-1 signaling alterations, and to also process and store tumor and host cell skin samples (and plasma) for delineation of the associated mechanisms. I will use the well-established multi-stage chemical carcinogenesis mouse system in which a chemical carcinogen and inducer are applied to mouse skin to induce skin papillomas. This will be performed on three long-lived mouse models: CR mice, the Snell dwarf pituitary mutant mice, and growth hormone receptor knockout (GHRKO) mice. There

are several reports of successful use of this multi-stage chemical carcinogenesis on CR mice that demonstrate that CR works to limit skin papilloma emergence, but this systems has never been performed on the GHRKO and Snell dwarf mice. The use of all three mouse models will allows us to determine to what extend the shared or independent pathway alterations work to limit tumor growth. My primary goal for the first year will be optimize the system (dosage, timing, feeding, processing of tumor/skin tissue) to display significant effects of CR, and then, with the help these optimizations, recapitulate skin tumor formation resistance in long-lived mutant mice. Various candidate biochemical and cellular processes will be measured (some in the first year) in order to determine mechanisms for altered tumor formation rates. This project will lead to long term investigations into strategies to limit carcinogenesis and to delineate cross-talk between aging and cancer pathways.

11. 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.

12. 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.

13. 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 more susceptible to *Clostridioides difficile* with an increased risk of developing disease-related complications. We are specifically interested in understanding how age-related changes in the microbiota affect the outcomes of infection with *Clostridioides difficile*.

14. 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.

DEVELOPMENT PROJECTS (2 Development Projects Listed)

1. Project Title: Software tools for separable covariance models in multivariate longitudinal data/repeated measures analysis

Leader: Andrzej Galecki; Julie Bynum

Core(s): Design, Data, and Biostatistics Core (DDBC)

Software tools for separable covariance models in multivariate longitudinal data/repeated measures analysis

2. Project Title: Develop a real time sensor to detect hyponatremia

Leader: James Ashton-Miller

Core(s): Biomechanics (Biomechanics)

Develop a real time sensor to detect hyponatremia

RESEARCH (28 Projects Listed)

1. Project Title: PAUL F. GLENN CENTER FOR AGING RESEARCH AT THE UNIVERSITY OF MICHIGAN

**Leader(s): MILLER, RICHARD A
UNIVERSITY AT MICHIGAN AT ANN ARBOR
PAUL F. GLENN FOUNDATION / (2018 - 2022)**

Core(s):

This project will focus on exploiting and expanding the growing evidence that drugs can slow aging and postpone diseases in animal models. The Center's activities will be directed towards three linked aims: (1) using simple model systems to rapidly identify and characterize new compounds that target evolutionarily conserved pathways that control aging; (2) facilitating the process by which candidate drugs are selected for longevity testing in mice; and (3) discovering the mechanisms by which drugs that extend lifespan achieve their effects. The central theme will be that learning how to slow aging in model systems will lead to breakthrough discoveries in our understanding of what times aging and how aging times the diseases of older adults, and that these breakthroughs, in turn, will lead to the development of practical anti-aging medications that postpone human diseases and extend healthy human lifespan.

2. 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.

3. Project Title: LongROAD Study: Multicenter observational study of older drivers and the impact of health, function, and technology on changes in driving behavior

**Leader(s): SILVEIRA, MARIA
UNIVERSITY AT MICHIGAN AT ANN ARBOR
AAA FOUNDATION FOR TRAFFIC SAFETY / (2014 - 2022)**

Core(s):

The overall goal is to generate empirical evidence for understanding the dynamics, mechanisms, determinants and consequences of mobility in senior drivers and for developing effective interventions to ensure safe mobility for older people.

4. Project Title: The Relationship between Overall Health and Gut/Skin/Oral Microbiome in Healthy Middle-aged Adults

**Leader(s): YUNG, RAYMOND; YOUNG, VINCENT
UNIVERSITY AT MICHIGAN AT ANN ARBOR**

ACCESS BUSINESS GROUP LLC / (2021 - 2022)**Core(s):**

To examine the relationship between the gut/oral/skin microbiome and the overall health of 60 individuals participated in the original protocol.

5. Project Title: Transfer Trauma in Nursing Home Long-Term Care Residents

Leader(s): MONTOYA, ANA
UNIVERSITY AT MICHIGAN AT ANN ARBOR
DONAGHUE FOUNDATION / (2020 - 2022)

Core(s):

Our main research question is are there adverse consequences of facility transfers among nursing home residents that can be measured and monitored prospectively to prevent transfer trauma in the future.

6. Project Title: ENHANCE: Developing a Clinical Geography Tool to Intervene in Cognitive Decline through Neighborhood Design

Leader(s): FINLAY, JESSICA MARIE
UNIVERSITY OF MICHIGAN AT ANN ARBOR
NIH F32AG064815 / (2020 - 2022)

Core(s):

Although the majority of Americans with Alzheimer s disease and related dementias (ADRD) live independently, the neighborhood contexts in which they develop and navigate cognitive impairment are largely ignored. Environmental factors may significantly increase the risk of or buffer against ADRD, yet strategies to address cognitive decline to date largely overlook the role of neighborhoods. Residence in advantaged neighborhoods may promote cognitive functioning and/or buffer against dementia in part through greater density of physical and social resources (e.g., recreation centers, parks, libraries, coffee shops) that benefit cognitive reserve and maintain mental function through physical activity, mental stimulation, and social engagement. This project proposes to develop the new niche of clinical geography by translating geographic knowledge into a preliminary tool designed to facilitate place-based interventions that maintain and improve cognition among aging residents. First, the project aims to identify built and social environmental factors linked to changes in cognitive function over time and the onset of cognitive impairment based on secondary data analysis of a national, racially diverse, population-based sample. The dataset includes multiple measures of cognitive function and residential geographic coordinates for 30,000+ aging Americans tracked annually since 2003. Interpretations of longitudinal generalized linear mixed models will focus on identifying environmental factors relevant to trajectories of cognitive decline and onset of cognitive impairment. Second, the project aims to translate this knowledge into a preliminary diagnostic tool: Environmental Neighborhood Health Assessment to Nurture Cognitive Enhancement (ENHANCE). A community advisory board (CAB) will be formed to develop ENHANCE through diverse input from gerontologists, ADRD experts, dementia community advocates, urban planners, and older adults. The CAB will discuss how environmental factors can impact cognitive decline, develop the tool, and refine ENHANCE based upon preliminary feasibility and pilot testing. The F32 fellowship will facilitate Dr. Finlay s career development and future as a successful independent health researcher. It complements and extends her expertise in health geography and environmental gerontology through mentored training in five new areas: 1) advanced quantitative analysis; 2) cognitive function and ADRD; 3) clinical observation of cognitive impairment; 4) tailored design of environmental audits; and 5) NIH grant skills. The interdisciplinary and supportive training environment at the University of Michigan provides a foundation for Dr. Finlay to pursue translational research throughout her career. Her long-term research objective is to develop a new concept of cognability (a measure of how supportive an area is to cognitive functioning and how it buffers against cognitive impairment) with a reliable and efficient instrument to evaluate relevant macro and micro environmental conditions. Resulting tailored, place-specific interventions are intended to help aging individuals reduce risk for cognitive impairment and ADRD, live independently longer, and lessen need for long-term care.

7. Project Title: USING METABOLOMICS TO IDENTIFY NOVEL BIOMARKERS FOR KNEE OSTEOARTHRITIS RISK

Leader(s): **KARVONEN-GUTIERREZ, CARRIE ANNE**
UNIVERSITY OF MICHIGAN AT ANN ARBOR
NIH K01AG054615 / (2017 - 2022)

Core(s):

ABSTRACT Osteoarthritis (OA), a debilitating age-related disease associated with pain, stiffness and poor functioning is a major risk factor for mobility disability. Although early osteoarthritic changes within the joint commence during mid-life (40-65 years of age), early detection of disease is limited given the lack of robust and reliable OA biomarkers. Currently detection relies upon costly imaging modalities. Late detection of OA compromises the opportunity for early intervention and prevention of disease progression, leaving only symptom management or, ultimately, joint replacement as strategies for treatment. Recent evidence and scientific appreciation that underlying metabolic dysfunction is a risk factor for osteoarthritis incidence and progression suggests that biomarkers which identify individuals with disordered metabolism may be relevant for subclinical markers of OA. Metabolomics, a newly evolving field, analyzes small molecules (metabolites) in biological specimens. Metabolomics analysis has successfully identified novel biomarkers for diagnosis, monitoring and treatment for age-related diseases such as prostate cancer, diabetes and stenosis and autoimmune diseases such as rheumatoid arthritis. A small but growing number of studies in animal and human populations have reported that metabolomics yields potential biomarkers with good discrimination between OA patients and normal controls including metabolites associated with collagen, branched chain amino acid, energy, and tryptophan metabolism. However, no studies to date have neither used metabolomics to identify biomarkers for OA incidence nor evaluated biomarkers among individuals matched for age and body size. We propose to conduct a metabolomics analysis of osteoarthritis risk within the longitudinal Michigan Study of Women's Health Across the Nation (MI-SWAN). Specifically, 63 MI-SWAN women who developed radiographic knee OA during follow-up will be age- and BMI-matched with 63 MI-SWAN women who remained OA-free during follow-up. Banked plasma specimens from baseline (when all subjects were OA-free) will be used to conduct metabolomics analyses using the targeted lipids eicosanoids platform (Aim 1) which includes profiles from 28 eicosanoids, the lipidomics platform (Aim 2) which profiles lipids from over 10 classes including 431 unique lipid species, and an untargeted platform (Aim 3) which profiles at least 250 known compounds to identify candidate biomarkers for knee osteoarthritis risk. Relative quantitation of these metabolites will be compared within the matched pairs of women who did and did not develop incident knee OA during follow-up. This K01 award will provide needed training and skill development in metabolomics, the associated bioinformatics considerations, and translation to clinical care and yield preliminary data to support the submission of an R01 application. This training will enable the candidate to develop as an independent investigator providing leadership in the application of metabolomics research in aging with the long-term goal of applying this approach to identify key metabolic pathways involved in aging and the disablement process.

8. Project Title: **USING METABOLOMICS TO IDENTIFY NOVEL BIOMARKERS FOR KNEE OSTEOARTHRITIS RISK**

Leader(s): **KARVONEN-GUTIERREZ, CARRIE ANNE**
UNIVERSITY OF MICHIGAN AT ANN ARBOR
NIH K01AG054615 / (2017 - 2022)

Core(s):

ABSTRACT Osteoarthritis (OA), a debilitating age-related disease associated with pain, stiffness and poor functioning is a major risk factor for mobility disability. Although early osteoarthritic changes within the joint commence during mid-life (40-65 years of age), early detection of disease is limited given the lack of robust and reliable OA biomarkers. Currently detection relies upon costly imaging modalities. Late detection of OA compromises the opportunity for early intervention and prevention of disease progression, leaving only symptom management or, ultimately, joint replacement as strategies for treatment. Recent evidence and scientific appreciation that underlying metabolic dysfunction is a risk factor for osteoarthritis incidence and progression suggests that biomarkers which identify individuals with disordered metabolism may be relevant for subclinical markers of OA. Metabolomics, a newly evolving field, analyzes small molecules (metabolites) in biological specimens. Metabolomics analysis has successfully identified novel biomarkers for diagnosis, monitoring and treatment for age-related diseases such as prostate cancer, diabetes and stenosis and autoimmune diseases such as rheumatoid arthritis. A small but growing number of studies in animal and human populations have reported that metabolomics yields potential biomarkers with good discrimination between OA patients and normal controls including metabolites associated with collagen, branched chain amino acid, energy, and tryptophan metabolism. However, no studies to date have neither used metabolomics to identify biomarkers for OA incidence nor evaluated biomarkers among individuals matched for age and body size. We propose to conduct a metabolomics analysis of osteoarthritis risk within the longitudinal Michigan Study of Women's Health Across the Nation (MI-SWAN). Specifically, 63 MI-SWAN women who developed radiographic knee OA

during follow-up will be age- and BMI-matched with 63 MI-SWAN women who remained OA-free during follow-up. Banked plasma specimens from baseline (when all subjects were OA-free) will be used to conduct metabolomics analyses using the targeted lipids eicosanoids platform (Aim 1) which includes profiles from 28 eicosanoids, the lipidomics platform (Aim 2) which profiles lipids from over 10 classes including 431 unique lipid species, and an untargeted platform (Aim 3) which profiles at least 250 known compounds to identify candidate biomarkers for knee osteoarthritis risk. Relative quantitation of these metabolites will be compared within the matched pairs of women who did and did not develop incident knee OA during follow-up. This K01 award will provide needed training and skill development in metabolomics, the associated bioinformatics considerations, and translation to clinical care and yield preliminary data to support the submission of an R01 application. This training will enable the candidate to develop as an independent investigator providing leadership in the application of metabolomics research in aging with the long-term goal of applying this approach to identify key metabolic pathways involved in aging and the disablement process.

9. 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 Michigan's 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.

10. Project Title: CUMULATIVE AND SYNERGISTIC IMPACT OF CHRONIC DISEASES ON PHYSICAL FUNCTIONING IN OLDER ADULTS: DEVELOPMENT AND VALIDATION OF A NOVEL MEASURE OF MULTIMORBIDITY

Leader(s): WEI, MELISSA
UNIVERSITY OF MICHIGAN AT ANN ARBOR

NIH K23AG056638 / (2017 - 2022)**Core(s):**

Project Summary / Abstract Multimorbidity, the coexistence of multiple chronic conditions, poses a major and growing challenge to aging adults, their families, and healthcare systems. Most older adults have multiple chronic conditions that interact to profoundly affect physical functioning and health-related quality of life. Despite this, critical gaps remain in the measurement of multimorbidity. In particular, there are few practical tools to guide clinicians, researchers, and policymakers who seek to improve the care for older adults. Current measures for multimorbidity have used mortality, healthcare cost, and utilization, but have not focused on patient-centered outcomes to quantify burden of disease. Statistical limitations in traditional methods to measure disease interactions beyond simple two-way disease interactions have also hampered our epidemiologic understanding of multimorbidity and its full impact on health and functional outcomes. To bridge these gaps, this proposal aims to 1) Develop and validate a new multimorbidity index for use in ICD-coded conditions; 2) Refine the multimorbidity index by incorporating multiple-order disease interactions and determine the incremental value of their inclusion; and 3) Assess the utility of the multimorbidity index through its association with key functional outcomes including physical and cognitive performance, basic and instrumental activities of daily living, depression, and mortality. The proposed studies will use unique data linkages between patient-reported outcomes in the nationally-representative Health and Retirement Study and Medicare claims to develop and internally validate a multimorbidity index for International Classification of Diseases (ICD)-coded chronic conditions weighted to physical functioning. Novel approaches to data shrinkage techniques will be used to select significant interactions among multiple potential disease combinations associated with physical functioning. The utility of the multimorbidity index will be assessed through its prospective associations with physical and cognitive performance, basic and instrumental activities of daily living, and mortality. The successful completion of these studies will yield a validated multimorbidity measure that captures the impact of coexisting chronic diseases on physical functioning in older adults relevant for clinical care, research, and policy. Through this award, the candidate will achieve immediate career goals to gain new specialized skills in using administrative claims, ICD coded data, and novel statistical approaches to high-dimension data, and achieve a deeper understanding of measuring key health outcomes in older adults with multimorbidity. The facilities, sponsoring department, and intellectual resources at the University of Michigan provide an exceptional milieu for this career development award and Early Stage Investigator. The training and professional development acquired through this award will contribute to the candidate's long-term goal to be an independent clinician-investigator focused on improving the management, quality of care, and prognosis of vulnerable older adults with multimorbidity.

11. 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.

12. 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.

13. Project Title: Decision Making for Cardiovascular Therapy in Adults with Mild Cognitive Impairment

Leader(s): LEVINE, DEBORAH
UNIVERSITY OF MICHIGAN AT ANN ARBOR
NIH R01AG051827 / (2016 - 2022)

Core(s):

DESCRIPTION (provided by applicant): There is a fundamental gap in understanding how mild cognitive impairment (MCI) influences treatment and decision making for serious illnesses, like cardiovascular disease (CVD), in older patients. Poor understanding of clinical decision making is a critical barrier to the design of interventions to improve the quality and outcomes of CVD care of in older patients with MCI. The long-term goal of this research is to develop, test, and disseminate interventions aimed to improve the quality and outcomes of CVD care and to reduce CVD-related disability in older Americans with MCI. The objective of this application is to determine the extent to which people with MCI are receiving sub-standard care for the two most common CVD events, acute myocardial infarction (AMI) and acute ischemic stroke, increasing the chance of mortality and morbidity in a population with otherwise good quality of life, and to determine how MCI influences patient preferences and physician recommendations for treatment. AMI and acute ischemic stroke are excellent models of serious, acute illnesses with a wide range of effective therapies for acute management, rehabilitation, and secondary prevention. Our central hypothesis is that older adults with MCI are undertreated for CVD because patients and physicians overestimate their risk of dementia and underestimate their risk of CVD. This hypothesis has been formulated on the basis of preliminary data from the applicants' pilot research. The rationale for the proposed research is that understanding how patient preferences and physician recommendations contribute to underuse of CVD treatments in patients with MCI has the potential to translate into targeted interventions aimed to improve the quality and outcomes of care, resulting in new and innovative approaches to the treatment of CVD and other serious, acute illnesses in adults with MCI. Guided by strong preliminary data, this hypothesis will be tested by pursuing two specific aims: 1) Compare AMI and stroke treatments between MCI patients and cognitively normal patients and explore differences in clinical outcomes associated with treatment differences; and 2) Determine the influence of MCI on patient and surrogate preferences and physician recommendations for AMI and stroke treatment. Under the first aim, a health services research approach- shown to be feasible in the applicants' hands-will be used to quantify the extent and outcomes of treatment differences for AMI and acute ischemic stroke in older patients with MCI. Under the second aim, a multi-center, mixed-methods approach and a national physician survey, which also has been proven as feasible in the applicants' hands, will be used to determine the influence of MCI on patient preferences and physician recommendations for AMI and stroke treatment. This research proposal is innovative because it represents a new and substantially different way of addressing the important public health problem of enhancing the health of older adults by determining the extent and causes of underuse of effective CVD treatments in those with MCI. The proposed research is significant because it is expected to vertically advance and expand understanding of how MCI influences treatment and decision making for AMI and ischemic stroke in older patients. Ultimately, such knowledge has the potential to inform the development of targeted interventions

that will help to improve the quality and outcomes of CVD care and to reduce CVD-related disability in older Americans.

14. 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.

15. 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.

16. 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.

17. 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 1 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.

18. 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.

19. 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 JDRE, 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 albuminuria. 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.

20. 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.

21. 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.

22. 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 racial/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 disparities. The long-term goal of this research is to develop, test, and disseminate interventions that prevent CID and can be applied to diverse populations. The objectives of this study are to quantify the effects of racial/ethnic differences in BP control on racial/ethnic differences in CID, to quantify the potential impact of optimal BP treatment intensity to reduce racial/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 disparities 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 important. Under Aim 1, a health services research approach with pooled cohort studies shown to be feasible in the applicants' hands will be used to measure the effects of BP levels and use of antihypertensive medication from young adulthood to late-life on CID risk. Under Aims 2 and 3, a simulation modeling approach, which also has been proven as feasible in the applicants' hands, will be used to quantify the individual and societal effects of eliminating racial/ethnic differences 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 cohorts 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 intensity 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 prevention of CID and to reduce CID-related disability in older Americans particularly minorities.

23. Project Title: IMPLEMENTING MAGIC TO IMPROVE PICC APPROPRIATENESS AND PATIENT OUTCOMES

**Leader(s): CHOPRA, VINEET
UNIVERSITY OF MICHIGAN AT ANN ARBOR
AHRQ R18HS025891 / (2018 - 2022)**

Core(s):

Use of peripherally inserted central catheters (PICCs) for intravenous antibiotics, infusion of chemotherapy or invasive hemodynamic monitoring has grown substantially in hospitalized patients. Although such use reflects advantages of PICCs (such as safer insertion in veins of the arm compared to veins of the neck or chest for conventional central venous catheters), not all PICCs are placed for appropriate reasons. Furthermore, PICCs are associated with important complications, including venous thromboembolism (VTE) and central line-associated bloodstream infection (CLABSI). Identifying and balancing the risks and benefits related to PICCs is critical to ensuring patient safety. The long-term objective of this study is to improve use and outcomes of PICCs across hospitals in the United States. Supported by funding from an AHRQ K award, the PI for this proposal developed the Michigan Appropriateness Guide to Intravenous Catheters (MAGIC), an evidence-based tool to inform and improve PICC use in hospital settings. This research project now aims to (a) implement MAGIC across 48-hospitals to determine whether it can improve appropriateness of PICCs; (b) evaluate whether improvements in PICC appropriateness are associated with fewer complications; and (c), identify what aspects of implementation at the hospital level led to the greatest change in appropriateness and complications. The study will leverage a large Blue Cross/Blue Shield of Michigan-funded collaborative quality improvement consortium: the Michigan Hospital Medicine Safety (HMS) consortium. Given a robust infrastructure for data collection and 48-member hospitals all actively engaged in improving PICC safety, HMS is the ideal setting to test MAGIC. Knowledge generated from this study will be seminal to making healthcare safer and understanding what provider and systems factors are associated with hospital performance both priority areas for AHRQ. This project will be the first large scale implementation of a tool that has the potential to substantially improve the safety of thousands of patients that receive PICCs. Exceptional resources and team with extensive expertise in implementation science, patient safety and health services research make the University of Michigan an ideal environment for this proposal.

24. 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.

25. 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.

26. 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 α -estradiol (17 α E2), 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 17 α E2. 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.

27. 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.

28. 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.

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Bartke A, Sun LY, Li X, Miller RA

Front Endocrinol (Lausanne), 2022, 13: 797581<https://doi.org/10.3389/fendo.2022.797581> | PMID: 35282433 | PMCID: PMC8916564

Citations: 1 | AltScore: 1.25

2. COVID-19 vaccine side effects among nursing home residents and staff.

Bhatnagar S, Jones K, Montoya A

J Med Virol, 2022 Apr 1, 94(8): 3491-3493<https://doi.org/10.1002/jmv.27756> | PMID: 35365909 | PMCID: PMC9088376

Citations: | AltScore: 2.25

3. Physician Diagnosis and Knowledge of Mild Cognitive Impairment.

Blair EM, Zahuranec DB, Forman J, Reale BK, Langa KM, Giordani B, Fagerlin A, Kollman C, Whitney RT, Levine DA

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Citations: | AltScore: 7

4. Multimorbidity Accumulation Among Middle-Aged Americans: Differences by Race/Ethnicity and Body Mass Index.

Botosaneanu A, Markwardt S, Nagel CL, Allore HG, Newsom JT, Dorr DA, Quiñones AR

J Gerontol A Biol Sci Med Sci, 2022 Feb 3, 77(2): e89-e97<https://doi.org/10.1093/gerona/qlab116> | PMID: 33880490 | PMCID: PMC8824553

Citations: | AltScore: 19.33

5. Anticholinergic medication burden and cognitive function in participants of the ASPREE study.

Broder JC, Ryan J, Shah RC, Lockery JE, Orchard SG, Gilmartin-Thomas JF, Fravel MA,

Owen AJ, Woods RL, Wolfe R, Storey E, Murray AM, Ernst ME

Pharmacotherapy, 2022 Feb, 42(2): 134-144<https://doi.org/10.1002/phar.2652> | PMID: 34866212 | PMCID: PMC8863638

Citations: | AltScore: 8.3

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Debarba LK, Jayarathne HSM, Miller RA, Garratt M, Sadagurski M

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8. Long-Term Blood Pressure Variability and Kidney Function in Participants of the ASPREE Trial.

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RL, Beilin L, Margolis KL, Murray AM, Polkinghorne KR

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Citations: 1 | AltScore: 1.25

9. **Association of Exposure to High-risk Antibiotics in Acute Care Hospitals With Multidrug-Resistant Organism Burden in Nursing Homes.**

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<https://doi.org/10.1001/jamanetworkopen.2021.44959> | PMID: 35103795 | PMCID: PMC8808331

Citations: 1 | AltScore: 44.45

10. **Advancing Clinical Trials in Nursing Homes: A Proposed Roadmap to Success.**

Gurwitz JH, Quinn CC, Abi-Elias IH, Adams AS, Bartel R, Bonner A, Boxer R, Delude C, Gifford D, Hanson B, Ito K, Jain P, Magaziner JS, Mazor KM, Mitchell SL, Mody L, Nace D, Ouslander J, Reifsnnyder J, Resnick B, Zimmerman S

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Jayarathne HSM, Debarba LK, Jaboro JJ, Ginsburg BC, Miller RA, Sadagurski M

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Larouche JA, Fraczek PM, Kurpiers SJ, Yang BA, Davis C, Castor-Macias JA, Sabin K,

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16. **Association Between Informant-Reported Sleep Disturbance and Incident Dementia: An Analysis of the National Alzheimer's Coordinating Center Uniform Data Set.**
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Marshall C, Havis I, Herreshoff E, Lewis C, Kotagal V
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Mody L, Gill TM, Zieman SJ

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<https://doi.org/10.1093/gerona/glab188> | PMID: 34216218 | PMCID: PMC8824556

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Neumann JT, Riaz M, Bakshi A, Polekhina G, Thao LTP, Nelson MR, Woods RL, Abraham G, Inouye M, Reid CM, Tonkin AM, McNeil J, Lacaze P

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Polenick CA, Lei L, Zhou AN, Birditt KS, Maust DT

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Sato T, Shapiro JS, Chang HC, Miller RA, Ardehali H

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Sheng Y, Carpenter JS, Ashton-Miller JA, Miller JM

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Shi X, Endicott SJ, Miller RA

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Solomon DH, Colvin A, Lange-Maia BS, Derby C, Dugan S, Jackson EA, Ruppert K, Karvonen-Gutierrez C, Santacroce L, Strotmeyer ES, Avis NE

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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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37. **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

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Wink L, Miller RA, Garcia GG

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Wu Z, Woods RL, Wolfe R, Storey E, Chong TTJ, Shah RC, Orchard SG, McNeil JJ, Murray AM, Ryan J, ASPREE Investigator Group.

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Citations: | AltScore: 4

118. **Effect of Statin Therapy on Cognitive Decline and Incident Dementia in Older Adults.**

Zhou Z, Ryan J, Ernst ME, Zoungas S, Tonkin AM, Woods RL, McNeil JJ, Reid CM, Curtis AJ, Wolfe R, Wrigglesworth J, Shah RC, Storey E, Murray A, Orchard SG, Nelson MR, ASPREE Investigator Group.

J Am Coll Cardiol, 2021 Jun 29, 77(25): 3145-3156

<https://doi.org/10.1016/j.jacc.2021.04.075> | PMID: 34167639 | PMCID: PMC8091356

Citations: 4 | AltScore: 249.5

119. **Commentary: Special care considerations in older adults hospitalized with COVID-19.**

Zietlow KE, Wiggins J, Jenq G, Patel PK, Mody L, Dewar S

Aging Health Res, 2021 Sep, 1(3): 100023

<https://doi.org/10.1016/j.ahr.2021.100023> | PMID: 34151316 | PMCID: PMC8196475

Citations: 1 | AltScore: NA

EXTERNAL ADVISORY BOARD MEMBERS

Kenneth Schmader
Duke University
Serving since 2017 (5 years)

Alex Smith
San Francisco VA Medical Center
Serving since 2021 (1 years)

Rozalyn Anderson
University of Wisconsin
Serving since 2021 (1 years)

RECOGNITION AND AWARDS (2021-2022)

Jenq, Grace (2021)

- Chairs Award For Impact

Mody, Lona (2021)

- MICHR Distinguished Clinical and Translational Research Mentor Award

MINORITY RESEARCH

General Brief Description of Minority Activities:

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:

Briceño EM, Mehdipanah R, Gonzales XF, Heeringa SG, Levine DA, **Langa KM**, Zahs D, Garcia N, Longoria R, Morgenstern LB. Bilingualism, assessment language, and the Montreal Cognitive Assessment in Mexican Americans. *J Am Geriatr Soc.* 2021 Jul;69(7):1971-1981. doi: 10.1111/jgs.17209. Epub 2021 May 7. PMID: 33963535; PMCID: PMC8273138.

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.

Jones LM, Moss KO, Mitchell J, Still C, **Hawkins J**, Tang E, Wright KD. Challenges to dietary hypertension self-management as described by a sample of African American older adults. *Worldviews Evid Based Nurs.* 2022 Feb;19(1):64-72. doi: 10.1111/wvn.12555. Epub 2022 Jan 22. PMID: 35064763.

Leggett AN, Strominger J, Robinson-Lane SG, **Maust DT**. Disparities in Health Care Task Participation and Provider Communication by Family Caregiver Race J Gen Intern Med. 2022 Apr;37(5):1321-1324. doi: 10.1007/s11606-021-06766-w. Epub 2021 Apr 8. PMID: 33830417; PMCID: PMC8971267.

Tipirneni R, Karmakar M, **Maust DT**. Trends and Disparities in Functional Impairment among US Adults Age 55-64, 2002 to 2016. J Gen Intern Med. 2021 Dec;36(12):3903-3906. doi: 10.1007/s11606-020-06209-y. Epub 2020 Sep 11. PMID: 32918202; PMCID: PMC8642514.

Minority Trainee(s):

- Emily Briceño-Abreau, PhD, Assistant Professor, Physical Medicine and Rehabilitation
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, Ph.D. , Assistant Professor, University of Michigan School of Social Work, Associate Director of the Gender and Health Research Lab'
REC & PESC Recipient 2020 Type 2 Diabetes Self-Management in Older African American Men: A Peer Leader Pilot Intervention

Minority Grant(s):

MOUNT SINAI MEDICAL CENTER

Claude D. Pepper Older Americans Independence Center

Albert L. Siu, M.D. Principal Investigator	212-241-4290	albert.siu@mssm.edu
R. Sean Morrison, MD Co-Principle Investigator	212-241-1466	sean.morrison@mssm.edu
Christian Espino Program Administrator	212-241-4632	christian.espino@mssm.edu

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 supports 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)

Leader 1: Albert Siu, MD, MSPH albert.siu@mssm.edu

Leader 2: 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)

Leader 1: Nathan Goldstein, MD nathan.goldstein@mssm.edu

Leader 2: 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)

Leader 1: Kenneth Boockvar, MD, MS kenneth.boockvar@mssm.edu

Leader 2: 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: Amy Kelley, MD, MSHS amy.kelley.mssm.edu

Leader 2: Katherine Ornstein, PhD katherine.ornstein@mssmn.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: Carolyn Zhu, PhD carolyn.zhu@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

Rita C Crooms

2020-2022 /

Instructor / Mount Sinai Department of Neurology

6 (total)

Palliative Care for High-Grade Glioma

5 (1st/Sr)

Specific Aims: High grade gliomas (HGG) account for 80-85% of primary brain tumors. Despite advances in cancer-directed therapy, patients with HGG have poor prognosis and median survival on the order of months. Patients have significant supportive care needs, but are referred to palliative care and hospice less frequently and later in their disease course than patients of other cancer types. The reasons for these discrepancies are not clearly described in the literature. There have been a number of studies, both qualitative and quantitative, suggesting that this population has a high burden of physical and psychosocial symptoms and substantial unmet need for comprehensive symptom management and palliation. However, despite evidence of unmet symptom management and advance care planning needs for glioma patients, it is not clear how much different potential barriers (at the level of patient, provider, and system) contribute to these gaps in care and thus should be the targets of clinical and/or policy interventions. To characterize these barriers and the extent to which they impact care quality, this proposal has the following aims: 1. a. To quantify the degree to which palliative care needs, including comprehensive symptom assessment, psychosocial support, and advance care planning for HGG patients are currently being met relative to established standards of palliative care, as well as to characterize at what point in the disease trajectory specialty palliative care involvement becomes appropriate. Hypothesis: HGG patients have a broad range of palliative care needs that are not being met or are addressed at a very advanced stage of disease. b. To assess existing structural approaches to providing supportive care services in a range of neuro-oncology treatment settings. Hypothesis: Some neuro-oncology centers have some supportive care structures in place that incompletely address palliative care needs and should be taken into account when designing new interventions. 2. a. To determine the preferences of HGG patients and their caregivers regarding approaches for introducing palliative care closer to time of diagnosis. Hypothesis: HGG patients are open to receiving palliative care when it is introduced and framed in a way that accurately reflects the role of palliative care as an additional layer of specialized support to augment, rather than replace, cancer-directed treatment and that emphasizes palliative care as distinct from hospice and end of life care. b. To characterize neuro-oncologist attitudes regarding the timing, method of delivery, and perceived impact of palliative care for HGG patients. Hypothesis: Neuro-oncologists are reluctant to refer patients to palliative care

Leah Blank

2020-2022 /

Assistant Professor / Mount Sinai Department of Neurology

17 (total)

Guideline Concordant Prescription in Older Adults with New Epilepsy:

9 (1st/Sr)

Determinants and Outcomes

Epilepsy incidence peaks in older adults and over 95% of persons with epilepsy (PWE) are on anti-seizure medication (ASM), yet up to 40% of newly diagnosed patients are still started on medications that carry unnecessary risk. Older adults are more vulnerable to medication adverse effects due to comorbidities and polypharmacy. While neurologic societies have created evidence-based recommendations for the initial use of particular agents (e.g. levetiracetam, lamotrigine) that mitigate drug adverse events, these recommendations remain inconsistently applied, likely related to ineffective knowledge dissemination strategies. Initial drug choice in epilepsy is particularly important because once a drug is prescribed it is often not changed. This clinical inertia exists because 1) most will experience seizure reduction with their first drug, and 2) drug switching can be dangerous, leading to breakthrough seizures. Therefore, older adults with epilepsy are often exposed to their first drug long-term. Furthermore, initial drug discontinuation is associated with future non-adherence, putting those who receive sub-optimal first prescriptions at higher risk of long-term seizure related injury and mortality. As our population ages, epilepsy incidence is expected to continue to grow with the overwhelming majority of new cases in the older adult population. In this growing population, epilepsy is associated with a range of cognitive and psychological comorbidities which may additionally complicate decision-making around prescription choice. The ultimate goal of this work is to improve epilepsy outcomes in older adults by improving evidence-based prescribing in new-onset epilepsy.

In order to develop and implement a point-of-care decision aid for evidence-based first prescription we must first define determinants of suboptimal prescription as well as the short-term adverse outcomes associated with non-guideline-concordant prescription.

Julia L. Frydman

Instructor / Mount Sinai Department of Geriatrics & Palliative Medicine
Predictors of Inpatient Palliative Care Consultation for Older Adults with COVID-19

2020-2022 /
 12 (total)
 7 (1st/Sr)

Specific Aims: Current literature regarding palliative care for patients with COVID-19 is limited, documenting challenges of prognostication in the setting of limited clinical information, changes in code status after consultation, and expansion of palliative care services during the pandemic. Understanding referral patterns to specialty palliative care consultation is crucial to ensuring all patients have equal access to high-quality serious illness communication at the right time in their illness trajectories. Given the widely recognized disparities in morbidity and mortality during the COVID-19 pandemic, it is particularly important to assess whether race was a predictor of inpatient palliative care consultation. Significant racial disparities in palliative care existed prior to the pandemic. Although not studied in the context of palliative care specifically, provider implicit racial bias, or the unconscious reliance on negative cultural stereotypes, is hypothesized to be one determinant of racial disparities in healthcare. Studies have shown that physicians, like the population at large, have pro-White implicit bias. Furthermore, there is evidence that implicit racial bias has a tangible impact on provider behavior. It is important to know whether primary providers' implicit racial bias may have influenced consultative practice for patients with COVID-19. The exacerbators of implicit bias – time pressure and clinical uncertainty – were ubiquitous at the height of the pandemic, potentially leading to reliance on negative cultural stereotypes: Did providers assume that Black patients had worse prognoses compared to White patients of similar illness severity? And, did this assumption lead them to pursue palliative care consults earlier as a substitute for disease-directed therapy?

Zainab Totah Osakwe

PhD, MSN, RN, NP. Assistant Professor / College of Nursing and Public Health, Adelphi University
National Perspectives of Nurse Practitioner (NP) Provider Home Based Medical Care (HBMC) in Assisted Living Communities

2021-2022 /
 8 (total)
 5 (1st/Sr)

Persons with Alzheimer's disease and related dementias (ADRD) who live in the community have particularly high unmet needs for consistent medical care and use the emergency department (ED) for episodic care more frequently than their counterparts in nursing homes.^{1,2} By bringing medical care to the homes of individuals who have difficulty accessing office-based care, home based medical care (HBMC) appears to be one approach to preventing poor outcomes associated with potentially avoidable hospital use.^{3,4} Despite the apparent benefits, wide scale implementation of HBMC has been slow, mainly because of the critical shortage of HBMC providers.⁴ Consequently, other health care providers such as physician assistants and nurse practitioners (NPs) have been utilized to augment the physician workforce in the delivery of HBMC. In 2013, NPs made 1.1 million home visits and were the most common provider of home visits to rural residents in the U.S.^{5,6} In 2017, NPs provided over 2 million home visits and continued to be the predominant provider of home visits to older Americans including rural residents.⁷ Despite this high utilization of NP-provided HBMC, factors that may impact utilization of NP-home visits has not been adequately studied. Studies show wide variation in utilization of NP-HBMC based on NP state scope-of-practice laws.⁸ Recent data highlights that the growth of HBMC is driven by care delivered in the assisted living(AL) setting, and not private homes. Although a large share of AL residents are living with cognitive impairment and dementia, ^{9,10} we do not have insight into factors such as NP scope of practice laws, that may impact the use of NP-HBMC in AL settings. The proposed study will take a comprehensive approach to account for state and community-level factors that impact the use of NP-HBMC in AL communities nationwide. The proposed research builds upon an existing longitudinal study (Home-Based Clinical Care for Persons with Dementia; NIH P01 AG066605/ RP4), to achieve 2 specific aims. Aim 1. Examine variations in use of NP-HBMC across states in relations to state regulators environment in AL communities' policies. We will use Medicare Provider Utilization and Payment Data will be linked to Census/American Community Survey (socioeconomic disadvantage predictors), to examine the effect of state regulations (NP SOP and AL staffing for regulations for nursing – [registered nurse (RN) or licensed practical nurse (LPN) on NP provider availability in the delivery of HBMC. Our working hypothesis is that

restricted state NP SOP and AL regulations will be associated with decreased utilization of NP-HBMC. Aim 2. Identify factors associated with use of NP-HBMC in AL settings. We will identify areas with high and low/no utilization of NP HBMC and examine provider and community-level factors associated with greater use of NP-HBMC. Data on community characteristics of NP-HBMC provider locations will be linked to Medicare Provider Utilization and Payment Data

Past Scholars

Lili Chan, Mount Sinai Division of Nephrology (2019-2020)

Raj G. Kumar, Mount Sinai Department of Rehabilitation and Human Performance (2020-2021)

Aaron Baum, Mount Sinai Division of General Internal Medicine (2020-2021)

Matthew R Augustine, Mount Sinai Division of General Internal Medicine (2020-2021)

PILOT/EXPLORATORY PROJECTS (5 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 gleaned 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.

DEVELOPMENT PROJECTS (0 Development Projects Listed)

No development projects.

RESEARCH (0 Projects Listed)

PUBLICATIONS**2022****1. Impact of Comorbid Dementia on Patterns of Hospice Use.**

Aldridge MD, Hunt L, Husain M, Li L, Kelley A

J Palliat Med, 2022 Mar, 25(3): 396-404<https://doi.org/10.1089/jpm.2021.0055> | PMID: 34665050 | PMCID: PMC8968839

Citations: 1 | AltScore: 23.25

2. The Experience of Homebound Older Adults During the COVID-19 Pandemic.

Ankuda CK, Kotwal A, Reckrey J, Harrison KL, Ornstein KA

J Gen Intern Med, 2022 Feb 15, 37(5): 1177-1182<https://doi.org/10.1007/s11606-021-07361-9> | PMID: 35167063 | PMCID: PMC8853401

Citations: | AltScore: 5.5

3. Improving the Approach to Defining, Classifying, Reporting and Monitoring Adverse Events in Seriously Ill Older Adults: Recommendations from a Multi-stakeholder Convening.

Baim-Lance A, Ferreira KB, Cohen HJ, Ellenberg SS, Kuchel GA, Ritchie C, Sachs GA, Kitzman D, Morrison RS, Siu A

J Gen Intern Med, 2022 May 17<https://doi.org/10.1007/s11606-022-07646-7> | PMID: 35581446

Citations: | AltScore: NA

4. Prognostic disclosure in oncology - current communication models: a scoping review.

Bloom JR, Marshall DC, Rodriguez-Russo C, Martin E, Jones JA, Dharmarajan KV

BMJ Support Palliat Care, 2022 Jun, 12(2): 167-177<https://doi.org/10.1136/bmjspcare-2021-003313> | PMID: 35144938 | PMCID: PMC9119949

Citations: | AltScore: 4.5

5. Trends in Geriatric Conditions Among Older Adults Admitted to US ICUs Between 1998 and 2015.

Cobert J, Jeon SY, Boscardin J, Chapman AC, Ferrante LE, Lee S, Smith AK

Chest, 2022 Jan 11, 161(6): 1555-1565[pii: S0012-3692\(22\)00020-4. https://doi.org/10.1016/j.chest.2021.12.658](https://doi.org/10.1016/j.chest.2021.12.658) | PMID: 35026299 |

PMCID: PMC9248079

Citations: 1 | AltScore: 30.04

6. Access to Palliative Care Consultation for Hospitalized Adults with COVID-19 in an Urban Health System: Were There Disparities at the Peak of the Pandemic?

Frydman JL, Aldridge M, Moreno J, Singer J, Zeng L, Chai E, Morrison RS, Gelfman LP

J Palliat Med, 2022 Jan, 25(1): 124-129<https://doi.org/10.1089/jpm.2021.0313> | PMID: 34637349 | PMCID: PMC8721492

Citations: | AltScore: 6.25

7. Telemedicine Utilization in the Ambulatory Palliative Care Setting: Are There Disparities?

Frydman JL, Berkalieva A, Liu B, Scarborough BM, Mazumdar M, Smith CB

J Pain Symptom Manage, 2022 Mar, 63(3): 423-429<https://doi.org/10.1016/j.jpainsymman.2021.09.019> | PMID: 34644615 | PMCID:

PMC8854351

Citations: 1 | AltScore: 3.1

8. The Digital Divide: Do Older Adults with Serious Illness Access Telemedicine?

Frydman JL, Gelfman LP, Goldstein NE, Kelley AS, Ankuda CK

J Gen Intern Med, 2022 Mar, 37(4): 984-986

<https://doi.org/10.1007/s11606-021-06629-4> | PMID: 33559064 | PMCID: PMC7870026

Citations: 4 | AltScore: 9

9. Telemedicine Uptake Among Older Adults During the COVID-19 Pandemic.

Frydman JL, Li W, Gelfman LP, Liu B

Ann Intern Med, 2022 Jan, 175(1): 145-148

<https://doi.org/10.7326/M21-2972> | PMID: 34748380 | PMCID: PMC8845076

Citations: 1 | AltScore: 46.054

10. Attitudes toward deprescribing among older adults with dementia in the United States.

Growdon ME, Espejo E, Jing B, Boscardin WJ, Zullo AR, Yaffe K, Boockvar KS, Steinman MA

J Am Geriatr Soc, 2022 Mar 10, 70(6): 1764-1773

<https://doi.org/10.1111/jgs.17730> | PMID: 35266141 | PMCID: PMC9177826

Citations: | AltScore: 110.25

11. Life expectancy for community-dwelling persons with dementia and severe disability.

Harrison KL, Ritchie CS, Hunt LJ, Patel K, Boscardin WJ, Yaffe K, Smith AK

J Am Geriatr Soc, 2022 Mar 31, 70(6): 1807-1815

<https://doi.org/10.1111/jgs.17767> | PMID: 35357694 | PMCID: PMC9177709

Citations: | AltScore: 35.25

12. Incidence of potentially disruptive medical and social events in older adults with and without dementia.

Hunt LJ, Morrison RS, Gan S, Espejo E, Ornstein KA, Boscardin WJ, Smith AK

J Am Geriatr Soc, 2022 Feb 5, 70(5): 1461-1470

<https://doi.org/10.1111/jgs.17682> | PMID: 35122662 | PMCID: PMC9106866

Citations: | AltScore: 27.25

13. Improving Patient Activation among Older Veterans: Results from a Social Worker-Led Care Transitions Intervention.

Koufacos NS, May J, Judon KM, Franzosa E, Dixon BE, Schubert CC, Schwartzkopf AL, Guerrero VM, Traylor M, Boockvar KS

J Gerontol Soc Work, 2022 Jan, 65(1): 63-77

<https://doi.org/10.1080/01634372.2021.1932003> | PMID: 34053407 | PMCID: PMC8982469

Citations: | AltScore: NA

14. Development and Validation of a Functionally Relevant Comorbid Health Index in Adults Admitted to Inpatient Rehabilitation for Traumatic Brain Injury.

Kumar RG, Zhong X, Whiteneck GG, Mazumdar M, Hammond FM, Egorova N, Lercher K, Dams-O'Connor K

J Neurotrauma, 2022 Jan, 39(1-2): 67-75

<https://doi.org/10.1089/neu.2021.0180> | PMID: 34779252 | PMCID: PMC8917887

Citations: | AltScore: 2.85

15. A national profile of health-focused caregiving activities prior to a new cancer diagnosis.

Liu B, Kent EE, Dionne-Odom JN, Alpert N, Ornstein KA

J Geriatr Oncol, 2022 May, 13(4): 454-461

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Citations: 1 | AltScore: 4.7

16. Examining variation in state spending on medicaid long-term services and supports for older adults.

Mellgard G, Ankuda C, Rahman OK, Kelley A

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Citations: | AltScore: NA

17. **Impact of radiotherapy on daily function among older adults living with advanced cancer (RT impact on function in advanced cancer).**

Nehlsen A, Agarwal P, Mazumdar M, Dutta P, Goldstein NE, Dharmarajan KV

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<https://doi.org/10.1016/j.jgo.2021.07.007> | PMID: 34362714 | PMCID: PMC9044675

Citations: | AltScore: 1.25

18. **The Safety and Efficacy of Radiation Therapy with Concurrent Dexamethasone, Cyclophosphamide, Etoposide, and Cisplatin-Based Systemic Therapy for Multiple Myeloma.**

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

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Citations: | AltScore: 4.6

19. **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](https://doi.org/10.1016/j.jgo.2022.02.007) | PMID: 35227626 |

PMCID: PMC9283217

Citations: | AltScore: 6.35

20. **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

[pii: S1525-8610\(21\)01103-8. https://doi.org/10.1016/j.jamda.2021.12.029](https://doi.org/10.1016/j.jamda.2021.12.029) | PMID: 35063398

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Citations: | AltScore: 1.6

21. **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

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PMC9122661

Citations: 1 | AltScore: 3.85

22. **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

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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: | AltScore: 30.5

24. 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: | AltScore: 4.35

25. 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

Citations: 1 | AltScore: 2.75

26. 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

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2021

1. Service Availability in Assisted Living and Other Community-Based Residential Settings at the End of Life.

Aldridge MD, Ornstein KA, McKendrick K, Reckrey J

J Palliat Med, 2021 Apr 7, 24(11): 1682-1688

<https://doi.org/10.1089/jpm.2020.0625> | PMID: 33826855 | PMCID: PMC8823677

Citations: 3 | AltScore: 4.45

2. Intensification of Diabetes Medications at Hospital Discharge and Clinical Outcomes in Older Adults in the Veterans Administration Health System.

Anderson TS, Lee AK, Jing B, Lee S, Herzig SJ, Boscardin WJ, Fung K, Rizzo A, Steinman MA

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3. Patterns of Material Hardship and Food Insecurity Among Older Adults During the COVID-19 Pandemic.

Ankuda CK, Fogel J, Kelley AS, Byhoff E

J Gen Intern Med, 2021 Nov, 36(11): 3639-3641

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Citations: 1 | AltScore: 6.2

4. Population-Based Screening for Functional Disability in Older Adults.

Ankuda CK, Freedman VA, Covinsky KE, Kelley AS

Innov Aging, 2021, 5(1): igaa065

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Citations: 1 | AltScore: 1

- 5. Opening the black box: Evaluating the care of people with serious illness in Medicare Advantage.**
Ankuda CK, Hunt LJ
J Am Geriatr Soc, 2021 Oct, 69(10): 2795-2798
<https://doi.org/10.1111/jgs.17344> | PMID: 34192344 | PMCID: PMC8497412
Citations: | AltScore: 25.05
- 6. The dynamics of being homebound over time: A prospective study of Medicare beneficiaries, 2012-2018.**
Ankuda CK, Husain M, Bollens-Lund E, Leff B, Ritchie CS, Liu SH, Ornstein KA
J Am Geriatr Soc, 2021 Jun, 69(6): 1609-1616
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Citations: 4 | AltScore: 29.3
- 7. Association of the COVID-19 Pandemic With the Prevalence of Homebound Older Adults in the United States, 2011-2020.**
Ankuda CK, Leff B, Ritchie CS, Siu AL, Ornstein KA
JAMA Intern Med, 2021 Dec 1, 181(12): 1658-1660
<https://doi.org/10.1001/jamainternmed.2021.4456> | PMID: 34424269 | PMCID: PMC8383159
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Ankuda CK, Morrison RS, Aldridge MD
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Citations: | AltScore: 29
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Citations: 2 | AltScore: 0.5
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Boockvar KS, Mak W, Burack OR, Canter BE, Reinhardt JP, Spinner R, Farber J, Weerahandi H
J Am Med Dir Assoc, 2021 Nov, 22(11): 2270-2271
<https://doi.org/10.1016/j.jamda.2021.09.002> | PMID: 34599885 | PMCID: PMC8429357
Citations: 1 | AltScore: NA
- 11. The Impact of Dementia on Cancer Treatment Decision-Making, Cancer Treatment, and Mortality: A Mixed Studies Review.**
Caba Y, Dharmarajan K, Gillezeau C, Ornstein KA, Mazumdar M, Alpert N, Schwartz RM, Taioli E, Liu B
JNCI Cancer Spectr, 2021 Jun, 5(3): pkab002
<https://doi.org/10.1093/jncics/pkab002> | PMID: 34056540 | PMCID: PMC8152697
Citations: 3 | AltScore: 6.75
- 12. Palliative Care Consultation for Hospitalized Patients with Primary and Secondary Brain Tumors at a Single Academic Center.**
Crooms RC, Lin HM, Neifert S, Deiner SG, Brallier JW, Goldstein NE, Gal JS, Gelfman LP
J Palliat Med, 2021 Sep, 24(10): 1550-1554
<https://doi.org/10.1089/jpm.2021.0088> | PMID: 34166114 | PMCID: PMC8568778

Citations: | AltScore: 0.25

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Diaz-Ramirez LG, Lee SJ, Smith AK, Gan S, Boscardin WJ
Comput Methods Programs Biomed, 2021 Jun, 204: 106073
<https://doi.org/10.1016/j.cmpb.2021.106073> | PMID: 33831724 | PMCID: PMC8098121
Citations: 1 | AltScore: NA
14. **Impact of event notification services on timely follow-up and rehospitalization among primary care patients at two Veterans Affairs Medical Centers.**
Dixon BE, Judon KM, Schwartzkopf AL, Guerrero VM, Koufacos NS, May J, Schubert CC, Boockvar KS
J Am Med Inform Assoc, 2021 Nov 25, 28(12): 2593-2600
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Franzosa E, Traylor M, Judon KM, Guerrero Aquino V, Schwartzkopf AL, Boockvar KS, Dixon BE
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<https://doi.org/10.1093/jamia/ocab074> | PMID: 33997903 | PMCID: PMC8324223
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Frydman JL, Gelfman LP, Lindenberger EC, Smith CB, Berns S, Kelley AS, Dow LA
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Gelfman LP, Mather H, McKendrick K, Wong AY, Hutchinson MD, Lampert RJ, Lipman HI, Matlock DD, Swetz KM, Pinney SP, Morrison RS, Goldstein NE
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Citations: 2 | AltScore: 12.25
19. **Palliative Care as Essential to a Hospital System's Pandemic Preparedness Planning: How to Get Ready for the Next Wave.**
Gelfman LP, Morrison RS, Moreno J, Chai E
J Palliat Med, 2021 May, 24(5): 656-658
<https://doi.org/10.1089/jpm.2020.0670> | PMID: 33373533 | PMCID: PMC8064944
Citations: 1 | AltScore: 1.85
20. **Polypharmacy among older adults with dementia compared with those without dementia in the United States.**

Growdon ME, Gan S, Yaffe K, Steinman MA

J Am Geriatr Soc, 2021 Jun 8, 69(9): 2464-2475

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Citations: | AltScore: 7

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Hua M, Fonseca LD, Morrison RS, Wunsch H, Fullilove R, White DB

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[pii: S0885-3924\(21\)00397-3. https://doi.org/10.1016/j.jpainsymman.2021.06.015](https://doi.org/10.1016/j.jpainsymman.2021.06.015) | PMID:

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24. Instead of wasting money on aducanumab, pay for programs proven to help people living with dementia.

Hunt LJ, Harrison KL, Covinsky KE

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Kalicki AV, Moody KA, Franzosa E, Gliatto PM, Ornstein KA

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Citations: 6 | AltScore: 51.3

26. The Serious Illness Population: Ascertainment via Electronic Health Record or Claims Data.

Kelley AS, Hanson LC, Ast K, Ciemins EL, Dunning SC, Meskow C, Ritchie CS

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Kotwal AA, Cenzer IS, Waite LJ, Covinsky KE, Perissinotto CM, Boscardin WJ, Hawkey LC, Dale W, Smith AK

J Am Geriatr Soc, 2021 Jul 11, 69(11): 3081-3091

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JAMA Intern Med, 2021 Nov 1, 181(11): 1528-1530
<https://doi.org/10.1001/jamainternmed.2021.3775> | PMID: 34309620 | PMCID: PMC8314172
Citations: | AltScore: 296.32
29. **Association between Lifetime History of Traumatic Brain Injury, Prescription Opioid Use, and Persistent Pain: A Nationally Representative Study.**
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Citations: 1 | AltScore: 10
30. **Design Considerations for Mobile Health Applications Targeting Older Adults.**
Li C, Neugroschl J, Zhu CW, Aloysi A, Schimming CA, Cai D, Grossman H, Martin J, Sewell M, Loizos M, Zeng X, Sano M
J Alzheimers Dis, 2021, 79(1): 1-8
<https://doi.org/10.3233/JAD-200485> | PMID: 33216024 | PMCID: PMC8837196
Citations: 4 | AltScore: NA
31. **The 32-Item Multilingual Naming Test: Cultural and Linguistic Biases in Monolingual Chinese-Speaking Older Adults.**
Li C, Zeng X, Neugroschl J, Aloysi A, Zhu CW, Xu M, Teresi JA, Ocepek-Welikson K, Ramirez M, Joseph A, Cai D, Grossman H, Martin J, Sewell M, Loizos M, Sano M
J Int Neuropsychol Soc, 2021 Jun 18, 28(5): 511-519
<https://doi.org/10.1017/S1355617721000746> | PMID: 34140060 | PMCID: PMC8729172
Citations: | AltScore: 10
32. **Barriers to learning a new technology to go online among older adults during the COVID-19 pandemic.**
Li W, Ornstein KA, Li Y, Liu B
J Am Geriatr Soc, 2021 Nov, 69(11): 3051-3057
<https://doi.org/10.1111/jgs.17433> | PMID: 34409589 | PMCID: PMC8446986
Citations: 4 | AltScore: 3.6
33. **Trends of hospitalizations among patients with both cancer and dementia diagnoses in New York 2007-2017.**
Liu B, Ornstein KA, Alpert N, Schwartz RM, Dharmarajan KV, Kelley AS, Taioli E
Healthc (Amst), 2021 Sep, 9(3): 100565
<https://doi.org/10.1016/j.hjdsi.2021.100565> | PMID: 34252707 | PMCID: PMC8453053
Citations: | AltScore: 7
34. **The Influence of Increasing Levels of Provider-Patient Discussion on Quit Behavior: An Instrumental Variable Analysis of a National Survey.**
Liu B, Zhan S, Wilson KM, Mazumdar M, Li L
Int J Environ Res Public Health, 2021 Apr 26, 18(9):
[pii: 4593. https://doi.org/10.3390/ijerph18094593](https://doi.org/10.3390/ijerph18094593) | PMID: 33926078 | PMCID: PMC8123707
Citations: | AltScore: NA
35. **Retrospective analysis of characteristics associated with higher-value radiotherapy episodes of care for bone metastases in Medicare fee-for-service beneficiaries.**
Marshall D, Aldridge MD, Dharmarajan K
BMJ Open, 2021 Oct 19, 11(10): e049009
<https://doi.org/10.1136/bmjopen-2021-049009> | PMID: 34667003 | PMCID: PMC8527129

Citations: | AltScore: 1.75

36. **All you need is love: Yet another social determinant of health.**

Meier DE, Morrison RS

J Am Geriatr Soc, 2021 Nov, 69(11): 3020-3022

<https://doi.org/10.1111/jgs.17421> | PMID: 34409585 | PMCID: PMC8595554

Citations: 1 | AltScore: 52.75

37. **Senior Associate Editor's Response to Readers' Comments to Morrison: Advance Directives/Care Planning: Clear, Simple, and Wrong (DOI: 10.1089/jpm.2020.0272).**

Morrison RS

J Palliat Med, 2021 Jan, 24(1): 14-15

<https://doi.org/10.1089/jpm.2020.0526> | PMID: 33095092 | PMCID: PMC9206472

Citations: 1 | AltScore: 3.35

38. **What's Wrong With Advance Care Planning?**

Morrison RS, Meier DE, Arnold RM

JAMA, 2021 Oct 26, 326(16): 1575-1576

<https://doi.org/10.1001/jama.2021.16430> | PMID: 34623373

Citations: 9 | AltScore: 449.472

39. **Deprescribing Blood Pressure Treatment in Long-Term Care Residents.**

Odden MC, Lee SJ, Steinman MA, Rubinsky AD, Graham L, Jing B, Fung K, Marcum ZA, Peralta CA

J Am Med Dir Assoc, 2021 Dec, 22(12): 2540-2546.e2

<https://doi.org/10.1016/j.jamda.2021.07.009> | PMID: 34364847 | PMCID: PMC8627463

Citations: 2 | AltScore: 34.5

40. **Engagement in Meaningful Activities Among Older Adults With Disability, Dementia, and Depression.**

Oh A, Gan S, Boscardin WJ, Allison TA, Barnes DE, Covinsky KE, Smith AK

JAMA Intern Med, 2021 Apr 1, 181(4): 560-562

<https://doi.org/10.1001/jamainternmed.2020.7492> | PMID: 33492334 | PMCID: PMC7835951

Citations: 1 | AltScore: 83.19

41. **Medicare-funded home-based clinical care for community-dwelling persons with dementia: An essential healthcare delivery mechanism.**

Ornstein KA, Ankuda CK, Leff B, Rajagopalan S, Siu AL, Harrison KL, Oh A, Reckrey JM, Ritchie CS

J Am Geriatr Soc, 2021 Dec 22, 70(4): 1127-1135

<https://doi.org/10.1111/jgs.17621> | PMID: 34936087 | PMCID: PMC8986555

Citations: 1 | AltScore: 12.5

42. **Prospective assessment of dementia on transitions in homeboundness using multistate Markov models.**

Ornstein KA, Liu SH, Husain M, Ankuda CK, Bollens-Lund E, Kelley AS, Garrido MM

J Am Geriatr Soc, 2021 Dec 23, 70(4): 1117-1126

<https://doi.org/10.1111/jgs.17631> | PMID: 34951008 | PMCID: PMC8986556

Citations: | AltScore: 11.85

43. **Expanding the Palliative Care Workforce during the COVID-19 Pandemic: An Evaluation of Core Palliative Care Skills in Health Social Workers.**

Pelleg A, Chai E, Morrison RS, Farquhar DW, Berglund K, Gelfman LP

J Palliat Med, 2021 Nov, 24(11): 1705-1709

<https://doi.org/10.1089/jpm.2021.0027> | PMID: 34191595 | PMCID: PMC8823669

Citations: | AltScore: 5.35

44. **A national profile of kinlessness at the end of life among older adults: Findings from the Health and Retirement Study.**
Plick NP, Ankuda CK, Mair CA, Husain M, Ornstein KA
J Am Geriatr Soc, 2021 Apr 21, 69(8): 2143-2151
<https://doi.org/10.1111/jgs.17171> | PMID: 33880751 | PMCID: PMC8373783
Citations: 1 | AltScore: 28.35
45. **Prevalence of Memory-Related Diagnoses Among U.S. Older Adults With Early Symptoms of Cognitive Impairment.**
Qian Y, Chen X, Tang D, Kelley AS, Li J
J Gerontol A Biol Sci Med Sci, 2021 Sep 13, 76(10): 1846-1853
<https://doi.org/10.1093/gerona/glab043> | PMID: 33575783 | PMCID: PMC8436977
Citations: | AltScore: 15.05
46. **Paid Caregivers in the Community-based Dementia Care Team: Do Family Caregivers Benefit?**
Reckrey JM, Boerner K, Franzosa E, Bollens-Lund E, Ornstein KA
Clin Ther, 2021 Jun, 43(6): 930-941
<https://doi.org/10.1016/j.clinthera.2021.03.022> | PMID: 33972126 | PMCID: PMC8440352
Citations: 4 | AltScore: NA
47. **Family Caregiving for Those With and Without Dementia in the Last 10 Years of Life.**
Reckrey JM, Bollens-Lund E, Husain M, Ornstein KA, Kelley AS
JAMA Intern Med, 2021 Feb 1, 181(2): 278-279
<https://doi.org/10.1001/jamainternmed.2020.4012> | PMID: 33252607 | PMCID: PMC7851727
Citations: 4 | AltScore: 18.4
48. **Barriers to implementation of STRIDE, a national study to prevent fall-related injuries.**
Reckrey JM, Gazarian P, Reuben DB, Latham NK, McMahon SK, Siu AL, Ko FC
J Am Geriatr Soc, 2021 Feb 13, 69(5): 1334-1342
<https://doi.org/10.1111/jgs.17056> | PMID: 33580718 | PMCID: PMC8177692
Citations: 3 | AltScore: 10.35
49. **Receipt of Hospice Aide Visits Among Medicare Beneficiaries Receiving Home Hospice Care.**
Reckrey JM, Ornstein KA, McKendrick K, Tsui E, Morrison RS, Aldridge M
J Pain Symptom Manage, 2021 Dec 22, 63(4): 503-511
[pii: S0885-3924\(21\)00678-3. https://doi.org/10.1016/j.jpainsymman.2021.12.019](https://doi.org/10.1016/j.jpainsymman.2021.12.019) | PMID: 34954065 | PMCID: PMC8930441
Citations: | AltScore: 40
50. **RESEARCHRacial and Socioeconomic Disparities in Access to Telehealth.**
Rivera V, Aldridge MD, Ornstein K, Moody KA, Chun A
J Am Geriatr Soc, 2021 Jan, 69(1): 44-45
<https://doi.org/10.1111/jgs.16904> | PMID: 33075143 | PMCID: PMC8726710
Citations: 9 | AltScore: 25.4
51. **Challenges in Measuring Applied Cognition: Measurement Properties and Equivalence of the Functional Assessment in Acute Care Multidimensional Computerized Adaptive Test (FAMCAT) Applied Cognition Item Bank.**
Teresi JA, Ocepek-Welikson K, Kleinman M, Cheville A, Ramirez M
Arch Phys Med Rehabil, 2021 Feb 5, 103(5S): S118-S139
[pii: S0003-9993\(21\)00136-2. https://doi.org/10.1016/j.apmr.2020.12.029](https://doi.org/10.1016/j.apmr.2020.12.029) | PMID: 33556349 | PMCID: PMC8344387
Citations: 1 | AltScore: 1.5

52. Differential Item Functioning Analyses of the Patient-Reported Outcomes Measurement Information System (PROMIS?) Measures: Methods, Challenges, Advances, and Future Directions.

Teresi JA, Wang C, Kleinman M, Jones RN, Weiss DJ

Psychometrika, 2021 Sep, 86(3): 674-711

<https://doi.org/10.1007/s11336-021-09775-0> | PMID: 34251615 | PMCID: PMC8889890

Citations: | AltScore: 1.25

53. Depression and anxiety symptoms are related to pain and frailty but not cognition or delirium in older surgical patients.

Wang S, Cardieri B, Mo Lin H, Liu X, Sano M, Deiner SG

Brain Behav, 2021 Jun, 11(6): e02164

<https://doi.org/10.1002/brb3.2164> | PMID: 33949810 | PMCID: PMC8213643

Citations: 2 | AltScore: 3

54. Discharge processes in a skilled nursing facility affected by COVID-19.

Weerahandi H, Mak W, Burack OR, Canter BE, Reinhardt JP, Boockvar KS

J Am Geriatr Soc, 2021 Sep, 69(9): 2437-2439

<https://doi.org/10.1111/jgs.17228> | PMID: 33955557 | PMCID: PMC8242513

Citations: 2 | AltScore: NA

EXTERNAL ADVISORY BOARD MEMBERS

Christine Ritchie
UCSF
Serving since 2011 (11 years)

Jay Magaziner
University of Maryland
Serving since 2011 (11 years)

Vincent Mor
Brown University
Serving since 2011 (11 years)

Ken Langa
University of Michigan
Serving since 2017 (5 years)

RECOGNITION AND AWARDS (2021-2022)

Carolina Crooms (2021)

- Received a 2022 Exceptional Scholar Award from the Icahn School of Medicine at Mount Sinai for her project focusing on palliative care for older adults with high-grade gliomas. June 2022.

Fred Ko (2021)

- Fred C. Ko, MD named among the New York Times Super Geriatrics Doctors. May 2021
- Named among Castle Connolly's Top Doctors in Geriatrics
- named Fellow of the National Initiative on Gender, Culture and Leadership in Medicine (C-Change) Mentoring & Leadership Institute, Brandeis University. 2021-2022.

Julia L. Frydman (2021)

- Appointed Assistant Professor for the Brookdale Department of Geriatrics and Palliative Medicine. Dr. Frydman will join our faculty as a Clinical Investigator. September 2021.

Laura Gelfman (2021)

- Recipient of the AAHPM 2021 Early Career Investigator Award. February 2021.
- Recipient of the 2020 Sojourns Scholar Leadership Program Grant from the Cambia Health Foundation. January 2021.
- Selected as a 2020 Sojourns Scholar Leader from Cambia Health Foundation and the Sojourns Scholar Leadership Program's National Advisory Board. December 2020.

Maria Loizos (2021)

- Received the 2020 Faculty Idea Prize for "SMART-PC: An accessible, palliative care mHealth tool for patients with serious illness" from Mount Sinai Innovation. December 2020.

Stephanie Chow (2021)

- Awardee of an Office of Wellbeing and Resilience grant to Enhance Team-Based Care in Primary Care Geriatrics Practices through Patient Coordinators. November 2020.

MINORITY RESEARCH

General Brief Description of Minority Activities:

Not defined.

No minority trainee information specified.

No minority grant information specified.

NORTHWESTERN UNIVERSITY
Claude D. Pepper Older Americans Independence Center

Michael S Wolf, PhD, MPH Principal Investigator	312-503-5592	mswolf@northwestern.edu
Jeffrey A. Linder, MD, MPH Principal Investigator	312-503-6202	jlinder@northwestern.edu
Julia Benavente Center Manager	312-503-5585	julia.benavente@northwestern.edu

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 5 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: Emily Lattie, PhD emily.lattie@northwestern.edu

Leader 3: Maia Jacobs, PhD maia.jacobs@northwestern.edu

Leader 4: 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
<p>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></p>	2022-2024 / 18 (total) 5 (1st/Sr)
<p>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></p>	2022-2024 / 15 (total) 5 (1st/Sr)
<p>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></p>	2022-2024 / 21 (total) 3 (1st/Sr)
<p>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></p>	2022-2024 / 25 (total) 6 (1st/Sr)
<p>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></p>	2022-2024 / 27 (total) 9 (1st/Sr)
<p>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></p>	2021-2023 / 2 (total) 0 (1st/Sr)
<p>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></p>	2021-2023 / 3 (total) 1 (1st/Sr)

<p>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></p>	<p>2021-2023 / 3 (total) 2 (1st/Sr)</p>
<p>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 Secretary Phenotype and frailty in older persons with HIV</u></p>	<p>2021-2023 / 3 (total) 1 (1st/Sr)</p>
<p>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></p>	<p>2021-2023 / 1 (total) 0 (1st/Sr)</p>
<p>Rachel O'Connor, PhD, MPH Assistant Professor / Northwestern University, Feinberg School of Medicine, Department of Medicine (General Internal Medicine & Geriatrics) <u>Management of Complex Medication Regimens Among Older Adults with Alzheimer's Disease and Related Dementias and their Caregivers</u></p> <ul style="list-style-type: none"> • Management of Complex Medication Regimens Among Older Adults with Alzheimer's Disease and Related Dementias and their Caregivers (K01AG070107) • Establishing a Community-Based Research Partnership to Develop a Culturally Tailored, Family-Centered Dementia Caregiving Program (ARCC) • The Health Effects of Prolonged Social Isolation & Loneliness During the COVID-19 Pandemic (OAIC Coordinating Center Collaborative Pilot) 	<p>2020-2022 / 7 (total) 1 (1st/Sr)</p>
<p>Miriam Rafferty, DPT PhD Assistant Professor / Northwestern University, Feinberg School of Medicine, Department of Physical Medicine & Rehabilitation <u>Pilot Implementation Trial of Proactive Physical Therapy to Improve Exercise in Parkinson's Disease</u></p> <ul style="list-style-type: none"> • Pilot Implementation Trial of Proactive Physical Therapy to Improve Exercise in Parkinson's Disease 	<p>2020-2022 / 7 (total) 1 (1st/Sr)</p>
<p>Katherine O'Brien, MD Assistant Professor / Northwestern University, Feinberg School of Medicine, Department of Medicine (General Internal Medicine & Geriatrics) <u>Intelligent Personal Assistant for Managing Depression in Homebound Older Adults</u></p>	<p>2020-2022 / 9 (total) 4 (1st/Sr)</p>

Theresa Rowe, DO MS	2020-2022 /
Assistant Professor / Northwestern University, Feinberg School of Medicine, Department of Medicine (General Internal Medicine & Geriatrics)	5 (total) 2 (1st/Sr)
<u>Improving Infection Prevention and Control in Nursing Homes in the Era of COVID</u>	
• Improving Diagnostic Stewardship for Older Adults in Nursing Homes (GEMMSTAR)	

Sadiya Khan, MD MSc	2020-2022 /
Assistant Professor / Northwestern University, Feinberg School of Medicine, Department of Medicine (Cardiology) and Department of Preventive Medicine (Epidemiology)	49 (total) 5 (1st/Sr)
<u>Prevalence of Microvascular Dysfunction and Association with Functional Limitation in Older Adults with Chronic Obstructive Pulmonary Disease</u>	
• Cardiopulmonary health across the life course (R01HL159250)	
• Risk-Based Primary Prevention of Heart Failure (R21HL156182)	
• CHicago Center for Accelerating nextGen Omics, deep phenotyping, and data science in Heart Failure (CHICAGO-HF) (U01HL160279)	
• PRegnancy OuTcomEs and subclinical Cardiovascular disease sTudy: (PROTECT) (R01HL161514)	

Past Scholars

PILOT/EXPLORATORY PROJECTS (10 Pilot Projects Listed)**1. Project Title: Improving Infection Prevention and Control in Nursing Homes in the Era of COVID****Leader: Theresa Rowe, DO, MS**

Primary care has historically been delivered in the outpatient ambulatory setting. However, as our population ages, many older adults reside in long-term care facilities (LTCFs, i.e. nursing homes) where they receive primary care. Almost half of older adults who live in a nursing home are over the age of 85 and many have functional and cognitive impairments such as Alzheimer's dementia. These multiple comorbidities and the congregate living environment put residents of LTCFs at increased risk from communicable diseases such as influenza and more recently the novel coronavirus (SARS-COV2).

To perform this project we will examine two large national databases including the 1) national healthcare safety network (NHSN) managed by the CDC and 2) nursing home health citations managed by CMS. This proposal will merge two large publically available nursing home databases using the LTCF identification code to determine if current methods for detecting deficiencies in IPC are effective in minimizing the spread of communicable diseases. The findings from this project may provide useful information to how we approach and evaluate infection prevention and control policies in nursing homes, especially for the older adult residents who reside in facilities long-term.

2. Project Title: Intelligent Personal Assistant for Managing Depression in Homebound Older Adults**Leader: Katherine O'Brien, MD**

Homebound older adults with MCC are more likely than their ambulatory peers to suffer from depression. While over 70% receive pharmacotherapy, most homebound older adults with depression cannot access needed psychological services. Family caregivers commonly play the role of care coordinator, implementing clinician recommendations and encouraging the loved one with depression. Older adults have often been on the fringe of benefitting from technology. However, voice-controlled intelligent personal assistants (VIPAs; e.g. Google Home, Amazon Echo) may be useful to homebound older adults with depression, connecting them to caregivers and primary care; providing functional, cognitive, and social stimulation; and improving anti-depressant medication adherence through reminders. The objective of this pilot study is to design and pilot VIPAs to provide caregivers with skills and tools manage the care of older adults with depression.

Building off prior work with VIPAs where their current real-world use by older adults with MCC and their caregivers was explored, the specific aims of PES-2 are to: (1) Design a VIPA application for improving depression care and communication for homebound older adults, including their caregivers; (2) Assess the feasibility and implementation of VIPA and its impact on clinical and functional outcomes for older adults with depression.

3. 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.

4. Project Title: Remote Sensor-Based Frailty Detection in Older Adults**Leader: Whitney Welch, PhD**

Over 30% of older adults report at least one fall each year, with 20% reporting multiple falls. These falls are often associated with serious injury that need medical attention, in addition to lasting disability, loss of independence, and decreased quality of life. Additionally, falls place a significant burden on the healthcare system with an estimated yearly cost of 19.2 billion dollars due to fall-related medical care. With a large aging population, numbers of falls are projected to substantially increase over the next 15 years placing a significant burden on the healthcare system. Due to this substantial healthcare burden, it is critical to first accurately and reliably identify older adults who are at high risk of falling. Further, due to COVID-19, there has been a shift in provider care with a significant increase in telehealth visits. Therefore, there is an immediate and essential need to remotely monitor and detect those patients at high risk for falls.

Strong evidence exists showing that physical activity reduces decline in physical functioning and subsequent risk of falls in older adults. However, less than 10% of older adults meet physical activity guidelines. More recently during the COVID-19 pandemic, these low activity levels have become even further pronounced.

The Specific Aims are:

Aim 1. Calibrate a fall risk machine learning algorithm integrating remote movement sensor data, in addition to electronic health records (health history, patient characteristics) to remotely monitor and identify older adults who are at high risk of falling. The end product will be an algorithm using data integrated from movement sensors and electronic health records that can accurately predict older adults at high risk for falling.

Aim 2. Validate a fall risk machine learning algorithm integrating remote movement sensor data, in addition to electronic health records (health history, patient characteristics, psychosocial

factors) to remotely monitor and identify older adults who are at high risk of falling in an independent sample of older adults.

Aim 3. Identify factors (cognitive functioning, psychosocial factors) that may mediate the relationship between sensor-derived variables (physical function, physical activity) and fall risk.

Results from this study will inform the administration of a preventative, remote physical activity fall risk program in order to increase physical functioning and help to preserve long-term independence and quality of life.

5. 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.

6. 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.

7. 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.

8. 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.

9. 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.

10. 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.

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: Emily Lattie, 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: Emily Lattie, 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'Connor 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'Connor 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):

Depression is one of the most common psychological comorbidities experienced throughout the cancer continuum. 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 information technologies (HIT) provide an ideal opportunity to expedite the administration, scoring, and of depression screening with well-validated, brief and precise measurement tools that can capture actionable data to screen for depression, and deliver pragmatic and scalable evidence-based interventions that are proven to reduce depressive symptomatology across various other cancer populations. 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 intervention 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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Citations: | AltScore: NA

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Citations: | AltScore: 7.83

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Citations: | AltScore: NA
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MacDonald J, Doyle L, Moore JL, Rafferty MR
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J Prim Care Community Health, 2021 Jan-Dec, 12: 21501327211024411

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Citations: 1 | AltScore: NA

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Pierce JB, Harrington K, McCabe ME, Petito LC, Kershaw KN, Pool LR, Allen NB, Khan SS

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Citations: 9 | AltScore: 6.25

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Polan RM, Barber EL

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Citations: 1 | AltScore: 19.65

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Rafferty MR, Held Bradford EC, Fritz S, Hutchinson KJ, Miczak K, Resnick A, Billinger SA

J Neurol Phys Ther, 2021 Sep 9, 46(2): 103-117

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Citations: | AltScore: 11.55

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Richards AR, Linder JA

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Citations: 3 | AltScore: 11.75

27. **Transplant regimen adherence for kidney recipients by engaging information technologies (TAKE IT): Rationale and methods for a randomized controlled trial of a strategy to promote medication adherence among transplant recipients.**

Serper M, Ladner DP, Curtis LM, Nair SS, Hur SI, Kwasny MJ, Ho B, Friedewald J, Reese PP, Abecassis MMI, Wolf MS

Contemp Clin Trials, 2021 Apr, 103: 106294

<https://doi.org/10.1016/j.cct.2021.106294> | PMID: 33515781 | PMCID: PMC8089037

Citations: 3 | AltScore: 5.4

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Shah NS, Agarwal A, Huffman MD, Gupta DK, Yancy CW, Shah SJ, Kanaya AM, Ning H, Lloyd-Jones DM, Kandula NR, Khan SS

J Card Fail, 2021 Nov, 27(11): 1214-1221

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Citations: | AltScore: 26.4

29. **Outcomes in patients hospitalized for COVID-19 among Asian, Pacific Islander, and Hispanic subgroups in the American Heart Association COVID-19 registry.**

Shah NS, Giase GM, Petito LC, Kandula NR, Rodriguez F, Hsu JJ, Wang DR, Khan SS

Am J Med Open, 2021, 1: 100003

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Citations: | AltScore: 16.45

30. **Trends in Gestational Diabetes at First Live Birth by Race and Ethnicity in the US, 2011-2019.**

Shah NS, Wang MC, Freaney PM, Perak AM, Carnethon MR, Kandula NR, Gunderson EP, Bullard KM, Grobman WA, O'Brien MJ, Khan SS

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Citations: 9 | AltScore: 202.05

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Am J Prev Med, 2021 Dec 7, 62(4): e223-e231

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Citations: 2 | AltScore: 16.4

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Sinha A, McNally EM, Khan SS

JAMA Cardiol, 2021 Jul 1, 6(7): 849-850

<https://doi.org/10.1001/jamacardio.2021.0835> | PMID: 33978672

Citations: | AltScore: 1

33. **Race- and Sex-Specific Population Attributable Fractions of Incident Heart Failure: A Population-Based Cohort Study From the Lifetime Risk Pooling Project.**

Sinha A, Ning H, Carnethon MR, Allen NB, Wilkins JT, Lloyd-Jones DM, Khan SS

Circ Heart Fail, 2021 Mar 25, 14(4): e008113

<https://doi.org/10.1161/CIRCHEARTFAILURE.120.008113> | PMID: 33761754 | PMCID:

PMC8058263

Citations: 5 | AltScore: 4

34. **Sustained physical activity in peripheral artery disease: Associations with disease severity, functional performance, health-related quality of life, and subsequent serious adverse events in the LITE randomized clinical trial.**

Slysz JT, Rejeski WJ, Treat-Jacobson D, Bazzano LA, Forman DE, Manini TM, Criqui MH, Tian L, Zhao L, Zhang D, Guralnik JM, Ferrucci L, Kibbe MR, Polonsky TS, Spring B, Sufit

R, Leeuwenburgh C, McDermott MM

Vasc Med, 2021 Oct, 26(5): 497-506

<https://doi.org/10.1177/1358863X21989430> | PMID: 33829920

Citations: | AltScore: 6.55

35. **VI Never Get Better Without an Antibiotic\:** Antibiotic Appeals and How to Respond.

Szymczak JE, Keller SC, Linder JA

Mayo Clin Proc, 2021 Mar, 96(3): 543-546

<https://doi.org/10.1016/j.mayocp.2020.09.031> | PMID: 33673907

Citations: 1 | AltScore: 18.55

36. **Global Differences in Heart Failure With Preserved Ejection Fraction: The PARAGON-HF Trial.**

Tromp J, Claggett BL, Liu J, Jackson AM, Jhund PS, K?ber L, Widimsk? J, Boytsov SA, Chopra VK, Anand IS, Ge J, Chen CH, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, Van Veldhuisen DJ, Zannad F, Zile MR, Rizkala AR, Inubushi-Molessa A, Lefkowitz MP, Shi VC, McMurray JJV, Solomon SD, Lam CSP, PARAGON-HF Investigators.

Circ Heart Fail, 2021 Apr, 14(4): e007901

<https://doi.org/10.1161/CIRCHEARTFAILURE.120.007901> | PMID: 33866828

Citations: 1 | AltScore: 6.1

37. **Deaths from hepatocellular carcinoma are more likely to occur in medical facilities than deaths from other cancers: 2003-2018.**

Truitt K, Khan SS, Gregory DL, Chuzi S, VanWagner LB

Liver Int, 2021 May 1, 41(7): 1489-1493

<https://doi.org/10.1111/liv.14915> | PMID: 33932082 | PMCID: PMC8822953

Citations: 1 | AltScore: 3.5

38. **Association of pre-pregnancy cardiovascular risk factor burden with adverse maternal and offspring outcomes.**

Wang MC, Freaney PM, Perak AM, Allen NB, Greenland P, Grobman WA, Lloyd-Jones DM, Khan SS

Eur J Prev Cardiol, 2021 Jul 20, 29(4): e156-e158

[pii: zwab121. https://doi.org/10.1093/eurjpc/zwab121](https://doi.org/10.1093/eurjpc/zwab121) | PMID: 34284496 | PMCID:

PMC8967477

Citations: 2 | AltScore: 245.08

39. **Trends in prepregnancy cardiovascular health in the United States, 2011-2019.**

Wang MC, Freaney PM, Perak AM, Allen NB, Greenland P, Grobman WA, Phillips SM, Lloyd-Jones DM, Khan SS

Am J Prev Cardiol, 2021 Sep, 7: 100229

<https://doi.org/10.1016/j.ajpc.2021.100229> | PMID: 34401862 | PMCID: PMC8353467

Citations: | AltScore: 27.5

40. **Trends in Prepregnancy Obesity and Association With Adverse Pregnancy Outcomes in the United States, 2013 to 2018.**

Wang MC, Freaney PM, Perak AM, Greenland P, Lloyd-Jones DM, Grobman WA, Khan SS

J Am Heart Assoc, 2021 Sep 7, 10(17): e020717

<https://doi.org/10.1161/JAHA.120.020717> | PMID: 34431359 | PMCID: PMC8649260

Citations: 6 | AltScore: 14.2

41. **Gestational Diabetes and Overweight/Obesity: Analysis of Nulliparous Women in the U.S., 2011-2019.**

Wang MC, Shah NS, Petit LC, Gunderson EP, Grobman WA, O'Brien MJ, Khan SS

Am J Prev Med, 2021 Dec, 61(6): 863-871

<https://doi.org/10.1016/j.amepre.2021.05.036> | PMID: 34446313 | PMCID: PMC8608700

Citations: | AltScore: 12.75

42. **Dysphagia Characteristics of Patients Post SARS-CoV-2 During Inpatient Rehabilitation.**

Webler K, Carpenter J, Hamilton V, Rafferty M, Cherney LR

Arch Phys Med Rehabil, 2021 Oct 29, 103(2): 336-341

[pii: S0003-9993\(21\)01517-3. https://doi.org/10.1016/j.apmr.2021.10.007](https://doi.org/10.1016/j.apmr.2021.10.007) | PMID: 34757074 |

PMCID: PMC8555115

Citations: | AltScore: 3.45

43. **The Relationship Between COVID-19 Related Stress and Medication Adherence Among High-Risk Adults During the Acceleration Phase of the US Outbreak.**

Zhao C, Batio S, Lovett R, Pack AP, Wolf MS, Bailey SC

Patient Prefer Adherence, 2021, 15: 1895-1902

<https://doi.org/10.2147/PPA.S310613> | PMID: 34511885 | PMCID: PMC8418366

Citations: 1 | AltScore: 2

EXTERNAL ADVISORY BOARD MEMBERS

Albert Siu, MD
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University of Michigan
Serving since 2021 (1 years)

RECOGNITION AND AWARDS (2021-2022)

Mary M. McDermott, MD (2021)

- SGIM John M. Eisenberg National Award for Career Achievement in Research

MINORITY RESEARCH

General Brief Description of Minority Activities:

Not defined.

Minority Trainee(s):

- 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
- 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

Minority Grant(s):

UNIVERSITY OF PITTSBURGH
Claude D. Pepper Older Americans Independence Center

Susan L. Greenspan, M.D. Principal Investigator	412-692-2477	greenspn@pitt.edu
Bari Guzikowski Program Manager	412-692-2477	bmg96@pitt.edu

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)

Leader 1: Daniel E. Forman, MD formand@pitt.edu

Leader 2: Fabrisia Ambrosio, PhD, MPT faa7@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)

Leader 1: Toren Finkel, MD, PhD FINKELT@pitt.edu

Leader 2: 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 well 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
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 (12 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- β) pathway with baseline and 7-10-year change in physical function among older adults.

Brief Background: The TGF- β signaling pathway is a strong biological candidate pathway that may negatively impact skeletal muscle and physical function with aging. TGF- β induces pathogenic tissue fibrosis, negatively regulates skeletal muscle differentiation and repair, and contributes to mitochondrial dysfunction. TGF- β 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- β signaling pathway, using a custom-designed TGF- β 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- β 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- β , 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 α -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, α -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 \geq 70-y) residing in Pittsburgh at baseline, for 80% power with $\alpha=0.05$ for detection of $R^2=0.065$ 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 be 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 neurostructural, 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 will 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

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 studies¹⁹ 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, the participant's survival component of the joint model is given by $\lambda(t; \mathbf{X}, \mathbf{Z})$, where $\lambda(t)$ is the true unobserved value of gait speed at time t , \mathbf{X} is the history of such information up to time t , \mathbf{Z} are covariates, and $\lambda_0(t)$ is the baseline hazard function, typically approximated with a piecewise-constant form $\lambda_0(t) = \sum_{j=1}^k \lambda_{0j} I(t \in T_j)$ where T_j 's define a partition of the time scale. The longitudinal component for observed gait speeds is $\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\epsilon}$, where $\boldsymbol{\beta}$ and $\boldsymbol{\epsilon}$ 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 direction^{23,25,26}. 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 (31 Projects Listed)**1. Project Title: Establishing a Distribution Approach for the On the Move Group Exercise Program**

Leader(s): BRACH, JENNIFER
UNIVERSITY OF PITTSBURGH AT PITTSBURGH
PCORI EADI-19784 / (2021 - 2022)

Core(s):

Mobility is a critical component of independence for older adults. Through a PCORI-funded trial, the project team demonstrated that the On the Move (OTM) group exercise program both improved mobility in older adults and was more effective than a standard exercise program for improving mobility. Though the project team and others have demonstrated the benefits of improving mobility through exercise, the programs are seldom used outside of the research setting. A fundamental obstacle to successful dissemination and implementation of evidence-based exercise programs is the lack of a systematic approach for marketing and distribution.

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 and mortality. As a traditional epidemiologist with unique expertise in skeletal muscle aging and physical function, I have researched lifestyle interventions (weight loss, aerobic and resistance training) to prevent age-related declines in physical function. However, lifestyle changes are difficult to adopt, especially for those at the highest risk for functional decline. To extend the benefits of these interventions, it is imperative to understand biological processes underlying changes in function with aging and following intervention. As such, the current proposal will provide the candidate with advanced training in molecular epidemiology and biology of aging, yield novel insight on the genetic and biological basis of physical function among older adults and lay the foundation for future research. Specially, Aim 1 will identify genes and genetic variants for physical function and changes in physical function with aging. Aim 2 will examine blood RNA expression for components of the transforming growth factor beta (TGF- β) 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- β and procollagen type 3 N-terminal propeptide (P3NP - a biomarker of pathogenic fibrosis) are related physical function among older adults. I will leverage robustly collected physical function measures, biological samples, and an ultra-high-density genome-wide polymorphism map from the NIA-funded Long Life Family Study (LLFS), a multi-center study of exceptional aging and longevity in families and from The 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-related conditions there have been no human studies that have examined the relationship between TGF- β or P3NP and physical function. Further, LLFS has a large number of oldest old, who are understudied and at the highest risk for functional decline. There has also been limited research on the genetics of physical function. The proposed career development award will provide the applicant with essential new mentorship, knowledge and skills in human genetics and molecular epidemiology 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 transition to an independent research career in aging and molecular epidemiology with a focus on physical function. As an epidemiologist with expertise in both traditional and molecular methods, I will be well-positioned to contribute to the advancement 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, an assistant professor of health policy and management at the University of Pittsburgh Graduate School of Public Health, will establish Dr. Roberts as a health economist with expertise in health insurance and health care policy for aging and low-income populations. Research proposed for this K01 award will harness natural experiments created by eligibility thresholds and policy variation within Medicare subsidy programs to rigorously evaluate how these programs affect patients' use of care, access to providers, and health. This project will focus on two subsidy programs for low-income Medicare beneficiaries: the Medicare Savings Programs (MSPs), which are partial Medicaid benefits that defray out-of-pocket costs for physician services and inpatient care, and the Part D Low-Income Subsidy (LIS), which helps to pay for prescription drugs. Using the Health and Retirement Study linked to Medicare and Medicaid claims, Dr. Roberts will examine how discontinuities in subsidy eligibility affect patients' use of care including medication adherence, physician visits, and hospitalizations and health status. Dr. Roberts will also examine the relationship between state Medicaid policies specifically, provider payment rates and rules for recertifying program eligibility with MSP enrollment and patients' access to care. Evidence generated from this research can guide reforms to increase the benefits of the MSPs and LIS to low-income Medicare beneficiaries and to the Medicare program. This project draws on Dr. Roberts' quantitative training, knowledge of Medicare and Medicaid policy, and prior research on health disparities. This work will extend Dr. Roberts' scholarship into the field of aging while incorporating methods in pharmaceutical health services research. Therefore, for this K01 award, Dr. Roberts will engage in training and career development activities that focus on acquiring expertise in aging and pharmaceutical health services research. Through mentorship from health services researchers and clinical experts, Dr. Roberts will also focus on applying training in these content areas to health policy research. This training plan complements the proposed research and will equip Dr. Roberts to establish an independent research 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)

ABSTRACT Access to high-quality post-intensive care unit (ICU) recovery services is a major problem for thousands of older Americans living in rural communities who survive critical illness each year. They and their families often experience uncoordinated care, poor health, reduced independence and quality of life, and high ongoing healthcare utilization. Any scalable solution will require the flexibility to address multimorbidity, physical, cognitive, and psychological dysfunction, caregiver stress, and end-of-life transitions, all of which are common. To address this problem: (1) The principal investigator will acquire new skills that position her as an independent implementation physician scientist specializing in improving the quality of geriatric critical care in the post-ICU period. 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, a nurse practitioner and occupational therapist will deliver transitional care, family training and support, and skills-based rehabilitation to rural-dwelling older adults, starting at ICU transfer. From discharge until graduation back to primary care, they will partner with home health providers via telehealth to implement the care plan. Instead of developing TeleRecovery de novo, we will use stakeholder engagement to adapt transitional care (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 first step 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 including payers 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 quality, 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, older ICU 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 implementation 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 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: MIDCAREER INVESTIGATOR AWARD IN TRANSLATIONAL PATIENT-ORIENTED RESEARCH IN AGING
Leader(s): BRACH, JENNIFER S
THE UNIVERSITY OF PITTSBURGH
NIH K24AG057728 / (2017 - 2022)
Core(s):
 - Clinical and Population Outcomes Core (CPOC)
 - Integrative Systems Core (ISC)

Midcareer Investigator Award in Translational Patient-Oriented Research in Aging This application is for a K24 Midcareer Investigator Award in Patient-Oriented Research to promote mentoring and career development in dissemination and implementation research that improves mobility and prevents disability in community-dwelling older adults. Dr. Jennifer Brach, PI of the proposed award, is a physical therapist, epidemiologist and scientist committed to mentoring health professional trainees and junior faculty and working to improve the mobility and quality of life of older adults. For over 15 years, she has conducted patient-oriented research studies focused on increasing successful aging among vulnerable older adults and she has built a strong multi-disciplinary network of research collaborators who are available to co-mentor trainees and junior faculty. Her long-term goal is to bridge the gap between clinical research, public health, and everyday practice by transferring the findings from clinical trials to practice settings and communities, where the findings will improve mobility and prevent disability in older adults and to train health professionals and junior faculty for a successful career in academic investigation. Dr. Brach seeks support from a NIA K24 career award to: 1) establish a research training and mentoring program that will prepare beginning scholars to become successful, independent patient-oriented researchers in disability prevention in aging, 2) obtain additional training and participate in practical experiences in dissemination and implementation science that will enhance her translational research skills, and 3) extend her currently funded work to bridge the gap between clinical research and practice settings and the community. Dr. Brach has a substantial and growing track record of mentorship of trainees from a variety of disciplines; the requested K24 support would allow her to curtail teaching and administrative responsibilities so that she can focus the majority of her time on research and mentoring.

11. 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.

12. 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)

ABSTRACT Biobehavioral Studies of Cardiovascular Disease (P01-HL040962) This Program Project (P01) continuation application focuses on the human brain substrates of behavioral and socio-environmental influences on cardiovascular disease (CVD) risk in midlife adults. Proposed are 3 Projects that are conceptually cross-linked and supported by 3 Core Units. Collaborative investigators represent multiple disciplines, including psychology, neuroscience, biophysics, medicine, psychoneuroimmunology, epidemiology, machine learning, bioinformatics, and statistics. Project 1 aims to elucidate functional and structural brain phenotypes that predict the multiyear progression of preclinical vascular disease and dysfunction, 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 aims to establish whether functional characteristics of these visceral control circuits moderate the influences of stress-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 model of CVD risk. Project 2 also tests for the first time whether daily life physical activity associates with daily life stress physiology through its effects on neural circuits for visceral control. Project 3 aims to extend those of the other Projects by elucidating the neural and peripheral processes linking physical activity with physiological and psychophysiological markers of CVD risk (including

daily life affect and stress physiology) using an experimental intervention methodology. These P01 aims are unique in cardiovascular behavioral medicine, and they will be pursued in the context of multi-component data collection efforts that satisfy all project-specific aims. As a result, the P01 will create new opportunities for integrative and translational science on the human neurobiology of CVD risk that cuts across multiple methods and levels of analysis. Helping to advance its parent field, the P01 will generate and disseminate original and expansive public-domain resources and tools to the broader scientific and clinical communities through comprehensive data and software sharing and educational objectives. Enabling a precise focus on early CVD etiology, the study cohorts comprise nearly 900 midlife adults without clinically apparent CVD, and study methods will include novel combinations of neuroimaging, ecological momentary assessments of experienced environments, ambulatory hemodynamic monitoring, 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 for synergy 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.

13. Project Title: RESTORING CENTRAL MOTOR CONTROL TO IMPROVE COMMUNITY MOBILITY OF OLDER ADULTS

**Leader(s): ROSSO, ANDREA L
THE UNIVERSITY OF PITTSBURGH
NIH R01AG057671 / (2018 - 2022)**

Core(s): - Clinical and Population Outcomes Core (CPOC)
- Data Management, Analysis and Informatics Core (DMAIC)

Project Summary/Abstract As many as 30 million older adults in the US have walking limitations which could impact community mobility. Restriction in community mobility contribute to disability, institutionalization, and poor quality of life. Compared to walking in clinical settings, community mobility requires rapid negotiation of complex, multi-sensorial, and often variable and unpredictable environments. Successful community mobility requires rapid integration of information both external (e.g. surface quality, distances) and internal (e.g. fatigue, pain) to the individual. Integration of these inputs primarily occurs at the level of the central nervous system. Under normal conditions, this integration favors automatic motor control with few demands on attention-related networks, primarily located in the prefrontal cortex (PFC). As automatic motor control diminishes in older adults, activation of the PFC during walking tasks increases. Age-related impairments in body systems (e.g. musculoskeletal, cardiopulmonary) increase the demands of walking while concurrent impairments in the brain can reduce capacity for motor control. The mismatch in demands and capacity can be magnified when walking occurs in the context of complex community environments (e.g. uneven surfaces, attentional demands); therefore, automatic motor control is likely a critical component of community mobility. Motor skill training (MST) is an integrated intervention approach developed to improve walking. The goal of MST is restoration of automatic motor control and behavioral flexibility during walking, which are needed for addressing environmental challenges during community mobility. The MST approach may restore automatic motor control and provide older individuals with the capacity to address environmental challenges and maintain community mobility. We propose to test the effects of MST on community mobility and motor control. Community mobility will be quantified by state of the art, objective measures from global position system (GPS) tracking, including activity space (the area travelled by an individual in daily activities) and time away from home. Central motor control will be assessed by wireless functional near-infrared spectroscopy (fNIRS) at the PFC during dual-task walking. Further, we will assess the influence of individuals cognitive function and neighborhood environments by neighborhood socioeconomic status and walkability audits on changes in community mobility. We will leverage an ongoing randomized, 12-week efficacy trial of standard therapy compared to standard plus MST (R01AG045252; PI: Jennifer Brach) that is enrolling individuals aged 65 years and older with gait speeds 0.6-1.2 m/s (n=248). The primary outcome of the parent trial is gait speed; our proposal will extend the outcome from clinic-based measures to real world community mobility at baseline and 12, 24, and 36 week follow-up visits. Results will provide evidence for intervention approaches to improve community mobility of older adults.

14. 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's disease or other dementias. For those over the age of 65, the prevalence of cognitive impairment is 8.8% in whites and 23.9% in African Americans. Even in the age range of 55-64, African Americans are 4 times more likely to experience cognitive impairment than their age-matched white counterparts. Increased risk of dementia among African 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 are recognized as risk factors for dementia. A critical public health question emerges from these statistics that we intend to address in this proposal: Is there an effective method for reducing or eliminating the race disparities in cognitive and brain health? Fortunately, physical activity (PA) interventions may be effective at improving neurocognitive function and reducing risk for dementia. Despite these promising results, prior PA interventions have had few African Americans making it difficult to stratify results by race to determine whether African Americans 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) could be 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 are assigned to either a moderate intensity African Dance group 3 days per week (N=90) or to an African Education 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 to identify 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 African Americans. In addition, it could establish a platform (i.e., dance) to implement future interventions targeting minority 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, cerebral blood flow, and resting state connectivity. Aim 3. Explore potential physiological and socioemotional mechanisms of the dance intervention. We will collect measures of physical and psychosocial health such as waist circumference, blood pressure, blood glucose and lipid levels, mood, anxiety, depression, and loneliness and examine whether intervention-related changes to these measures mediate improvements in cognitive performance.

15. 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 declines in older adults. These declines are at least partially attributed to failed muscle healing. Muscle regeneration is predominantly dictated by the action of muscle stem, or satellite, cells (MuSCs), a reserve cell population that typically 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 from the surrounding microenvironment. Indeed, expanding recognition of the influence of the microenvironment on stem cell behavior has led to a recent surge in the development of bioinspired and engineered extracellular matrix (ECM) approaches for the treatment of skeletal muscle injuries. Still lacking, however, is an in-depth knowledge of whether and how pathogenic instructional characteristics of the native ECM disrupt MuSC function and skeletal muscle regeneration. While it is evident that MuSC activation, self-renewal, proliferation and differentiation are influenced by physical and dynamic niche interactions, a mechanistic understanding of the direct impact of age-related ECM alterations on skeletal muscle regenerative capacity is unknown. The overarching goal of this project is to test our central hypothesis that age-related biophysical alterations in the skeletal muscle ECM promotes a fibrogenic conversion in MuSCs, ultimately driving impaired skeletal muscle regeneration. Further, we hypothesize that these pathogenic biophysical changes may be reverted, at least partially, by mechanical stimulation. To achieve this goal, we will employ an integrated approach that encompasses cutting-edge super-resolution imaging and 3-D tissue engineering methods to address two specific aims. Aim 1 studies will measure, manipulate, and mimic the biophysical properties of young and aged skeletal muscle ECM in order to dissect the effect of age-related architectural and elastic ECM modifications on MuSC fate. Aim 2 studies will identify mechanisms by which mechanical stimulation modulates

biophysical properties of the aged ECM to promote MuSC myogenicity and muscle regeneration. Successful achievement of these aims will further our understanding of 1) the instructional capabilities of the native ECM on MuSC lineage specification, 2) how these instructional capabilities change over time, and 3) the molecular mechanisms controlling age-related declines in skeletal muscle regenerative potential. Taken together, successful completion of these studies may provide a foundation for the identification of novel ECM targets in the treatment of skeletal muscle injuries for a geriatric population. 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 of aging and stem cell biology.

16. 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.

17. 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.

18. 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.

19. 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.

20. 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.

21. 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.

22. 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)

ABSTRACT Impaired swallowing (oropharyngeal dysphagia or OPD) causes nearly 150,000 annual hospitalizations and over 220,000 additional hospital days, and prolongs hospital lengths of stay by 40%. OPD risk is typically identified through subjective standard institutional screening (SIS) protocols and those identified through screening 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 into their 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 approach based on high-resolution cervical auscultation (HRCA) to accurately predict OPD-related adverse events, and initiate 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 analytic tools are powerful approaches to automate and improve existing dysphagia screening protocols. The rationale is that a reliable, robust early-warning instrumental OPD screening approach will reduce adverse events in patients 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 signal signatures 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 and aspiration in a randomized, controlled trial. Under the first aim, we will collect HRCA swallow signatures from unimpaired people, and combine and analyze them along with our large database of swallows of people with OPD to characterize the entire range of swallowing function from unimpaired through severe OPD. Under the second aim, we will develop HRCA OPD severity cutoffs and match them to gold standard derived OPD impairment cutoffs to establish HRCA's ability as a diagnostic surrogate that differentiates clinically significant OPD and aspiration from benign swallowing impairments. Under the third aim, we will test HRCA in a clinical setting 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 will combine technology with clinical judgment to shift the OPD screening paradigm and fundamentally improve efforts to reduce morbidity and mortality caused by OPD. Our work is significant, because it will translate to an early-warning HRCA screening tool that will elevate the current standard of patient care by ensuring that patients with OPD are correctly identified before adverse events can occur.

23. Project Title: EFFECT OF REDUCING SEDENTARY BEHAVIOR ON BLOOD PRESSURE

Leader(s): BARONE GIBBS, BETHANY
THE UNIVERSITY OF PITTSBURGH
NIH R01HL134809 / (2017 - 2022)

- Core(s):**
- Clinical and Population Outcomes Core (CPOC)
 - Integrative Systems Core (ISC)

PROJECT ABSTRACT Elevated blood pressure (BP), including hypertension (HTN) and preHTN, affects 2 in 3 American adults and is a major contributor to cardiovascular disease (CVD) morbidity, mortality, and healthcare costs. Despite widespread use of pharmacotherapy, only about half of HTN is controlled, highlighting a need for innovative strategies to decrease the burden of elevated BP. Though regular exercise in the form of moderate-to-vigorous physical activity (MVPA) occurring in bouts of at least 10 minutes is recommended to decrease BP, we propose that reducing time spent sitting or 'sedentary behavior' (SED) is a distinct, novel strategy that could lower BP in individuals with preHTN and HTN. Recent occupational and leisure changes (e.g., computers, video streaming) have resulted in more than half of the American day being spent in SED. At the same time, many observational studies have linked excessive SED with adverse outcomes, including HTN and CVD. Moreover, some day laboratory studies suggest that reducing or interrupting SED decreases BP acutely and our preliminary data suggest that systolic BP (SBP) is reduced by 4-6 mmHg after a 12-week SED intervention. Yet, there have been no robust, randomized trials of sufficient size and duration to demonstrate that reducing SED has sustained benefits on BP. Before clinical or public health SED recommendations can be made, such experimental evidence is imperative. Thus, the goal of this application is to demonstrate the efficacy of SED reduction to decrease BP in a 3-month randomized, clinical trial (intervention vs. control) in 300 adults (150 per group) with pre-to-Stage IHTN who have structured, prolonged SED as desk workers. We will use our proven approach that intervenes on multiple levels (individual, environmental modification with a sit-stand desk attachment) and utilizes behavioral strategies (individual counseling, self-monitoring, external prompting with a wrist-worn

monitor light-intensity physical activity (LPA) (standing, light movement) and short spurts (

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 bioenergetic capacity and modulating cell death thresholds. For nearly fifty years, mitochondria were known to have a selective calcium-selective pore in the inner mitochondrial membrane. Entry of calcium through this pore, often termed the calcium uniporter, was believed to be essential in boosting ATP production by augmenting the activity of multiple calcium-sensitive mitochondrial matrix enzymes. This increase in mitochondrial calcium therefore allowed for a rapid but regulated increase in mitochondrial ATP under conditions of increased energetic demand. While under these conditions, the entry of calcium appears beneficial, additional evidence suggested that excessive calcium entry triggers a mitochondrial cell death program characterized by opening of the mitochondrial permeability transition pore (mPTP). Such situations appear to be particularly relevant to tissue injury occurring in the setting of ischemia-reperfusion injury. While considerable electrophysiological, biophysical and physiological data existed on the mitochondrial inner membrane calcium pore, its molecular identity remained elusive for over fifty years. That situation has demonstrably changed in the last five years with the rapid identification 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-sensitive regulators MICU1 and MICU2. The molecular identity of the MCUC paved the way for the creation 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 of mitochondrial calcium in regulating both bioenergetics and cell death. Here, we propose to analyze the role of the MCUC in basal and stress-induced cardiovascular physiology. Our particular emphasis will be on the role of the MCUC in ischemia/reperfusion injury, metabolism and aging. This analysis, we believe, will increase our fundamental understanding of both mitochondrial biology and cardiac physiology and potentially pave the way for new treatment strategies 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 pursue successful independent research in the etiology of Alzheimer's Disease and other age-related dementia (ADRD). Eligible applicants 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 related disciplines. We request support for 3 pre-doctoral and 2 post-doctoral positions annually, with a period of training of up to 3 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 of our aging population, and rapid technological advancements in health measurements in general and in brain science in particular. Our successes in extending lifespan, with marginal improvements in healthspan, have not only increased the number of adults reaching very old ages, but they have also increased the heterogeneity of age-related neurocognitive phenotypes. For these new older adults, there is a very high burden of chronic conditions affecting the central nervous system 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 in very complex ways and are all strong drivers of increased risks of developing dementia. While it is reasonable to expect brain integrity to decline and dementia rates to increase over time, we cannot assume that chronological years and years spent with a disease would have linearly additive effects on brain integrity. Understanding these complex pathways is fundamentally important to conduct rigorous etiological research into causes and determinants of brain degeneration and dementia. Unfortunately, training and research in the field to date have focused 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 separate problems. However, it is clear that to understand these complex issues and improve the brain health of the growing population of elderly living with chronic diseases for a long time, it is necessary to have expertise in diseases of both the brain/central nervous system and also other

organ systems. We are also living through a time of great technological advances in non-invasive and automated methods to measure brain abnormalities, the application of which is providing ever more precise phenotypes but also very large and complex datasets. Such data require careful sampling designs and analytical approaches infused with an understanding of the condition being studied to effectively produce new knowledge to move research to treatment and prevention. We propose that the successful clinical neuroepidemiological investigators of 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 to cross-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 of Public Health (Biostatistics), Medicine (Neurology, Biomedical Informatics), Arts and Science (Neuroscience, Psychology), and Information Science, as well as several University Centers and Institutes: the Alzheimer Disease Research Center, the Center for the Neural Basis of Cognition, the Brain Institute, the Center for Aging, Population and Health, the Claude Pepper, the Aging Institute. Our curriculum responds to the changing landscape of career pathways, by including: a) foundational knowledge in data science; b) availability of multi-center and international databases; c) enhanced training in cutting-edge multimodal methodologies to measure brain changes with age, including neuroimaging and post-mortem assessments; d) hands-on experiences with internet-based designs for recruitment and data collection. Training in the responsible 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, NICOLA AS 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 in peripheral systems. We have recently discovered that ~20% of older adults maintain fast gait speed even in the presence of common locomotor risk factors, thus appearing resilient. Our work suggests that the nigrostriatal dopamine (DA) system may be a source of this resilience. We hypothesize that higher nigrostriatal DA neurotransmission drives resilience to locomotor risk factors via higher connectivity with sensorimotor networks, 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 vascular lesions and brain structural impairments, DA neurotransmission is potentially modifiable, thereby offering novel approaches to reduce age-related walking impairments. Although of substantial potential value to wellbeing in aging, there is a critical gap in knowledge of age-related mobility with simultaneous measures of nigrostriatal DA 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 dual task conditions and reduces the negative effects of cSVD and peripheral system impairment on walking performance. AIM 2: Assess DA-related automated control of walking, cross-sectionally and longitudinally. We hypothesize nigrostriatal DA neurotransmission acts synergistically with connectivity of sensorimotor networks to 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 a mechanistic target-engagement study in slow-walking older adults with cSVD and pronounced age-associated striatal DA loss. Exploratory AIM 3: To assess the effects of 1 week of L-DOPA administration on connectivity and gait speed as a function of molecular markers of striatal DA release in non-resilient elderly with pronounced age-associated striatal DA losses. This research is innovative in that it goes beyond explaining impairments, to revealing resilience factors and their mechanisms as the basis for novel interventions. It has high impact because recent findings suggest that pharmacological and behavioral interventions can improve DA signaling. Our team has unique expertise in the use 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: 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 UPMC 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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Citations: | AltScore: 0.25

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Stevens JM, Delitto A, Khoja SS, Patterson CG, Smith CN, Schneider MJ, Freburger JK, Greco CM, Freel JA, Sowa GA, Wasan AD, Brennan GP, Hunter SJ, Minick KI, Wegener ST, Ephraim PL, Friedman M, Beneciuk JM, George SZ, Saper RB

JAMA Netw Open, 2021 Feb 1, 4(2): e2037371

<https://doi.org/10.1001/jamanetworkopen.2020.37371> | PMID: 33591367 | PMCID: PMC7887659

Citations: 7 | AltScore: 238.056

62. The TOPAZ study: a home-based trial of zoledronic acid to prevent fractures in neurodegenerative parkinsonism.

Tanner CM, Cummings SR, Schwarzschild MA, Brown EG, Dorsey ER, Espay AJ, Galifianakis NB, Goldman SM, Litvan I, Luthra N, McFarland NR, Mitchell KT, Standaert DG, Bauer DC, Greenspan SL, Beck JC, Lyles KW

NPJ Parkinsons Dis, 2021 Mar 1, 7(1): 16

<https://doi.org/10.1038/s41531-021-00162-1> | PMID: 33649343 | PMCID: PMC7921548

Citations: 1 | AltScore: 21.95

63. Group Lifestyle Phone Maintenance for Weight, Health, and Physical Function in Adults Aged 65-80 Years: A Randomized Clinical Trial.

Venditti EM, Marcus MD, Miller RG, Arena VC, Greenspan SL, Rockette-Wagner B

J Gerontol A Biol Sci Med Sci, 2021 Jan 18, 76(2): 352-360

<https://doi.org/10.1093/gerona/glaa229> | PMID: 32918078 | PMCID: PMC7812425

Citations: 1 | AltScore: NA

64. Physical Therapists as Partners for Community Fall Risk Screenings and Referrals to Community Programs.

Vincenzo JL, Hergott C, Schrodt L, Perera S, Tripken J, Shubert TE, Brach JS

Front Public Health, 2021, 9: 672366

<https://doi.org/10.3389/fpubh.2021.672366> | PMID: 34249840 | PMCID: PMC8267879

Citations: 1 | AltScore: NA

65. Capitalizing on Virtual Delivery of Community Programs to Support Health and Well-Being of Older Adults.

Vincenzo JL, Hergott C, Schrodt L, Rohrer B, Brach J, Tripken J, Shirley KD, Sidelinker JC, Shubert TE

Phys Ther, 2021 Apr 4, 101(4):

[pii: pzab001. https://doi.org/10.1093/ptj/pzab001](https://doi.org/10.1093/ptj/pzab001) | PMID: 33439254 | PMCID: PMC8023634

Citations: 3 | AltScore: 68.45

66. Jump power, leg press power, leg strength and grip strength differentially associated with physical performance: The Developmental Epidemiologic Cohort Study (DECOS).

Winger ME, Caserotti P, Ward RE, Boudreau RM, Hvid LG, Cauley JA, Piva SR, Harris TB, Glynn NW, Strotmeyer ES

Exp Gerontol, 2021 Mar, 145: 111172

<https://doi.org/10.1016/j.exger.2020.111172> | PMID: 33245997 | PMCID: PMC7855418

Citations: 2 | AltScore: NA

EXTERNAL ADVISORY BOARD MEMBERS

Luigi Ferrucci, MD, PhD
National Institutes of Aging
Serving since 2004 (18 years)

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Pamela Duncan
Wake Forest
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Ken Covinsky MD, MPH
University of California San Francisco
Serving since 2021 (1 years)

Rozalyn Anderson, PhD
University of Wisconsin, Veterans Administration Hospital
Serving since 2021 (1 years)

RECOGNITION AND AWARDS (2021-2022)

C. Elizabeth Shaaban, PhD, MPH (2021)

- 2021. Admission to Advanced Psychometric Methods in Cognitive Aging Research 2021 Workgroup Sessions. (Competitive admission).
- 2021-Present. University of Pittsburgh Alzheimer Disease Research Center (ADRC) Research Education Component (REC) Scholar
- 2020-2021. University of Pittsburgh ADRC Optimizing Scientific Careers in AD Research (OSCAR) Scholar. Leadership apprenticeship.

Daniel Forman, MD (2022)

- Michael L. Pollock Established Investigator, American Assoc of CV and Pulmonary Rehabilitation

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

Lena Makaroun MD, MS (2021)

- 2019 - Presidential Poster Award, American Geriatrics Society Annual Meeting
- 2019 - Science and Innovation Walking Tour Selectee, American Geriatrics Society Annual Meeting
- 2021 - VA Pittsburgh Healthcare System Early Career Investigator Contest Poster Winner (HSR&D category)

Nami Safai Haeri, MD (2021)

- Helmsley Charitable Trust Abstract Award from The Endocrine Society

Neil Resnick, MD (2022)

- 2022 Joseph T. Freeman Award - a lectureship in geriatrics awarded to a prominent clinician in the field of aging, both in research and practice.

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."

Susan Greenspan, MD (2022)

- 2022 UPMC Grand Champion for the 14th Annual UPMC Celebrating Senior Champions

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
- Keisha Ward, MD, Pepper Novice Trainee
Alzheimers in minorities
- Mary Ackenbom, MD, Pepper Novice Trainee
Physical and cognitive impairment in older women after urogynecological surgery

Minority Grant(s):

UNIVERSITY OF CONNECTICUT HEALTH CENTER Claude D. Pepper Older Americans Independence Center

George A. Kuchel, Ph.D.
Principal Investigator

860-679-6796

kuchel@uchc.edu

Richard H. Fortinsky, Ph.D.
Co-Principal Investigator

fortinsky@uchc.edu

Anthony Barresi & Christine Zonghetti
Center Administrator

860-679-3959 860-679-4596

barresi@uchc.edu

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)

Leader 1: George Kuchel, MD kuchel@uchc.edu

Leader 2: Richard H. Fortinsky, PhD fortinsky@uchc.edu

Leader 3: 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)

Leader 1: David Steffens, MD steffens@uchc.edu

Leader 2: 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)

Leader 1: Lisa Barry, PhD libarry@uchc.edu

Leader 2: 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, biostatistical 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)

Leader 1: Laura Haynes, PhD lhaynes@uchc.edu

Leader 2: Duygu Ucar, PhD duygu.ucar@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 Sandra Jastrzebski (jastrzebski@uchc.edu).

Data Resource Core (Resource Core 2)

Leader 1: Richard H. Fortinsky, PhD fortinsky@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 Diggins (diggins@uchc.edu).

Recruitment and Community Engagement Core (Resource Core 1)

Leader 1: Julie Robison, PhD jrobison@uchc.edu

Leader 2: Wizdom Powell wpowell@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

The Effect of Metformin on Influenza Vaccine Responses in Aged Mice

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

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

Cristina Colòn-Semenza

Assistant Professor / Department of Kinesiology, UConn College of Agriculture, Health & Natural Resources

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 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

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

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

Roshanak Sharafieh, PhD

Assistant Professor / Department of Surgery, UConn School of Medicine

Biomarker Development to Promote Geroscience-Guided Approaches to Chronic Wound Management in Older Adults

2022-2024 /

2 (total)

0 (1st/Sr)

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

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 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 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 life and negative mental and health outcomes. 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 address the needs and concerns of African American older adults as a means of preventing or reducing depressive symptoms of disability.

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**

In years 1-2, Drs. Earp and Kwon will recruit a sex balanced cohort of 20 healthy young, 20 healthy old, 20 frail, and 20 frail and obese older adults. In years 2-3, fresh and frozen blood samples will permit Drs. Bartley, Kwon, Xu, and Nehar-Belaid to study immunometabolism, autophagy and mitophagy, p21 senescence markers and single cell genomics, respectively. This will offer opportunities for pilot studies to begin validating novel biomarkers helpful in the design and implementation of future geroscience-guided therapies.

3. Project Title: Apathy: An Early Manifestation of Frailty and Disability in Older Adults with Depression?**Leader: Kevin Manning, PhD (PI)**

This project will study whether apathy is an early manifestation of frailty and disability involving both behavioral and physical measures in older adults with depression. This approach may allow for earlier detection of risk factors for disability, with opportunities for some initial insights into role of inflammation, as well as opportunities for improved targeting of higher risk population subsets.

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 and determine the proportions of who opts in/out of joining 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: Analysis of scRNAseq data from metformin flu vaccine 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) 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 subpopulations. 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. The project will explore the role of specific biological hallmarks of aging associated with frailty, obesity and late life vulnerability. 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) as well as in future years prospective samples that will be obtained 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: Generation of scRNAseq data using samples from metformin flu vaccine study & HVAC pilot cohort

Leader: Laura Haynes, PhD (PL), Duygu Ucar, PhD (Jax GM; 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. The study will generate data using CITE-Seq and single cell ATAC-Seq to interrogate PBMCs using study samples generated by PESC3, The Heterogeneity of Vulnerabilities in Aging (HVAC) Cohort: A new resource for early biomarker discovery and validation Project Leaders: Laura Haynes and George Kuchel) in future years. In year 1, samples already generated collected in the 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 and single cell ATAC-Seq.

RESEARCH (5 Projects Listed)

- 1. 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 A42/40 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.

- 2. 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.

3. 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

4. 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.

5. 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 μm) 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 μm 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**2022**

1. **Hereditary hemochromatosis variant associations with incident non-liver malignancies: 11-year follow-up in UK Biobank.**
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[pii: cebp.0284.2022-3-14 11:22:41.207. https://doi.org/10.1158/1055-9965.EPI-22-0284](https://pubmed.ncbi.nlm.nih.gov/35709753/) |
PMID: 35709753
Citations: | AltScore: 3.75
2. **Cognitive Frailty is Associated With Elevated Proinflammatory Markers and a Higher Risk of Mortality.**
Diniz BS, Lima-Costa MF, Peixoto SV, Firmo JOA, Torres KCL, Martins-Filho OA, Teixeira-Carvalho A, Grady J, Kuchel GA, Castro-Costa E
Am J Geriatr Psychiatry, 2022 Jul, 30(7): 825-833
<https://doi.org/10.1016/j.jagp.2022.01.012> | PMID: 35227616 | PMCID: PMC9177532
Citations: 2 | AltScore: 0.25
3. **Prevalence of dementia and mild cognitive impairment before incarceration.**
Kuffel RL, Byers AL, Williams B, Fortinsky R, Li Y, Ruderman MA, Barry LC
J Am Geriatr Soc, 2022 Feb 25, 70(6): 1792-1799
<https://doi.org/10.1111/jgs.17724> | PMID: 35212389 | PMCID: PMC9177569
Citations: | AltScore: 6.8
4. **Geroscience-guided repurposing of FDA-approved drugs to target aging: A proposed process and prioritization.**
Kulkarni AS, Aleksic S, Berger DM, Sierra F, Kuchel GA, Barzilai N
Aging Cell, 2022 Apr, 21(4): e13596
<https://doi.org/10.1111/accel.13596> | PMID: 35343051 | PMCID: PMC9009114
Citations: 1 | AltScore: 49.858
5. **Senescence-induced changes in CD4 T cell differentiation can be alleviated by treatment with senolytics.**
Lorenzo EC, Torrance BL, Keilich SR, Al-Naggar I, Harrison A, Xu M, Bartley JM, Haynes L
Aging Cell, 2022 Jan, 21(1): e13525
<https://doi.org/10.1111/accel.13525> | PMID: 34962049 | PMCID: PMC8761018
Citations: 2 | AltScore: 34.608
6. **Chronic HIV Infection and Aging: Application of a Geroscience-Guided Approach.**
Masters MC, Landay AL, Robbins PD, Tchkonja T, Kirkland JL, Kuchel GA, Niedernhofer LJ, Palella FJ
J Acquir Immune Defic Syndr, 2022 Feb 1, 89(Suppl 1): S34-S46
<https://doi.org/10.1097/QAI.0000000000002858> | PMID: 35015744 | PMCID: PMC8751288
Citations: | AltScore: 2.5
7. **Markers of systemic inflammation are positively associated with influenza vaccine antibody responses with a possible role for ILT2(+)/CD57(+) NK-cells.**
Picard E, Armstrong S, Andrew MK, Haynes L, Loeb M, Pawelec G, Kuchel GA, McElhaney JE, Verschoor CP
Immun Ageing, 2022 May 26, 19(1): 26
<https://doi.org/10.1186/s12979-022-00284-x> | PMID: 35619117 | PMCID: PMC9134679

Citations: | AltScore: 3.7

8. 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

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Citations: | AltScore: 243.25

9. Association of 1-year change in neuroticism and 3-year change in cognitive performance among older depressed adults.

Steffens DC, Manning KJ, Wu R, Grady JJ

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<https://doi.org/10.1017/S1041610222000084> | PMID: 35287768 | PMCID: PMC9308569

Citations: | AltScore: 2

10. Targeting p21^{Cip1} highly expressing cells in adipose tissue alleviates insulin resistance in obesity.

Wang L, Wang B, Gasek NS, Zhou Y, Cohn RL, Martin DE, Zuo W, Flynn WF, Guo C, Jellison ER, Kim T, Prata LGPL, Palmer AK, Li M, Inman CL, Barber LS, Al-Naggar IMA, Zhou Y, Du W, Kshitiz, Kuchel GA, Meves A, Tchkonja T, Kirkland JL, Robson P, Xu M

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<https://doi.org/10.1016/j.cmet.2021.11.002> | PMID: 34813734 | PMCID: PMC8732323

Citations: 5 | AltScore: 191.118

2021

1. Older incarcerated persons' mental health before and during the COVID-19 pandemic.

DePalma A, Noujaim D, Coman E, Wakefield D, Barry LC

Int J Prison Health, 2021 Dec 3, ahead-of-print(ahead-of-print):

<https://doi.org/10.1108/IJPH-08-2021-0077> | PMID: 34854275 | PMCID: PMC9289938

Citations: | AltScore: 0.25

2. Strategies for Targeting Senescent Cells in Human Disease.

Gasek NS, Kuchel GA, Kirkland JL, Xu M

Nat Aging, 2021 Oct, 1(10): 870-879

<https://doi.org/10.1038/s43587-021-00121-8> | PMID: 34841261 | PMCID: PMC8612694

Citations: 5 | AltScore: 106.208

3. The Role of Citrate Transporter INDY in Metabolism and Stem Cell Homeostasis.

Kannan K, Rogina B

Metabolites, 2021 Oct 15, 11(10):

[pii: 705. https://doi.org/10.3390/metabo11100705](https://doi.org/10.3390/metabo11100705) | PMID: 34677421 | PMCID: PMC8540898

Citations: 3 | AltScore: 18.358

4. Accelerated aging in older cancer survivors.

Sedrak MS, Kirkland JL, Tchkonja T, Kuchel GA

J Am Geriatr Soc, 2021 Nov, 69(11): 3077-3080

<https://doi.org/10.1111/jgs.17461> | PMID: 34534355 | PMCID: PMC8595814

Citations: 1 | AltScore: 43.95

5. Granzyme B: a double-edged sword in the response to influenza infection in vaccinated older adults.

Verschoor CP, Pawelec G, Haynes L, Loeb M, Andrew MK, Kuchel GA, McElhaney JE

Front Aging, 2021, 2:

[pii: 753767. https://doi.org/10.3389/fragi.2021.753767](https://doi.org/10.3389/fragi.2021.753767) | PMID: 35441156 | PMCID:
PMC9015675

Citations: | AltScore: NA

EXTERNAL ADVISORY BOARD MEMBERS

Barbara Resnick, PhD, RN, CRNP, FAAN, FAANP
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Roland Thorpe, PhD MS
John Hopkins University, Center on Aging & Health
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RECOGNITION AND AWARDS (2021-2022)

David Steffens, MD (2022)

- Distinguished Life Fellow of the American Psychiatric Association

Richard H. Fortinsky, PhD (2021)

- Steven Wallace Lifetime Achievement Award from the Aging and Public Health Section of the American Public Health Association

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 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 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 life and negative mental and health outcomes.

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 address the needs and concerns of African American older adults as a means of preventing or reducing depressive symptoms and physical disability.

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 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.

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 Pre-K Scholar Career Development Award.

Minority Grant(s):

THE UNIVERSITY OF CALIFORNIA, SAN FRANCISCO (UCSF)
Claude D. Pepper Older Americans Independence Center

Kenneth Covinsky M.D., M.P.H. 415-221-4810 x 24363 Ken.Covinsky@ucsf.edu
Principal Investigator

Sarah Ngo 415-221-4810 x 25450 Sarah.ngo@ucsf.edu
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

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
<p>Kenneth Lam, MD Assistant Professor, Geriatrics / UCSF OAIC <u>Aging in place: a study of regional variation in risk-adjusted mean home time after hospitalization in older adults</u> “<i>Aging in place</i>” 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.</p>	2021-2023 / 5 (total) 3 (1st/Sr)
<p>Matt Miller, PT, PhD Assistant Professor, Physical Therapy / UCSF OAIC <u>Physical inactivity and physical therapy use among older adults with cognitive impairment</u> Physical therapists commonly provide rehabilitative services to older adults and recommend targeted exercises to restore or maintain function; yet it is not known how many of these patients have underlying cognitive impairment that could undermine their ability to adhere to and benefit from physical therapy recommendations. Furthermore, there is growing evidence that regular adherence to physical activity recommendations can improve cognitive outcomes in people with MCI, potentially even delaying the onset of AD/DRD. Although physical therapists are uniquely trained to use exercise to improve function and achieve patient-centered goals, there is no evidence about how physical therapists identify cognitive impairment and tailor exercise or physical activity recommendations for older adults with cognitive impairment. As a PhD-trained physical therapist, Dr. Miller’s career goal is to become a national leader whose work improves health, disability, and quality of life for older adults with cognitive impairment.</p>	2021-2022 / 2 (total) 2 (1st/Sr)
<p>Tasce Bongiovanni, MD MPP Assistant Professor, General Surgery / UCSF OAIC <u>Post-operative pain medication prescribing in older adults undergoing elective surgery</u> Understanding the patterns of postoperative pain medication prescribing in older adults, in particular among racial/ethnic minority groups, is an urgent public health concern. Accordingly, the overall objective of Dr. Bongiovanni’s REC project is to better understand pain medication prescribing in older adults in the postoperative period using national Medicare data. Her long-term career goal is to improve postoperative care and medication use in older adults.</p>	2021-2022 / 4 (total) 4 (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)

PILOT/EXPLORATORY PROJECTS (6 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, this study 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 disproportionately 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.

DEVELOPMENT PROJECTS (9 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.

RESEARCH (7 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 improving life 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 the University of California, San Francisco (UCSF). Dr. Harrison has 12-years of experience in qualitative methods and led the research enterprise of a large hospice prior to completing a UCSF aging research fellowship and implementation science certificate. Through the activities proposed in this application, Dr. Harrison will strengthen and address gaps in her experience through a training plan focused on: a) advanced statistical methods in linked datasets, b) ADRD clinical care and research, and c) translating mixed-methods data into ADRD interventions. Resources to foster her career development include UCSF's nationally-recognized Division of Geriatrics, Memory and Aging Center, Institute for Health Policy Studies, and K Scholar program. Dr. Harrison has assembled an extraordinary multidisciplinary team with extensive expertise. Alzheimer's disease and related dementias are progressive incurable illnesses causing significant public health burden. Palliative care focuses on reducing suffering and improving quality of life by attending to the multi-dimensional sources of distress for seriously ill individuals and families. Evidence for quality palliative care for advanced ADRD comes primarily from research in nursing homes. For the more than 700,000 older adults with advanced Alzheimer's disease who die at home each year, clinicians lack population-level evidence to guide caregivers and patients in anticipating and planning for disease changes. The proposed K01 will address critical knowledge gaps and develop a toolkit of resources to support basic palliative care provided by neurologists. Dr. Harrison will first use a nationally-representative dataset to longitudinally examine factors associated with mortality and nursing home stay among people living at home with severe and advancing ADRD. Second, she will use semi-structured interviews with older adults living at home with ADRD, current and bereaved caregivers to understand palliative and end-of-life experiences and opportunities to improve palliative care for ADRD. Third, Dr. Harrison will work with multiple stakeholders to refine and assess the feasibility of a toolkit of basic palliative care resources for use in neurology clinical practice (such as an assessment checklist, evidence-based strategies for discussing serious illness prognosis and advance care planning adapted for ADRD, referral and billing guides, and summarized evidence from Aims 1 and 2 on living at 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. The proposed research will provide Dr. Harrison with the preliminary data, training, and experience to support future 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 career goal is to develop a research niche that bridges the field of aging and surgery to improve the care of older surgical patients. The specific career development goals outlined in this application include developing expertise in implementation science, intervention development, clinical trial design/analysis, and building a research niche that 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 of Medicine 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 individualized mentorship 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 psychosocial intervention to improve depressive symptoms, coping skills, and social support. The central hypothesis of this project is that preoperative psychosocial vulnerability is associated with post-operative functional recovery, and a greater understanding of psychosocial vulnerability and interventions designed to mitigate its effects will improve post-operative outcomes, such as functional recovery. The specific aims of the project include (1) determining the independent association between pre-operative psychosocial vulnerability with 2-year overall mortality and functional decline following major surgery; (2) understanding how psychosocial vulnerability impacts post-operative recovery in older surgical patients through semi-structured interviews with older surgical patients and caregivers; and (3) comparing 6-month functional recovery outcomes between those randomized to a psychosocial intervention (navigator-led social support and problem-solving 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. The application is relevant to NIH and NIA because Dr. Tang's career goal is to leverage an understanding of the geriatric-specific risk factors to elucidate potential aspects needing interventions and to improve shared surgical 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/ABSTRACT This 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 a national leader in geriatric oncology research, improving cancer care for older adults by aligning treatments with individualized patient goals. More than 72% of older adults with cancer report that they would not choose a treatment that results in functional impairment, even if it improves survival. Yet, oncologists traditionally make treatment decisions based on cancer characteristics, often without discussing how treatment might affect function or eliciting patients' goals and values. To move from cancer-centered to patient-centered decision making, oncologists must both predict which older adults are at highest risk for functional decline and communicate complex information about benefits and harms to patients in a way that aligns treatments with their goals for function, quality of life, longevity, and other priorities. This proposal aims to 1) identify risk factors for functional decline in daily activities, physical performance, and life-space mobility during chemotherapy and/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 adults with lung cancer. In Aim 1's multi-site cohort study, patients age 65 and older with metastatic lung cancer will undergo serial geriatric assessments to measure functional status during chemotherapy and/or immunotherapy. In Aim 2A's focus group study, older adults with lung cancer, caregivers, and oncologists will participate in focus groups to elicit feedback aimed at adapting the BC/WC tool to incorporate function and other patient priorities into patient-centered decision making. In Aim 2B's pre-post pilot study, oncologists will be trained to use the adapted BC/WC tool; treatment discussions with older adults with lung cancer before and after training will be analyzed. Dr. Wong's exceptional multidisciplinary mentoring team is led by Dr. Louise Walter, an internationally recognized expert on individualized decision making for cancer screening in older adults. 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 decision making and decision-making interventions for older adults with functional or cognitive impairment; 3) clinical trial design to test decision-making interventions for older adults with cancer; and 4) leadership skills to direct multicenter research to transform geriatric oncology care. The results from this proposal will serve as the foundation for a multicenter cohort study to develop and validate a risk prediction score for functional decline during lung cancer treatment in older adults and a cluster-randomized trial to test the effect of the adapted BC/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/ABSTRACT Due in large part to the successful development of antiretroviral therapy, adults with HIV infection are living longer; in the United States, 47% of all people living with HIV are age 50 and older. This aging population increasingly experiences multimorbidity, polypharmacy, and significant mental health and psychosocial challenges. 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 and social complexity. Supporting a role for geriatric assessment, studies show that assessments can predict hospitalization and mortality among older HIV-positive adults and geriatric conditions are associated with poorer quality of life. Yet little is known on how to best integrate geriatric assessment and management in HIV care settings. Strategies developed need to be efficient, able to be administered by non-geriatrics trained clinicians, and also tailored to the unique aging issues that are influenced by HIV infection. Our proposal addresses this knowledge gap by developing and testing a tailored Geriatric Assessment and Initial Management 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 expert perspectives on the most important geriatric assessment domains and initial management steps; 2) examine HIV providers and staff attitudes towards G-AIM HIV and identify facilitators and barriers to its use; and 3) pilot G-AIM HIV in two HIV outpatient settings to evaluate feasibility, acceptability and preliminary patient reported outcomes such as quality of life. The objectives of this proposal support the career development activities of the PI Dr. Meredith Greene focused on 1) Delphi methodology and stakeholder engagement, 2) qualitative research methods, 3) intervention and clinical trial research with vulnerable populations, and 4) ongoing leadership development. Dr. Greene will conduct all work at the University of California, San Francisco with an exceptional mentoring team, led by Dr. Kenneth Covinsky. This K76 Beeson proposal will advance our knowledge of how to integrate geriatric principles into HIV care to improve quality of life for older HIV-positive adults. It will also provide advanced research skills and valuable data to launch Dr. Greene's career as an independent investigator and leader at the intersection of HIV and geriatric medicine.

5. Project Title: OPTIMIZING SURGICAL DECISION-MAKING FOR NURSING HOME RESIDENTS UNDERGOING SURGERY FOR BLADDER AND BOWEL DYSFUNCTION

Leader(s): SUSKIND, ANNE M.
UNIVERSITY OF CALIFORNIA SAN FRANCISCO
NIH R01AG058616 / (2018 - 2022)

Core(s):

PROJECT ABSTRACT: There is a fundamental gap in our understanding of outcomes related to surgery for bladder and bowel dysfunction, which are ubiquitous conditions among nursing home residents. Despite these procedures being relatively low risk, they are not without risk, particularly in an already functionally and cognitively limited cohort. Currently, the only available information on such outcomes are from studies conducted in younger and healthier individuals and they lack important functional and cognitive outcomes that are meaningful to older adults. Our overarching research objective is to improve care for nursing home residents with bladder and bowel dysfunction by providing them and their healthcare providers with realistic expectations about the risks and benefits of surgical treatment for these conditions. The objective for the proposed study is to better understand the surgical and functional outcomes of these procedures in the nursing home population and to provide patients and their providers with a prognostic tool to assist in the surgical decision-making process. The central hypothesis is that there are substantial and significant immediate and long-term complications resulting from these procedures, spanning from high rates of surgical morbidity and mortality (compared to community-dwelling controls) and poor functional outcomes measured by activities of daily living, cognition and specific bowel and bladder functional outcomes. This hypothesis will be tested by leveraging Minimum Data Set (MDS) for Nursing Home Resident Assessment and Medicare claims data (inpatient and outpatient) by the following three specific aims: 1) to compare short-term (30-day mortality, surgical complications, length of stay, readmission) and long-term (1-year mortality and intensity of care) surgical outcomes between nursing home residents and age-, sex- and comorbidity-matched community-dwelling older adults undergoing elective surgery for bladder and bowel dysfunction, 2) to determine longitudinal changes in functional status, cognition, and bladder and bowel function among nursing home residents following elective surgery for bladder and bowel dysfunction, and 3) to develop and internally validate a prognostic tool for nursing home residents considering elective surgery for bladder and bowel dysfunction to predict surgical morbidity, mortality and

postoperative function, cognition and bladder and bowel function. This study is innovative because it will measure and apply longitudinal functional and cognitive outcomes data to a prognostic tool for surgical procedures performed to improve function among an already functionally impaired population. The proposed research is significant because there is no information about outcomes for these common conditions in this large and vulnerable population. Development of a prognostic tool to aid in this decision-making process will serve to minimize the risks of potentially unsuccessful, unnecessary and even harmful procedures, while promoting the use of such procedures among individuals who are more likely to receive benefit.

6. 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 SUMMARY The decision to proceed with liver transplantation in a patient with end-stage liver disease depends not just on the risk of death without transplant but the risk of adverse outcomes after it. The transplant clinician's assessment of a cirrhotic patient's global functional health which we have conceptualized as his or her vulnerability to health stressors is a critical factor (oftentimes the sole factor) in this decision. Yet at the current time, no standardized, 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 facilitate transplant 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 after transplant. We have demonstrated that tools to quantify frailty and functional status in older adults have proven valuable to measure global functional health in cirrhotic patients and have developed an objective Liver Frailty Index, consisting of a composite of performance-based tests (grip strength, chair stands, and balance testing), to capture longitudinal changes in functional status specifically for use in the pre- and post-transplant settings. Building logically upon this work, we propose to determine the impact of pre-transplant functional status on 1-year post-transplant mortality and global functional health and develop/validate clinical prediction rules for these outcomes that incorporate pre-transplant functional status. To accomplish these goals, we will leverage our existing Multi-center Functional Assessment in Liver Transplantation Study, consisting of 5 US liver transplant centers (UCSF, Johns Hopkins, Columbia, Baylor, and Duke) with a track record of collaboration and high-impact research to obtain data on a minimum of 1,300 liver transplant recipients with assessments of functional status pre-transplantation and assessments of global functional health (including the Liver Frailty Index, disability, and quality of life) 1-year post-transplantation. These data will be used to develop and validate clinical prediction rules that incorporate both pre-transplant functional status, patient and donor characteristics to predict death, functional status, disability, and quality of life 1-year after transplantation. This project will positively impact the field by expanding our ability to measure the benefit of transplant both by how long a recipient will live as well as by how well a recipient will live after liver transplantation. Importantly, this project will facilitate clinical decision-making for patients and their clinicians through the precise understanding of how functional status impacts outcomes and what patients can expect after liver transplantation with respect to functional recovery. Given that functional status is modifiable in cirrhotic patients, our data will also support future investigations to develop effective strategies to improve pre-transplant functional status with the goal of reducing mortality and optimizing post-transplant functional health.

7. 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 / ABSTRACTS Some 2.8 million Americans seek medical attention for traumatic brain injury (TBI) annually, resulting in estimated annual costs of over \$75 billion. Older adults have the highest and fastest rising rate of TBI of any other age-group, with 1 in 50 adults age ≥ 75 seeking medical attention for TBI in 2013. Older adults with TBI experience higher mortality, slower recovery, worse outcomes, and may be at especially high risk for post-TBI dementia. There are few evidence-based guidelines for management, no tools to provide patients and families with reliable estimates of prognosis, and few proven treatments. Progress has been limited by: 1. systematic exclusion of older disabled patients from most prior prospective TBI studies, and 2. lack of age-appropriate TBI research tools. The overall objective is to launch a 2-site prospective geriatric TBI cohort study that will directly address these barriers by applying state-of-the-art geriatric research methods to the field of TBI to improve representation 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 2 foundational 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 but is not systematically measured in TBI research. The central hypothesis is that pre-injury health will be extremely heterogeneous in geriatric TBI and will be a key predictor of outcome in this population. An outstanding team of experts in TBI and aging research will achieve these Aims: Aim 1: Assemble a prospective cohort of patients age ≥ 65 presenting to the Emergency Department ≤ 72 h after TBI who underwent CT. Enroll 270 TBI patient/study-partner dyads and 90 controls; perform baseline assessments and blood draws, and assess longitudinal outcomes at 2wk, 3mo, 6mo (primary endpoint) and 12mo; offer enrollment in a brain donation 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 geriatric instruments and assess association of these predictors with outcome after TBI. 2b: Describe the natural history of geriatric TBI using validated TBI and geriatric outcomes and then use data-driven analytics to identify the most 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 prognostic blood-based biomarkers. This work will directly inform design of large-scale age-appropriate geriatric TBI clinical trials that are urgently needed to improve care and outcomes in this vulnerable population.

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Citations: 1 | AltScore: 1

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Bauer SR, Kenfield SA, Sorensen M, Subak LL, Phelan S, Gupta LR, Chen B, Suskind AM, Park AJ, Iglesia C, Gass M, Hohensee C, Breyer BN

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Citations: | AltScore: 13.85

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Citations: 9 | AltScore: 33.04

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Boccaccio DE, Cenzer I, Covinsky KE

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Citations: 2 | AltScore: 11.25

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Bongiovanni T, Hernandez S, Ledesma Y, Menza R, Wick E, Steinman M, Mackersie R, Stein DM, Coffin PO

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Citations: 1 | AltScore: 12.2

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Citations: | AltScore: 7.65

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Chen P, Covinsky K

J Gen Intern Med, 2021 Apr, 36(4): 861-862

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Citations: | AltScore: 6.25

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Dharmasukrit C, Ramaiyer M, Dillon EC, Russell MM, Dutt M, Colley A, Tang VL

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Comput Methods Programs Biomed, 2021 Jun, 204: 106073

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Citations: 1 | AltScore: NA

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Garrett SB, Nicosia F, Thompson N, Miaskowski C, Ritchie CS

Pain, 2021 Nov 1, 162(11): 2769-2779

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Citations: 1 | AltScore: 2.85

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Growdon ME, Gan S, Yaffe K, Steinman MA

J Am Geriatr Soc, 2021 Jun 8, 69(9): 2464-2475

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Citations: 2 | AltScore: 113.87

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Gustafson DH Sr, Mares ML, Johnston DC, Mahoney JE, Brown RT, Landucci G, Pe-Romashko K, Cody OJ, Gustafson DH Jr, Shah DV

JMIR Res Protoc, 2021 Feb 19, 10(2): e25175

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Citations: 2 | AltScore: 7.25

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Urology, 2021 Aug, 154: 281-287

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Citations: 1 | AltScore: 5.25

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Harrison KL, Leff B, Garrigues SK, Eaton England AL, Perissinotto CM, Sheehan OC, Mickler AK, Basyal PS, Ritchie CS

J Palliat Med, 2021 Apr, 24(4): 481-483

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Citations: 2 | AltScore: 3.25

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Heinbach M, Block A, Hubbard E, Cataldo J, Cooper B, Leutwyler H

Aging Ment Health, 2021 Dec, 25(12): 2229-2234

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Citations: | AltScore: NA

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Hickman SE, Torke AM, Heim Smith N, Myers AL, Sudore RL, Hammes BJ, Sachs GA

J Am Geriatr Soc, 2021 Jul, 69(7): 1933-1940

<https://doi.org/10.1111/jgs.17097> | PMID: 33760226 | PMCID: PMC8273119

Citations: 3 | AltScore: 32.45

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Hickman SE, Torke AM, Sachs GA, Sudore RL, Tang Q, Bakoyannis G, Heim Smith N, Myers AL, Hammes BJ

J Am Geriatr Soc, 2021 Jul, 69(7): 1865-1876

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Citations: 3 | AltScore: 53.35

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Hickman SE, Torke AM, Sachs GA, Sudore RL, Tang Q, Bakoyannis G, Smith NH, Myers AL, Hammes BJ

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<https://doi.org/10.1007/s11606-020-06292-1> | PMID: 33111241 | PMCID: PMC7878602

Citations: 4 | AltScore: 35

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Huang LW, Sun D, Link TM, Lang T, Ai W, Kaplan LD, Steinman MA, Andreadis C

Support Care Cancer, 2021 Mar 10, 29(9): 5399-5408

<https://doi.org/10.1007/s00520-021-06120-0> | PMID: 33694088 | PMCID: PMC8295123

Citations: | AltScore: 10.5

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Hunt LJ, Harrison KL

J Am Geriatr Soc, 2021 Jun, 69(6): 1457-1460

<https://doi.org/10.1111/jgs.17107> | PMID: 33855701 | PMCID: PMC8192462

Citations: 5 | AltScore: 53.29

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Hunt LJ, Harrison KL, Covinsky KE

J Am Geriatr Soc, 2021 Dec, 69(12): 3690-3692

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Citations: | AltScore: 161.35

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Johnson KT, Palakshappa D, Basu S, Seligman H, Berkowitz SA

Health Serv Res, 2021 Feb 17, 56(5): 864-873

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Citations: 4 | AltScore: 18.8

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Kobayashi M, Kwak MJ, Aguilar D, Goyal P, Holmes HM, Deshmukh AA, Aparasu RR
Am J Cardiol, 2021 Aug 1, 152: 168
<https://doi.org/10.1016/j.amjcard.2021.04.002> | PMID: 34045051 | PMCID: PMC9190247
Citations: | AltScore: NA
39. **The epidemiology of social isolation and loneliness among older adults during the last years of life.**
Kotwal AA, Cenzer IS, Waite LJ, Covinsky KE, Perissinotto CM, Boscardin WJ, Hawkley LC, Dale W, Smith AK
J Am Geriatr Soc, 2021 Jul 11, 69(11): 3081-3091
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Citations: 3 | AltScore: 132.59
40. **A peer intervention reduces loneliness and improves social well-being in low-income older adults: A mixed-methods study.**
Kotwal AA, Fuller SM, Myers JJ, Hill D, Tha SH, Smith AK, M Perissinotto C
J Am Geriatr Soc, 2021 Dec, 69(12): 3365-3376
<https://doi.org/10.1111/jgs.17450> | PMID: 34449870 | PMCID: PMC8648986
Citations: | AltScore: 60.18
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Kotwal AA, Steinman MA, Cenzer I, Smith AK
JAMA Intern Med, 2021 Nov 1, 181(11): 1528-1530
<https://doi.org/10.1001/jamainternmed.2021.3775> | PMID: 34309620 | PMCID: PMC8314172
Citations: | AltScore: 296.32
42. **Unmet Need for Equipment to Help With Bathing and Toileting Among Older US Adults.**
Lam K, Shi Y, Boscardin J, Covinsky KE
JAMA Intern Med, 2021 May 1, 181(5): 662-670
<https://doi.org/10.1001/jamainternmed.2021.0204> | PMID: 33749707 | PMCID: PMC7985819
Citations: 4 | AltScore: 283.146
43. **Tracking Lower Urinary Tract Symptoms and Tamsulosin Side Effects Among Older Men Using a Mobile App (PERSONAL): Feasibility and Usability Study.**
Lee AW, Kenfield SA, Wang EY, Enriquez A, Oni-Orisan A, Steinman MA, Sim I, Breyer BN, Bauer SR
JMIR Form Res, 2021 Dec 10, 5(12): e30762
<https://doi.org/10.2196/30762> | PMID: 34889745 | PMCID: PMC8709917
Citations: | AltScore: NA
44. **A Novel Metric for Developing Easy-to-Use and Accurate Clinical Prediction Models: The Time-cost Information Criterion.**
Lee SJ, Smith AK, Diaz-Ramirez LG, Covinsky KE, Gan S, Chen CL, Boscardin WJ
Med Care, 2021 May 1, 59(5): 418-424
<https://doi.org/10.1097/MLR.0000000000001510> | PMID: 33528231 | PMCID: PMC8026517
Citations: 1 | AltScore: 8.1
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Leng Y, Ackley SF, Glymour MM, Yaffe K, Brenowitz WD
Ann Neurol, 2021 Jan, 89(1): 177-181
<https://doi.org/10.1002/ana.25910> | PMID: 32951248 | PMCID: PMC8048405

Citations: 8 | AltScore: 44

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Li A, Williams B, Barry LC

J Appl Gerontol, 2021 Jul 23, 41(4): 1101-1110

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Citations: | AltScore: 2.5

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Makam AN, Grabowski DC

J Hosp Med, 2021 Mar, 16(3): 171-174

<https://doi.org/10.12788/jhm.3577> | PMID: 33617438 | PMCID: PMC7929615

Citations: 1 | AltScore: 9.7

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Martinez S, Yaffe K, Li Y, Byers AL, Peltz CB, Barnes DE

JAMA Neurol, 2021 Apr 1, 78(4): 473-477

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Citations: 2 | AltScore: 97.08

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McMahan RD, Tellez I, Sudore RL

J Am Geriatr Soc, 2021 Jan, 69(1): 234-244

<https://doi.org/10.1111/jgs.16801> | PMID: 32894787 | PMCID: PMC7856112

Citations: 7 | AltScore: 40.69

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Miller MJ, Cenzer I, Barnes DE, Covinsky KE

Aging Clin Exp Res, 2021 Oct 21, 34(4): 837-845

<https://doi.org/10.1007/s40520-021-01999-5> | PMID: 34674188 | PMCID: PMC9021326

Citations: | AltScore: 11.6

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Nagata JM, Seligman HK, Weiser SD

Adv Nutr, 2021 Mar 31, 12(2): 287-290

<https://doi.org/10.1093/advances/nmaa126> | PMID: 32970098 | PMCID: PMC7543276

Citations: 3 | AltScore: 26.65

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Nouri SS, Ritchie C, Volow A, Li B, McSpadden S, Dearman K, Kotwal A, Sudore RL

J Palliat Med, 2021 Mar, 24(3): 428-432

<https://doi.org/10.1089/jpm.2020.0200> | PMID: 32865472 | PMCID: PMC7894043

Citations: 1 | AltScore: 9.15

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Odden MC, Lee SJ, Steinman MA, Rubinsky AD, Graham L, Jing B, Fung K, Marcum ZA, Peralta CA

J Am Med Dir Assoc, 2021 Dec, 22(12): 2540-2546.e2

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Citations: 2 | AltScore: 34.5

54. Front-Line Hospice Staff Perceptions of Barriers and Opportunities to Discussing

Advance Care Planning With Hospice Patients and Their Families.

Oh A, Allison TA, Mahoney K, Thompson N, Ritchie CS, Sudore RL, Harrison KL

J Am Med Dir Assoc, 2021 Aug 13, 23(7): 1205-1214.e2

[pii: S1525-8610\(21\)00651-4. https://doi.org/10.1016/j.jamda.2021.07.014](https://doi.org/10.1016/j.jamda.2021.07.014) | PMID: 34391713

| PMCID: PMC8840996

Citations: | AltScore: 5.1

55. Engagement in Meaningful Activities Among Older Adults With Disability, Dementia, and Depression.

Oh A, Gan S, Boscardin WJ, Allison TA, Barnes DE, Covinsky KE, Smith AK

JAMA Intern Med, 2021 Apr 1, 181(4): 560-562

<https://doi.org/10.1001/jamainternmed.2020.7492> | PMID: 33492334 | PMCID: PMC7835951

Citations: 1 | AltScore: 83.19

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Pajka SE, Hasdianda MA, George N, Sudore R, Schonberg MA, Bernstein E, Tulsy JA, Block SD, Ouchi K

J Palliat Med, 2021 Jan, 24(1): 31-39

<https://doi.org/10.1089/jpm.2020.0067> | PMID: 32471321 | PMCID: PMC7757694

Citations: 5 | AltScore: 7.7

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Parks AL, Jeon SY, Boscardin WJ, Steinman MA, Smith AK, Fang MC, Shah SJ

J Am Geriatr Soc, 2021 Mar 5, 69(6): 1570-1578

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Citations: 1 | AltScore: 7.95

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Portacolone E, Chodos A, Halpern J, Covinsky KE, Keiser S, Fung J, Rivera E, Tran T, Bykhovsky C, Johnson JK

Gerontologist, 2021 Feb 23, 61(2): 251-261

<https://doi.org/10.1093/geront/gnaa201> | PMID: 33404634 | PMCID: PMC7901518

Citations: 8 | AltScore: 60.3

59. Functional Disability Among Older Versus Younger Adults With Advanced Non-Small-Cell Lung Cancer.

Presley CJ, Arrato NA, Janse S, Shields PG, Carbone DP, Wong ML, Han L, Gill TM, Allore HG, Andersen BL

JCO Oncol Pract, 2021 Jun, 17(6): e848-e858

<https://doi.org/10.1200/OP.20.01004> | PMID: 33939536 | PMCID: PMC8258136

Citations: 5 | AltScore: 11.75

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Presley CJ, Gomes F, Burd CE, Kanavarar R, Wong ML

J Clin Oncol, 2021 Jul 1, 39(19): 2115-2127

<https://doi.org/10.1200/JCO.21.00138> | PMID: 34043444 | PMCID: PMC8260908

Citations: 4 | AltScore: 69.6

61. Prisons and COVID-19: A Desperate Call for Gerontological Expertise in Correctional Health Care.

Prost SG, Novisky MA, Rorvig L, Zaller N, Williams B

Gerontologist, 2021 Jan 21, 61(1): 3-7

<https://doi.org/10.1093/geront/gnaa088> | PMID: 32706885 | PMCID: PMC7454571

Citations: 2 | AltScore: 52.5

62. Use of Services by People Living Alone With Cognitive Impairment: A Systematic Review.

Rosenwohl-Mack A, Dubbin L, Chodos A, Dulaney S, Fang ML, Merrilees J, Portacolone E
Innov Aging, 2021, 5(1): igab004

<https://doi.org/10.1093/geroni/igab004> | PMID: 33796795 | PMCID: PMC7990060

Citations: 2 | AltScore: 1

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Savin K, Morales A, Levi R, Alvarez D, Seligman H

Nutrients, 2021 Dec 4, 13(12):

pii: 4362. <https://doi.org/10.3390/nu13124362> | PMID: 34959914 | PMCID: PMC8707609

Citations: 2 | AltScore: NA

64. Lower urinary tract symptoms are associated with musculoskeletal pain among older men: Preliminary evidence for central sensitization as a mechanism?

Senders A, Bauer SR, Chen Y, Oken B, Fink HA, Lane NE, Sajadi KP, Marshall LM, For The Osteoporotic Fractures In Men MrOS Study Group

Neurourol Urodyn, 2021 Nov, 40(8): 1929-1938

<https://doi.org/10.1002/nau.24767> | PMID: 34396562 | PMCID: PMC8556292

Citations: | AltScore: 5.7

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Skolarus LE, Brown DL, Corches CL, Reynolds E, Bailey S, Mansour M, Robles MC, Rice T, Springer MV, Burke JF, Sudore RL

J Pain Symptom Manage, 2021 Jul, 62(1): e4-e9

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PMC8435356

Citations: | AltScore: 4.75

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Steinman MA, Boyd CM, Schmader KE

JAMA, 2021 Aug 10, 326(6): 475-476

<https://doi.org/10.1001/jama.2021.12134> | PMID: 34292309

Citations: 5 | AltScore: 59.35

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Steinman MA, Boyd CM, Spar MJ, Norton JD, Tannenbaum C

J Am Geriatr Soc, 2021 Dec, 69(12): 3693-3695

<https://doi.org/10.1111/jgs.17441> | PMID: 34499742 | PMCID: PMC8649037

Citations: | AltScore: 42.75

68. Comparative Outcomes for Pelvic Organ Prolapse Surgery among Nursing Home Residents and Matched Community Dwelling Older Adults.

Suskind AM, Zhao S, Boscardin WJ, Covinsky K, Finlayson E

J Urol, 2021 Jan, 205(1): 199-205

<https://doi.org/10.1097/JU.0000000000001331> | PMID: 32808855 | PMCID: PMC7725928

Citations: 3 | AltScore: 0.75

69. Comparative outcomes for older adults undergoing surgery for bladder and bowel dysfunction.

Suskind AM, Zhao S, Nik-Ahd F, Boscardin WJ, Covinsky K, Finlayson E
J Am Geriatr Soc, 2021 Aug, 69(8): 2210-2219
<https://doi.org/10.1111/jgs.17118> | PMID: 33818753 | PMCID: PMC8373651
Citations: 1 | AltScore: 1.6

70. Changes in functional status associated with radiation for prostate cancer in older veterans.

Ursem C, Diaz-Ramirez LG, Boscardin J, Lee S
J Geriatr Oncol, 2021 Jun, 12(5): 808-812
<https://doi.org/10.1016/j.jgo.2020.12.011> | PMID: 33388282 | PMCID: PMC8184565
Citations: 2 | AltScore: 0.25

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Valdez CE, London MJ, Gregorich SE, Lilly MM
PLoS One, 2021, 16(4): e0250221
<https://doi.org/10.1371/journal.pone.0250221> | PMID: 33857236 | PMCID: PMC8049256
Citations: | AltScore: 0.25

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Wang CW, Lebsack A, Sudore RL, Lai JC
Dig Dis Sci, 2021 May, 66(5): 1446-1451
<https://doi.org/10.1007/s10620-020-06369-1> | PMID: 32500286 | PMCID: PMC7714700
Citations: 4 | AltScore: 1.75

73. Perceptions of Older Men Using a Mobile Health App to Monitor Lower Urinary Tract Symptoms and Tamsulosin Side Effects: Mixed Methods Study.

Wang EY, Breyer BN, Lee AW, Rios N, Oni-Orisan A, Steinman MA, Sim I, Kenfield SA, Bauer SR
JMIR Hum Factors, 2021 Dec 24, 8(4): e30767
<https://doi.org/10.2196/30767> | PMID: 34951599 | PMCID: PMC8742207
Citations: | AltScore: NA

74. Applying the Multiphase Optimization Strategy for the Development of Optimized Interventions in Palliative Care.

Wells RD, Guastaferrero K, Azuero A, Rini C, Hendricks BA, Dosse C, Taylor R, Williams GR, Engler S, Smith C, Sudore R, Rosenberg AR, Bakitas MA, Dionne-Odom JN
J Pain Symptom Manage, 2021 Jul, 62(1): 174-182
<https://doi.org/10.1016/j.jpainsymman.2020.11.017> | PMID: 33253787 | PMCID: PMC8274323
Citations: 5 | AltScore: 13.6

75. Association of Coronary Artery Bypass Grafting vs Percutaneous Coronary Intervention With Memory Decline in Older Adults Undergoing Coronary Revascularization.

Whitlock EL, Diaz-Ramirez LG, Smith AK, Boscardin WJ, Covinsky KE, Avidan MS, Glymour MM
JAMA, 2021 May 18, 325(19): 1955-1964
<https://doi.org/10.1001/jama.2021.5150> | PMID: 34003225 | PMCID: PMC8132142
Citations: 2 | AltScore: 124.82

76. The growing geriatric prison population: A dire public health consequence of mass incarceration.

Williams B, DiTomas M, Pachynski A
J Am Geriatr Soc, 2021 Dec, 69(12): 3407-3409

<https://doi.org/10.1111/jgs.17454> | PMID: 34469589 | PMCID: PMC8648927

Citations: | AltScore: 16.5

77. Formal and informal social participation and elder mistreatment in a national sample of older adults.

Yang EZ, Kotwal AA, Lisha NE, Wong JS, Huang AJ

J Am Geriatr Soc, 2021 Jun 9, 69(9): 2579-2590

<https://doi.org/10.1111/jgs.17282> | PMID: 34105769 | PMCID: PMC8440381

Citations: | AltScore: 66.26

78. Evaluation of Time to Benefit of Statins for the Primary Prevention of Cardiovascular Events in Adults Aged 50 to 75 Years: A Meta-analysis.

Yourman LC, Cenzer IS, Boscardin WJ, Nguyen BT, Smith AK, Schonberg MA, Schoenborn NL, Widera EW, Orkaby A, Rodriguez A, Lee SJ

JAMA Intern Med, 2021 Feb 1, 181(2): 179-185

<https://doi.org/10.1001/jamainternmed.2020.6084> | PMID: 33196766 | PMCID: PMC7670393

Citations: 4 | AltScore: 275.39

EXTERNAL ADVISORY BOARD MEMBERS

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RECOGNITION AND AWARDS (2021-2022)

Recognition and Awards not specified.

MINORITY RESEARCH

General Brief Description of Minority Activities:

Not defined.

Minority Trainee(s):

- 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 underlying 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.

Minority Grant(s):

UNIVERSITY OF FLORIDA
Claude D. Pepper Older Americans Independence Center

Marco Pahor, M.D.
Principal Investigator

352-294-5800

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Connie Caudle
Program Administrator

352-294-5800

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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; and Data Science and Applied Technology 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 age-related 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)

Leader 1: Marco Pahor, MD mpahor@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)

Leader 1: Christiaan Leeuwenburgh, PhD cleeuwen@ufl.edu

Leader 2: 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)

Leader 1: Yenisel Cruz-Almeida, Ph.D. cryeni@ufl.edu

Leader 2: 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)

Leader 1: Stephen Anton, PhD santon@ufl.edu

Leader 2: Marco Pahor, MD mpahor@ufl.edu

The Clinical Research Core (RC 1) 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 RC 1 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)

Leader 1: Peihua Qiu, PhD pqiu@ufl.edu

The Biostatistics Core is one of four research cores in the OAIC at UF. The mission of the OAIC at UF 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 also is involved in all phases of these studies including initial study design and sample size calculations pre-proposal, randomization, and state-of-the-art statistical analyses once the data are completed. For study designs and data for which current methodology is lacking, the core has the expertise to develop new state of the art methodology to perform correct and appropriate analyses of data collected in the Center. 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)

Leader 1: Karyn Esser, PhD kaesser@ufl.edu

The new Circadian Rhythms research core within the UF OAIC will provide 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 will support 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 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 provides the infrastructure, laboratory space, trained personnel, consultative and collaborative scientific expertise and a wide spectrum of established and novel methodologies of biochemistry and molecular biology (Western blot and Quantitative-PCR, quantitative-Real-Time PCR, enzyme-linked immunosorbent assays, multiplex immunoassays), high resolution respirometry, and selected measures of metabolism (i.e., ATP measures and enzymes activities of metabolism) that will address a set of genetic and biological themes focused on causes for aging and disability. The Core utilizes this state-of-the-art technology to determine specific mechanisms of aging and sarcopenia and the cause of reduced physical function present in elderly populations. The Core provides support for numerous independently funded studies, development projects, pilot studies and exploratory studies. Analyses of levels of biomarkers or cell signaling molecules will help to identify specific biological pathways of aging

implicated in the development of sarcopenia. If the precise mechanisms underlying age-associated cellular deterioration can be identified, it will explain the loss of muscle mass and function with age and provide us with potential targets for intervention. In this context, we will also test if specific rehabilitation, physical activity and dietary interventions can attenuate biological pathways leading to aging and functional impairment. In addition, the Core supports preclinical phenotyping of various domains of function include Cognition, Physical, Motor, and Sensory/Hearing. Each of these sophisticated measures currently in use in our laboratories require expert oversight and the use of highly trained technicians. These assessment methodologies are conceptually similar to those used in humans and highly translatable.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications
<p>Lakeshia Cousin, PhD, APRN, AGPCNP-BC Assistant Professor / College of Nursing <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></p>	2022-2024 / 0 (total) 0 (1st/Sr)
<p>Feng Yue, PhD Assistant Professor / Department of Animal Sciences <u>Mechanisms of sepsis-induced myopathy in aging: insights from a new modified surgical sepsis model by single cell analysis</u></p>	2022-2024 / 0 (total) 0 (1st/Sr)
<p>Clayton Swanson, PhD, MS Assistant Professor / Department of Aging & Geriatric Research <u>Development of a Home-based Self-delivered Prehabilitation Intervention to Proactively Reduce Fall Risk in Older Adults</u></p>	2022-2024 / 0 (total) 0 (1st/Sr)
<p>Matthew R. Burns, MD, PhD Assistant Professor / Department of Neurology <u>Project Title: Mesocorticolimbic Dysfunction and Modulation in Aging and Synucleinopathy</u> Key Words: Mesocorticolimbic, cognitive function, synucleinopathy • K08</p>	2020-2022 / 0 (total) 0 (1st/Sr)
<p>Sudeshina A. Chatterjee, BPTch, MS, PhD Assistant Scientist / Department of Aging & Geriatric Research <u>Investing COMT Genotype Association with Mobility Decline and Falls in Older Adults</u> Key Words: Complex walking, fall risk, prefrontal cortex, genetics, precision medicine</p>	2020-2022 / 0 (total) 0 (1st/Sr)
<p>Mamoun Al Mardini, PhD Assistant Professor / Health Outcomes and Biomedical Informatics <u>Project Title: Developing an EHR-Based Frailty Index Using Machine Learning Approaches</u> Key Words: Frailty, machine learning, pre-operative screening, outcomes, decision-aid</p>	2020-2022 / 0 (total) 0 (1st/Sr)
<p>Samir K. Shah, MD, MPH Assistant Professor / Department of Surgery <u>Patient-Centered Outcomes After Abdominal Aortic Aneurysm Surgery</u> Key Words: Patient-centered outcomes, aging, mobility, wearables, ecological momentary assessment of symptoms, aortic aneurysms</p>	2020-2022 / 0 (total) 0 (1st/Sr)

Past Scholars

Dr. Rui Xiao, 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)

Dr. Joseph McQuail, PhD, Department of Neuroscience (2018-2019)

Dr. 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)

PILOT/EXPLORATORY PROJECTS (13 Pilot Projects Listed)**1. Project Title: Time Course Adaptations using Deuterated Creatine (D3Cr) method****Leader: Anoop Balachandran, PhD (Todd Manini, PhD)**

This pilot study is focused on assessing the time course adaptations in functional muscle mass and performance outcomes in response to a high-intensity resistance training intervention in low functioning older adults. It will provide critical clinical preliminary data for a successful extra-mural application for a future larger study. Specifically, the proposed future study will examine the impact of a high intensity resistance training intervention to increase skeletal muscle mass compared to an education control on physical performance outcomes, such as 400 m walk, lower body strength, balance, SPPB Short Physical Performance Battery (SPPB) in low functioning older adults.

2. Project Title: Circadian dysfunction in aging and chronic kidney disease**Leader: Michelle Gumz, PhD (Karyn Esser, PhD)**

The goal of this pilot study is to provide feasibility and supporting data for an R01 application. This new line of investigation is aimed at discerning mechanisms of and novel therapeutic interventions for chronic kidney disease. Chronic kidney disease is increasing in large part due to our aging population and it is associated with muscle wasting, decreased mobility, and increased disability. Our preliminary data for this pilot proposal strongly suggest that Dr. Esser's unique mouse model of circadian disruption and accelerated aging has a renal defect. The funds requested in this application are necessary to test our hypothesis that circadian disruption and accelerated aging lead to kidney damage and reduced renal function. These funds are needed to provide supporting data for a larger, long-term project in which we will further test the hypothesis that circadian disruption and accelerated aging lead to chronic kidney disease with consequences for cardiovascular mortality.

3. Project Title: Exosomal Mediation of Exercise induced benefits in aging**Leader: Brittney Yegla, PhD**

The goal of this pilot study is to examine intercellular signaling, specifically exosomes and their miRNA content, in aging with exercised and non-exercised Fischer-344 rats. The study proposes to investigate age- and sex-related differences in exercise-induced exosome release following either an acute or sustained exercise regimen and how this relates to the changes in musculature, cognition, metabolism, inflammation, and redox state in multiple organs with exercise. Young and aged male and female rats will undergo treadmill running for a single bout of exercise (acute; Aim 1) or for two months on a progressive workload schedule (sustained; Aim 2) to produce a 70% VO₂max. Following exercise rats will be evaluated for physical and cognitive capacity changes compared to sedentary controls. After final bout of exercise, rats will be euthanized, and the blood, muscle, liver, kidney, brain, and fat tissue will be collected to examine the impact of age, sex, and exercise on exosome-derived miRNA expression and metabolic and inflammatory marker levels. Regular sustained exercise is expected to produce quantitative and qualitative changes in exosome-derived miRNA expression, correlating with cellular, cognitive, and physical changes. It is predicted that continued exercise will shift the aging secretome to resemble a younger profile. The findings from this study will not only

establish the foundation for future NIH-funded experiments but also provide critical insight into age-related shifts in intercellular signaling and its sensitivity and responsiveness to exercise.

4. Project Title: Identification of novel circulating factors affecting skeletal muscle mass & function in advanced age

Leader: Russell T. Hepple, PhD

This pilot study aims to identify novel circulating (blood-borne) factors that can promote physical function and maintenance of skeletal muscle mass and function in advanced age. We will capitalize on substantial pre-existing data, banked blood serum and banked myoblast cultures that we collected in recent studies examining world-class octogenarian track & field athletes as a model of very healthy aging. We will complement this with study of pre-frail/frail elderly individuals with the objective of identifying both positive circulating factors (e.g., those found in serum of world class octogenarian athletes) and negative circulating factors (e.g., those found in serum of pre-frail/frail elderly) by doing advanced proteomics screening of serum from these subjects. Additionally, we will conduct preliminary evaluation of promising candidate proteins enriched in high functioning (octogenarian athletes) versus low functioning (pre-frail/frail elderly) individuals by screening for muscle and neuromuscular junction impact using human myoblast cultures. These highly novel and exciting studies will directly address factors that likely contribute to mobility and disability with aging.

5. Project Title: Estrogen and Prevention of Hearing Loss

Leader: Shinichi Someya, PhD

Numerous studies have reported gender differences in human auditory function. In general, the results of these studies show that women of virtually all ages demonstrate better hearing than men⁵⁻¹³. Considerable evidence also suggests that auditory function is diminished following menopause¹⁴⁻¹⁵, whereas estrogen therapy prevents decline of auditory function in postmenopausal women¹⁶⁻²⁰. Estrogen also has neuroprotective and glutathione antioxidant defense actions²¹⁻²⁴. However, the molecular mechanisms underlying these beneficial effects are largely unknown and prescribing estrogen therapy to women experiencing hearing problems remains controversial²⁵⁻²⁷. The central hypothesis of our research proposal is that estrogen protects hearing by enhancing glutathione transferase detoxification in the auditory system of females over the lifespan. The results of our proposed work will provide women, suffering from post-menopausal hearing loss, practical approaches to prevent decline of auditory function and disability associated with hearing loss.

6. 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”

7. 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.

8. 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.

9. 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 dysfunction; and 2. Determine the efficacy of exercise training for preventing cancer-induced 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”.

10. 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.

11. 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.

12. 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 cell-based 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 cost-effective 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 cost-efficient stem-cell therapy to facilitate in situ tissue repair and wound healing applications, to name a few.

13. Project Title: Fear of falling as an underlying mechanism of age-related altered walking mechanics

Leader: Francesca Wade, PhD, David Clark, PhD, Christopher Hass, PhD

As we age, our ability to independently move outside of the home environment wanes. Limiting out of home activity is often due to reduced confidence in walking, especially in situations where environment- and task-demands are heightened. Older adults also adopt slower walking speeds; a cautious walking strategy due to fear of falling (FoF). Walking speed is determined by forward propulsion; appropriately timed muscular forces and joint actions produce forces on the ground that efficiently move the person forward. Although older adults maintain the ability to generate the requisite ankle force for walking, they typically rely less on contributions from the ankle and more on contributions from the hip. Increased hip contributions to propulsion may lead to more stable gait; thus propulsive force generation at the ankle may be underutilized to adapt gait patterns to compensate for FoF. The proposed research will take a novel and interdisciplinary approach to understand how FoF may play a role in age-related changes in walking function. This is an important area to study, as the changes in walking function reduce independent mobility outside of the home. The relationship between FoF and walking biomechanics will be investigated in older adults, who have either high- or low- fear of falling. The proposal also includes an experiment to artificially increase fear of falling to obtain direct measures of its effects on walking function. Findings from the proposed research will be used as pilot data in part of a larger grant proposal investigating walking mechanics, fear of falling, when in the lifespan these changes occur, and eventually, to develop interventions to promote independence and mobility in the aging population.

DEVELOPMENT PROJECTS (2 Development Projects Listed)**1. Project Title: Development of Novel Measures to Assess Fuel Utilization and Circadian Rhythms in Overweight, Older Adults**

Leader: Stephen Anton, PhD, Karyn Esser, PhD, Christiaan Leeuwenburgh, PhD, Todd Manini, PhD, Marco Pahor, MD, Bhanuprasad Sandesara, MD, William Donahoo, MD, Peihua Qiu, PhD

Core(s): Clinical Research Core (RC1)
Data Science and Applied Technology Core (RC 4) (Data Science)
Metabolism and Translational Science (RC2) (Metabolism and Translational Science)

The purpose of this development project is to develop and test the feasibility of relatively non-invasive new measures of fuel utilization and circadian health that can provide an index of both cellular and mitochondrial health. Hence, with this development project, we propose to investigate the feasibility of obtaining relatively non-invasive measures of fuel utilization and circadian health biomarkers in older adults. If these measures are found to be feasible, they may become useful measurement tools to be included in future clinical trials conducted within the University of Florida's Pepper Center. In specific aim 1, we will test the feasibility of measuring fuel utilization within white blood cells through Seahorse XF Technology, a new measure that could detect shifts in fuel utilization at a cellular level. 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 in whole blood. We will also test the feasibility of measuring systemic measure of circadian health using Wearable Technology (i.e., the Oura ring) that continuously tracks heart rate, body temperature, activity levels, as well as sleep patterns. The reliability and variability in the new measures of fuel utilization and circadian health markers will be compared to that of our standard Clinical Research Core measures of cognitive and physical function.

2. 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):

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.

RESEARCH (36 Projects Listed)**1. 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)****Core(s):**

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-science research study of Northwestern University's 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. Aim 1A will test the hypothesis that mitochondrial (mt)DNA regions that encode the electron 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 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 SFRN's population/epidemiology study (PI Greenland). This project will recruit 50 participants with PAD and 50 without PAD and follow them longitudinally with baseline and 2-year follow-up biopsies. Of those with PAD, 30 will have an Ankle-Brachial Index (ABI) 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 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 health, compared to placebo. This project's overall goal is to identify specific mitochondrial defects 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)

2. Project Title: Longitudinal Modeling and Sequential Monitoring of Image Data Streams**Leader(s): QIU, PEIHUA****UNIVERSITY OF FLORIDA****National Science Foundation 1914639 / (2019 - 2022)****Core(s):**

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 sequence 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 applications in different disciplines and areas. Open source R packages will be developed and 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 high 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 analyzing image data streams, and study their statistical properties. The proposed longitudinal 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 monitoring 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 unequally spaced.

3. Project Title: Culturally sensitive, primary care clinic-based interventions by community health workers and trained physicians to promote and sustain weight loss among black women patients with obesity

**Leader(s): TUCKER, CAROLYN M
UNIVERSITY OF FLORIDA
PCORI AD-1609-36187 / (2020 - 2022)**

Core(s):

Black women have the highest prevalence of obesity in the U.S. More than half (56.6%) of black women have obesity. This disease increases the likelihood of having diabetes and other chronic diseases, and decreases quality of life and life expectancy. The U.S. Preventive Services Task Force recommends that all adults who have obesity participate in an evidence-based, intensive, multicomponent behavioral treatment for this disease. Such treatment has been shown to produce clinically significant weight loss among patients; however, this weight loss is typically not sustained over time. Patients at the primary care clinics in our pilot study and health care professionals nationally agree that treatment of obesity should be occurring and evaluated in primary care settings. A major research gap is the lack of evidence that the treatment for obesity recommended by the Task Force is effective within primary care settings and with black women patients at these settings. Another research gap is the lack of research to identify an effective role for physicians in treating obesity given their busy schedules. A third research gap is the absence of research to identify an effective way of integrating community health workers (CHWs) into primary care settings to assist physicians and other providers with health promotion/care such as obesity treatment. The proposed study addresses these research gaps and the views of patients in our pilot study that they wanted culturally sensitive obesity treatments that produce and sustain weight loss and include having their providers talk with them about their weight in culturally sensitive/respectful ways. We will test the effectiveness of a culturally sensitive, evidence-based, intense, multi-component, behavioral program for treating obesity called Health Smart™ when this program is (a) implemented for 6 months in 20 primary care clinics by health care team integrated CHWs with black women patients who have obesity and (b) followed by either of two physician implemented behavioral counseling programs to prevent weight gain that are implemented quarterly over 12 months. Specifically, we will compare the effects on weight loss and weight loss maintenance of (1) Health Smart plus the Patient-centered Culturally Sensitive Weight Loss Maintenance Program and (2) Health Smart plus the Standard Behavioral Weight Loss Maintenance Program. We expect that (a) the first of these programs will result in significantly greater weight loss and weight loss maintenance and (b) that the model used to integrate CHWs into the health care team at each clinic will result in high ratings of this integration by the CHWs and other clinic staff involved with this study. This study is important to black women patients because it tests an obesity treatment of interest to such patients. Patients and other stakeholder partners will be involved in planning and implementing the study and in analyzing and disseminating study results.

4. Project Title: SPANISH ONLINE & TELEPHONE INTERVENTION FOR CAREGIVERS OF VETERANS WITH STROKE

**Leader(s): FREYTES, IVETTE M
VETERANS HEALTH ADMINISTRATION
VA I01HX001860 / (2017 - 2022)**

Core(s):

Stroke is major cause of disability and a leading cause of outpatient medical utilization within the Veterans Health Administration (VHA). Non-paid caregivers, particularly family members, are the major sources of support for stroke survivors. Unlike other chronic diseases, strokes occur suddenly and family members have little time to prepare and adjust to their new, caregiving roles. Previous research has found that family members, particularly Hispanics, have high rates of depression and burden when their stroke survivors return home. Providing caregivers with culturally-appropriate information, support, and skills has the potential to reduce negative caregiver outcomes and increase the likelihood that stroke survivors remain in the community. Unfortunately, no studies have focused on support interventions specifically for Hispanic caregivers. The main objective is to test the efficacy of a brief, telephone and online problem-solving intervention, using the Spanish version of the VA RESCUE stroke caregiver website. The objectives are: 1) reduce caregiver burden and

depression, 2) improve caregivers' problem-solving abilities, self-efficacy, and quality of life, 3) improve Veterans' functional abilities and determine the intervention's impact on Veterans' healthcare utilization, 4) determine budgetary impact, and 5) determine caregivers' perceptions of the intervention. The long-term goal is to partner with leaders to implement a culturally relevant, accessible, and cost-effective intervention for caregivers of Veterans post-stroke throughout the VHA. The project is guided by the relational/problem solving model of stress. A two-arm (8-session intervention vs. standard care), randomized controlled clinical trial with three assessment points will be conducted. A sample of 290 stroke caregivers will be randomly assigned to either an intervention or a standard care group. Study participants will be recruited from the VA Caribbean Healthcare System in San Juan, Puerto Rico (PR). The intervention consists of a problem-solving intervention and information/tools on the previously developed, evidenced-based Spanish-version of the RESCUE stroke caregiver website to improve stroke caregiver outcomes. The intervention will be conducted via telephone by a trained rehabilitation counselor. The intervention consists of four components: 1. Introduction to the RESCUE website and the problem-solving method; 2. Illustrative example on how to use the problem-solving approach and the RESCUE website to address caregiving problems; 3. Individualized practice exercise to develop a personalized problem-solving plan; and 4. Summary of the problem-solving method. Baseline measurements will be conducted with the caregivers prior to the intervention. Post-test assessments will be collected at 1 and 12 weeks post- intervention. In addition, we will obtain pre- and post-test measures of Veteran-related variables via CPRS electronic health records. Qualitative interviews will be conducted to assess caregivers' perceptions of the intervention. The Advisory Consortium will collaborate in all aspects of the project. A general linear mixed model for repeated measures will be used to examine the relationship between treatment assignment and each outcome over time. We will measure the budgetary impact of providing intervention by comparing the costs of the intervention group to the costs of the control group.

5. 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.

6. 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)

Core(s):

Summary: My career goal is to become an independent geriatric pharmacoepidemiologist with expertise in pharmacotherapy quality measurement and outcomes evaluation in the fields of pain and aging. The clinical focus of my research has centered on the management of multi-morbidity in older adults and particularly, the interplay of mental and physical disease and its treatment. One example of combination of health problems is elderly patients who live with Alzheimer's disease and related dementia (ADRD) and also suffer from chronic pain. To date, data on quality of pain medication prescribing and the sequelae of poor pain control in patients with ADRD are scarce. Studies investigating these associations are limited by small sample size, and none has attempted to establish the effect of adequate pain control on preventing mental health (MH) disorders. The goal of my K01 proposed research is to provide preliminary data that improve our understanding of current pain medication prescribing and potential discrepancies between practices and pain guidelines, and to formulate 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 are linked to nursing home resident assessment data (Minimum Data Set, MDS, 3.0). Because it is unclear whether MDS 3.0 can accurately detect patients with pain and MH disorders, we first conduct a feasibility study of validating MDS-based pain, depression, and behavioral symptoms against medical records at two nursing homes (Aim 1). With the nationally representative Medicare-MDS data, we explore the quality of pharmacological pain management and its determinants among ADRD and non-ADRD residents with non-cancer pain (Aim 2). The quality will be examined based on five common clinical standards--pain medication selection, pain medication scheduling, pharmacological prevention of drug adverse event, contraindicated medication use, and overall pain control. We then explore the extent to which pain control is associated with a decreased risk for select MH disorders, including depression, behavioral symptoms, anxiety, and sleep disorders in ADRD (Aim 3). This project is well tailored for me to apply the knowledge and skills that will be obtained from training activities with my Primary Mentor, Dr. Almut Winterstein (pharmacoepidemiology, quality measurement and outcome assessment) and Co-Mentors: Drs. Roger Fillingim (pain), Marco Pahor (aging), Babette Brumback (advanced methods for longitudinal data), and Laurence Solberg (clinical geriatric care and assessment). For further guidance, I enlist the expertise of Dr. Siegfried Schmidt in the field of pain medicine and Dr. Steven DeKosky in ADRD. This K01 award will provide protected time for me to receive training needed to prepare an R01 grant application to examine pain medication practices and their impact on health outcomes in ADRD. The results from this line of research are expected to lead to better pharmacological pain management and improved pain and health outcomes in older adults with cognitive impairments.

7. 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 of 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.

8. 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.

9. Project Title: UNIVERSITY OF FLORIDA CLAUDE D. PEPPER OLDER AMERICANS INDEPENDENCE CENTER (OAIC)

**Leader(s): PAHOR, MARCO
UNIVERSITY OF FLORIDA
NIH P30AG028740 / (2007 - 2022)**

Core(s):

PROJECT SUMMARYThe 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; and Data Science and Applied Technology 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.

10. 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 United States, and they are the leading cause of disability worldwide. While pain affects individuals throughout the lifespan, older adults are disproportionately impacted and are at particularly increased risk for chronic pain and pain-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 and behavioral contributions to pain and disability among older adults. A critical barrier to progress in this area of research is the limited availability of investigators with appropriate interdisciplinary training in addressing later life pain and disability. With strong institutional support, the University of Florida (UF) Resource Center for Minority Aging Research (RCMAR) will be established to address these scientific and workforce development needs. The UF RCMAR has an educational objective to provide outstanding training and career development opportunities to promising investigators from underrepresented backgrounds. The UF RCMAR's research objective is to conduct innovative and impactful transdisciplinary social and behavioral research addressing pain and disability among older adults, including health disparities in later life pain and disability (e.g. racial and ethnic differences, sex and gender differences, and socioeconomic influences). The UF RCMAR will accomplish these objectives through the synergistic efforts of four Cores: an Administrative Core (AC), a Research Education Component (REC), an Analysis Core (AnC), and a Community Liaison and Recruitment Core (CLRC). In addition, the UF RCMAR will benefit from extensive collaborations with other UF entities, including The UF Pain Research & Intervention Center of Excellence (PRICE), the UF Institute on Aging (IOA), and the UF Clinical and Translational Science Institute (CTSI). The UF RCMAR boasts an outstanding interdisciplinary group of Core Faculty with expertise spanning the spectrum of clinical and translational research related to our theme of biopsychosocial contributions to pain and disability among older adults. In order to accomplish its objectives, the UF RCMAR will recruit and retain outstanding early stage investigators from unrepresented backgrounds and provide them with excellent mentoring and career development support. Through its research activities, the UF RCMAR will produce novel and important

information regarding social and behavioral contributors to pain and disability in older adults, and will develop and test innovative interventions to reduce later life pain and disability.

11. Project Title: ESTROGEN AND COGNITION OVER THE LIFESPAN

**Leader(s): FOSTER, THOMAS C; KUMAR, ASHOK ;
UNIVERSITY OF FLORIDA
NIH R01AG037984 / (2010 - 2023)**

Core(s):

Abstract Sex 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 sex hormone effects on sex differences in vulnerability. However, obstacles to sex steroid treatments include closing 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 on memory and the closing of the therapeutic window. Closing of the therapeutic window is marked by a decrease in E2-responsive 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 the hypothesis that E2 treatment, several days prior to testing, specifically influences NMDAR-dependent episodic memory, such that it can rescue an age-related decline in episodic memory examined on the water maze and novel object recognition tasks. Aim 2 will test the hypothesis that E2 effects on memory and NMDAR function are mediated by reversal of NMDAR hypofunction, mediated by redox regulation of phosphatase/kinase activity, similar to that previously described in aging males. Thus, it is predicted that prior to closing of the therapeutic window (i.e. in animals in which E2 treatment improves cognition and increases NMDAR function), E2 treatment will promote antioxidant enzyme activity, reduce oxidative stress, and minimize redox-mediated decrease in CaMKII activity and NMDAR function. Further, following closing of the therapeutic window (i.e. for animals in which E2 does not rescue cognition and NMDAR function), E2 treatment will not promote antioxidant enzyme activity or reduce oxidative stress, and the NMDAR response and 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 regulation through DNA methylation. It is predicted that decreased responsiveness of E2-sensitive genes will be associated 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 behavioral tests that are sensitive to NMDAR function, patch-clamp recording of NMDAR synaptic responses, measures of oxidative stress and enzyme activity, transcription, and DNA methylation.

12. 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/ABSTRACT Aging is the primary risk factor for the majority of chronic diseases. Studies in mice have implicated specific growth and differentiation factors (GDFs) and proteins secreted by senescent cells as potential modifiers of aging. 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), activin A (AA), and plasminogen activator inhibitor 2 (PAI2), as indicators of biological age and age-related conditions in humans. The central hypothesis is that circulating concentrations of GDFs and senescence-related proteins are associated with, and predictive of, clinically important health outcomes and can be altered by physical activity. Samples from the Lifestyle Interventions and Independence for Elders (LIFE) Study; the largest and longest 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 study findings. A novel multiplexed liquid chromatography-tandem mass spectrometry assay will be leveraged to accurately quantify GDFs, and an advanced multiplexing platform will be used to measure senescence-related proteins in LIFE and HABC biospecimens. In Specific Aim 1, a multidisciplinary team will first determine the extent to which baseline concentrations of GDF8, GDF11, CCL11, ICAM1, AA and PAI2 are associated with baseline 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 chronic conditions). In Specific Aim 2, the degree to which baseline concentrations of GDFs and senescence-related proteins predict longitudinal changes in a) gait speed and SPPB score, b) major mobility disability (i.e., the inability 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 (as in Aim 1), at 1 and 2 years in LIFE and at 2 and 4 years in HABC will be determined. Finally, Specific Aim 3 will address 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 which change in the concentrations of these proteins parallel change in the health outcomes described in Aim 2. The successful completion of the proposed research will fill an important translational gap in our understanding of how GDFs and senescence-related proteins predict and, therefore, potentially mediate aging related disability and disease in older women and men. Ultimately, these proteins may be viable targets for innovative therapies to extend human healthspan.

13. 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 pump inside inflatable cuffs that are wrapped around the feet, ankles, and calves and worn for two hours daily. Every 20 second, the cuffs rapidly inflate, followed by rapid deflation. During deflation, arterial blood return into the arteriovenous pressure gradient generates shear stress and stimulates nitric oxide production. Preliminary evidence suggests that IPC improves lower extremity blood flow and walking endurance in people with PAD and that benefits persist for up to 12 months after intervention completion. However, evidence is limited by small sample sizes, high loss to follow-up, lack of blinding, and lack of sham controls. Clinical practice guidelines 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 to exercise. Therefore, in people with PAD, we will determine whether IPC augments the benefits of exercise on walking endurance and whether IPC alone improves walking endurance compared to sham control. We will conduct 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 Group D: sham control + no exercise control. The IPC and sham interventions will be delivered for six months. In our primary specific aims, we will determine whether IPC combined with exercise improves the 6-minute walk at 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 IPC persist by re-measuring study outcomes at twelve-month follow-up, six months after the IPC intervention is completed. We will also delineate mechanisms by which IPC affects walking performance, by measuring changes in MRI-measured calf muscle perfusion, physical activity (measured with ActiGraph), and calf muscle biopsy measures of angiogenesis, muscle regeneration, mitochondrial biogenesis, mitochondrial activity, and autophagy. Based on preclinical evidence that IPC increases nitric oxide abundance and promotes vasodilation in skeletal muscle distant from the lower extremities, we will determine whether IPC improves systemic endothelial function, by measuring changes in brachial artery flow-mediated dilation. If the IPC intervention with and without exercise improves functional performance and prevents functional decline in PAD, this non-invasive and well tolerated intervention will have a major impact on preventing mobility loss and improving quality of life in the large and growing number of people with PAD.

14. 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, a rapidly growing segment of our population. The knee is the most commonly affected joint with pain being the primary symptom, negatively impacting physical, cognitive, and emotional functioning. Symptomatic knee OA has been traditionally attributed to peripheral mechanisms, but measures of joint damage only modestly account for the presence or severity of OA-related pain. The neuropeptide oxytocin (OT) has been recognized as a mediator of endogenous analgesia in animal and human studies. However, little is known about the neurobiological mechanisms underlying OT's pain-relieving properties. This proposal is based on a mechanistic model of OT's analgesic effects leveraging pilot data supporting efficacy and safety of self-administered intranasal OT over 4-weeks in older individuals. Relative to placebo (P), daily administration of intranasal OT diminished self-reported pain intensity, reduced experimental pain sensitivity, and increased self-reported physical and emotional functioning. Further, participants treated with OT, compared to P, showed decreases in brain metabolite concentrations associated with inflammation. Thus, our overarching goal is to evaluate the effects of intranasal OT on pain and function in aging and to determine the extent to which central and peripheral inflammatory mechanisms contribute to these analgesic responses. We aim to 1) determine the effect of intranasal OT administration on clinical and experimental pain sensitivity in older adults with symptomatic knee OA and 2) characterize inflammatory mechanisms contributing to the inter-individual variability in analgesic responses to OT. Older adults with symptomatic knee OA will self-administer intranasal OT or P over 4 weeks using a double-blinded, parallel study design. With strong support from the University of Florida and the McKnight Brain Institute, our interdisciplinary project, using a comprehensive multi-methods approach, will be the first to determine the potential benefit of OT as a novel analgesic therapy for knee OA pain in aging. OT is currently used in obstetrics and may be an inexpensive, effective method for pain management in older adults with little potential for addiction. Embedded in a biopsychosocial framework, our proposal will help pave the way for future investigations using a mechanism-based treatment optimization strategy for individuals suffering from chronic pain.

15. 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 Summary Age-dependent olfactory decline (presbyosmia) is widely present in many species, including humans. At least fifteen 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 presbyosmia often 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 motoric symptoms in these deadly neurological diseases. Despite the importance of olfaction to human physiology and health, the cellular and molecular mechanisms underlying presbyosmia are poorly understood (knowledge gap). As a major cell type in the nervous system, glial cells are typically considered as passive modulators during neural development and synaptic transmission. Whether glial cells play active roles in sensory transduction and brain aging is not well understood. *C. elegans* is a well-established model organism for neuroscience and aging 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 programs and 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 behavioral analysis to investigate and discover the molecular mechanisms through which the olfactory glial cells play active roles in odorant detection and age-dependent olfactory decline. Since both olfaction and aging are regulated by the evolutionarily conserved genes and signaling pathways, our innovative studies on *C. elegans* glial cells in olfaction and age-associated olfactory decline will provide mechanistic insights into similar processes in other species.

16. 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.

17. 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 quit 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.

18. 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.

19. 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.

20. 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 the environment. 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 normal health too. For example shiftwork, which repeatedly causes shifts in endogenous circadian rhythms, is an independent risk factor for cardiovascular disease. In mammals the suprachiasmatic nucleus (SCN) in the brain is the primary circadian pacemaker that helps to entrain 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 about this application is we determine how repeated changes in light cycle will impact molecular circadian signaling in the heart. Most cells have a molecular clock signaling mechanism that cycles with a periodicity of ~24 hours. We found genetic disruptions in the molecular clock mechanism of heart cells (cardiomyocytes) primarily causes abnormal 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 clock signaling 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 ion channel regulation. This project creates new knowledge at the interface between chronobiology and cardiac electrophysiology.

21. 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 SUMMARY Currently, in the United States, there are ~425,000 patients receiving hemodialysis (HD) and it is estimated that 30-60% of this population have some element of hand dysfunction after hemoaccess surgery. The underlying pathophysiologic mechanisms responsible for this devastating problem are poorly understood. The renal dysfunction (RD) milieu causes a variety of physiologic derangements in HD patients including increased oxidative stress (OS) and chronic inflammation that have been implicated as major contributors to accelerated atherosclerosis and elevated mortality. Profound changes in OS contribute to skeletal muscle and neuromuscular junction dysfunction associated with muscle atrophy and frailty in this population. AVF surgery causes significant hemodynamic changes in the extremity which presents an adaptive challenge to the skeletal muscle and neuromotor end-plate. Supported by our previous work, as well as preliminary data on RD associated skeletal muscle mitochondrial phenotypic changes, we propose that RD driven mitochondrial dysfunction alters skeletal muscle 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.

22. 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.

23. 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.

24. Project Title: EMOTIONAL ENGAGEMENT DRIVEN BY COMPLEX VISUAL STIMULI: NEURAL DYNAMICS REVEALED BY MULTIMODAL IMAGING

**Leader(s): DING, MINGZHOU; KEIL, ANDREAS ;
UNIVERSITY OF FLORIDA
NIH R01MH112558 / (2017 - 2022)**

Core(s):

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 neurophysiology 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 technique for combining electrophysiological recordings, high in temporal precision, with 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 activated 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 observer's emotional response, to address the following Aims: (1) We characterize the 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 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 treatment efficacy, a quantitative brain-based marker of emotional engagement opens 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.

25. 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 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 individuals. VLUs, which account for 70-90% of ulcers found in the lower leg, affect 2 million persons annually, including nearly 4% of people over age 65 years. To date, the basic biology underlying the development and persistence of VLUs and the influence of aging and multiple disease conditions on wound healing are generally not well understood. Individuals living with chronic VLU (CVLU) have a high symptom burden of 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 molecular mechanisms by which the immune activation that contributes to the development and persistence of CVLU also leads to the development, persistence and severity of PNS. The specific aims of the proposed study are to: (1) Characterize the strength of the associations at baseline among patient-host factors, systemic inflammation, 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 wound microenvironment; (b) Patient-host factors and wound microenvironment with systemic inflammation; (c) Patient-host factors, systemic inflammation, and wound microenvironment with wound healing; (d) Patient-host factors, 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 (PNS and 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 will fully 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 (local inflammation [Matrix metalloproteinase (MMP) enzymes C-reactive protein, cytokines], biofilm, and micro RNAs); symptoms (PNS [cognitive dysfunction, pain, fatigue, and depressive/anxiety symptoms] and wound-related); and wound characteristics and healing trajectory at the five timepoints. This knowledge is critical to provide a foundation for developing targeted interventions to address this critical health problem 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.

26. Project Title: OPTIMIZING AAV VECTORS FOR CENTRAL NERVOUS SYSTEM TRANSDUCTION

**Leader(s): HELDERMON, COY D
UNIVERSITY OF FLORIDA
NIH R01NS102624 / (2017 - 2022)**

Core(s):

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. Due to the neurodegenerative nature of this disease, optimal CNS transduction is necessary for human trials. Several groups have demonstrated improvement of the mouse model using different adeno-associated viral (AAV) vectors. We have recently demonstrated that AAV8 has better brain gene delivery in MPS IIIB than wild type mice. A similar finding of altered brain delivery in Sly Syndrome compared to wild type mice has been published for AAV9. However, for translation to human trials, it is essential to identify 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 and is phylogenetically distant compared to our 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 barcode AAV vector system that allows assessment of multiple AAV vector serotypes within the same animal, greatly reducing

the number of animals needed for statistical comparisons of brain delivery. This system has a 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 system to simultaneously identify brain delivery of 40 AAV serotypes and capsid variants in wild type and MPS III B mice as well as in non-human primates - the closest to human model available to us. We will identify whether injections into the body of the brain or the less invasive injection into the fluid around the brain method provides a better vector distribution. We will identify which wild-type AAV serotypes or capsid mutants 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 III B gene construct will be packaged into the optimal vector to assess treatment effect in MPS III B mice. We hypothesize that CNS transduction and distribution will differ by serotype and species and that some serotypes will transduce differently between wild type and Sanfilippo Syndrome mice. Our specific aims are therefore: 1. We will determine the brain delivery of AAV serotypes in non-human primates (NHP) and in wild type and MPS III B affected mice. We will use a novel 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 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 III B gene to treat the MPS III B mouse. We will use day/night activity, hearing, coordination, lifespan, lysosomal storage and 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 III B and other neurodegenerative disorders. If this project is successful, we will be in a position to quickly move towards such clinical trials.

27. Project Title: THE UNIVERSITY OF FLORIDA JACKSONVILLE AGING STUDIES CENTER (JAX-ASCENT)

**Leader(s): PAHOR, MARCO; ANTON, STEPHEN D ;
UNIVERSITY OF FLORIDA
NIH R33AG056540 / (2017 - 2022)**

Core(s):

Summary Older adults of racial minorities and low socioeconomic (SES) status represent particularly high risk populations who are underserved and are significantly underrepresented in clinical research. This has led to a gap in knowledge regarding the appropriate and/or optimal prevention and treatment approaches for this high risk group. Within the state of Florida, the city of Jacksonville (JAX) has a high proportion of minority and low SES individuals. By expanding existing research collaborations on both aging and health disparities at its JAX site, the University of Florida (UF) has a unique opportunity to conduct important research that can reduce this knowledge gap. These existing relationships include partnership in conducting multi-center NIH-funded clinical trials, along with several community outreach efforts both at UF Gainesville (GNV) and JAX. However, there is currently no cohesive, organized resource to integrate these important research collaborations in aging and health disparities at UF-JAX. At the UF GNV campus, we have a strong clinical translational research infrastructure with the Claude D. Pepper Older Americans Independence Center, Clinical Translational Science Institute and Disparities Research. In JAX, UF has a large health care facility in a densely populated minority and low SES area, but limited research infrastructure focused on aging research. To fully actualize the potential of this remarkable resource, we propose to develop a dedicated center for aging research focused on racial minorities and low SES older adults. This state-of-the-art clinical translational research facility for multidisciplinary research Jacksonville Aging Studies CENTER (JAX-ASCENT) will closely partner with the UF GNV campus and capitalize on our expertise and resources. Additionally, JAX-ASCENT will create an integrative physical and intellectual environment in which trainees at all levels and scientists from diverse disciplines can interact and conduct clinical and behavioral translational research on aging and independence of older adults. This focus will be pursued using an interdisciplinary approach that traverses a broad spectrum of biomedical investigation, including clinical research, behavioral sciences, social sciences, epidemiology, biostatistics, and health services, while implementing rigor and transparency in research. We will develop and partner regarding expertise on clinical trials, recruitment, adherence, retention, assessment of geriatric outcomes, biomarkers, and behavioral studies all focused and tailored on research in urban minorities and low SES older adults. We will apply a conceptual/logic model of community-based participatory research partnerships to improve community involvement and health outcomes, and to build a research participants registry. We will develop the physical and human infrastructure, mentor junior faculty towards leadership roles, and have JAX-ASCENT become self-sustaining.

JAX-ASCENT will expand knowledge in clinical translational research in largely understudied populations and both enlarge and enrich the diversity of research in older minority populations, clinical effectiveness, outcomes, and community engagement programs at UF.

28. 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

29. 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 future careers 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.

30. 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.

31. 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 care medicine physicians during the second or third year of their general residency programs, and expose them to two, three and even four years of mentored research in inflammation biology with highly productive basic science mentors focused on inflammation-related topics. Four training positions are requested. The overall research program will focus on mastery of molecular biology, functional genomics and gene regulation, as it applies broadly to inflammation research. Although the bulk of the training program will be in the laboratory of an experienced research mentor, trainees will be expected to participate in didactic experiences that complement their research experience. Select trainees will have the opportunity to complete a Ph.D. program in the Graduate School in three to four years. Other trainees can participate in graduate certificate programs which are formal collections of courses that together form a coherent program of study offered through an academic unit. This training program takes advantage of the unique strengths of the College of Medicine in the expanding field of functional genomics and molecular biology, as well as the existing collaborations between basic scientists and clinicians committed to the training of future clinical academicians. The interface between molecular biology and inflammation 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 scientists in the Surgery, Medicine, Pathology, Aging and Geriatric Research and Molecular Genetics and Microbiology Departments, who will serve as research mentors to the trainees. Clinical mentors from the Surgery, Medicine and Pathology Departments will interact with the trainees and the research faculty to assure that the trainees are being exposed to clinically-important issues in inflammation research. Overall direction of the program will rest with the Program Director and an Executive Committee. Candidates for the fellowship are recruited nationally and from the University of Florida

College of Medicine (Gainesville, Jacksonville). Successful applicants with the Executive Committee will identify a research and clinical mentor who will help formulate a formal training program and periodic review of the trainee's progress. Furthermore, trainees are expected to participate in basic science seminars in the Institute on Aging, Emerging Pathogens Institute and Genetics Institute, and in their own basic science departments, as well as laboratory research meetings. They will also be expected to attend clinical seminars, including Surgery and Critical Care Medicine Grand Rounds and the Department of Surgery Academic Research Conference. Based on our past experiences, it is anticipated that successful graduates of this training program will possess sufficient research skills to successfully compete for transitional funding in inflammation research and become leaders in academic surgery.

32. Project Title: UF PASS: REGULATION OF EXERCISE TRANSDUCERS
Leader(s): ESSER, KARYN A
UNIVERSITY OF FLORIDA
NIH U01AG055137 / (2016 - 2022)

Core(s):

Abstract Exercise is a powerful and pleiotropic physiological stimulus that helps prevent many chronic diseases and is used as a therapeutic for disease. While the beneficial effects of exercise are extensively acknowledged there is still very little understood about the molecular transducers of the systems-wide effects. The goal of this University of Florida Molecular Transducers of Physical Activity Preclinical Animal Study Sites 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 defined models of physical activity from tissues that cannot be obtained from humans as well as to conduct mechanistic studies that can 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 capture the dynamics of the exercise/adaptation responses we propose to: 1) Collect biospecimens at 5 selected timepoints following an acute bout of exercise on naive and trained rats; 2) Collect biospecimens following short duration training (after 5 bouts) and 3) Collect biospecimens following long-term (8 weeks) training. For Phase 2, our hypothesis is that factors released from muscle (i.e. myokines) are the molecular transducers that function throughout the system to improve the well-established stress tolerance. The goal of these studies will be to employ high throughput screening technologies to test up to 1500 myokines. We will then use secondary screening techniques to test 100 candidates from which we will select up to 3 candidates for in vivo testing. 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 will be pursued by the following Specific Aims: Specific Aim 1: Center Coordination Phase. Specific Aim 2: Phase 1 Studies. To perform endurance and resistance exercise using male and female F344BN rats 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 for improved stress tolerance.

33. 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 high societal and economic burden. NIH RFA-AG-18-019 solicits applications to investigate the central neural control of mobility in older adults using innovative and cutting-edge methods. Current approaches to study the neural control of walking are limited by either the inability to measure people during walking (functional magnetic 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 walking in older adults requires real time measurement of active regions throughout the brain during actual walking. We will 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 active cortical and subcortical brain regions with high spatial and temporal resolution during walking. The

result is unprecedented insight into the neural control of walking. Here, our overarching objective is to determine the central neural control of mobility in older adults by collecting EEG during walking and correlating these findings with a comprehensive set of diverse mobility outcomes (clinic-based walking, complex walking and community mobility measures). Our first aim is to evaluate the extent to which brain activity during actual walking explains mobility decline. In both cross sectional and longitudinal designs, we will determine whether poorer walking performance and steeper trajectories of decline are associated with the Compensation Related Utilization of Neural Circuits Hypothesis (CRUNCH). CRUNCH is a well-supported model of brain activity patterns that are seen when older individuals perform tasks of increasing complexity. CRUNCH describes the over-recruitment of frontoparietal brain networks that older adults exhibit in comparison to young adults, even at low levels of task complexity. CRUNCH also describes the limited reserve resources available in the older brain. These factors cause older adults to quickly reach a ceiling in brain resources when performing tasks of increasing complexity. 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 motor functions. In accordance with this call, our second aim is to characterize and harmonize high-density EEG during walking with fNIRS (during actual and imaged walking) and fMRI (during imagined walking). This will allow us to identify the most robust CRUNCH-related hallmarks of brain activity across neuroimaging modalities, which will strengthen our conclusions and allow for widespread application of our findings. Our third aim is to study the mechanisms related to CRUNCH during walking. Thus, our project will address a majority of the objectives in NIH RFA-AG-18-019 and will identify the neural correlates of walking in older adults, leading to unprecedented insight into mobility declines and dysfunction.

34. 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.

35. 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)

Core(s):

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 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.

36. 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 State University (FSU) CTSA hub will work within this environment to further the mission to improve human health by accelerating the translation of scientific discoveries and the implementation of evidence-based best practices for the diagnosis, treatment, prevention and cure of human diseases across the lifespan. The UF-FSU hub vision is think globally, act locally, offering research opportunities to underserved participants in North and North Central Florida, creating innovative career development and training opportunities, as well as collaborating across the country with the Accelerated Clinical Trials Network and PCORnet. Research strengths include precision medicine, team science, community engagement, implementation science and informatics which are conducted in diverse settings through the OneFlorida Clinical Research Consortium. The 2019-2024 period represents the next phase of evolution from creating a clinical and translational science infrastructure to enhancing the local, state and national impact of CTSI-led science. During this period, FSU will be integrated across all components and will engage six additional colleges. Hub activities will be centered around four strategic goals: (1) chart new pathways for developing the translational workforce by taking UF success in career

development and translating this success to the FSU and historically black colleges and universities; (2) strengthen the capacity of the learning health system environment and develop transferable models 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 the success of the personalized medicine program to use genomics data to improve patient outcomes; (3) expand statewide collaborations and opportunities to advance a participant-centered research agenda that reflects the health priorities and diversity of the catchment area by continuing to strengthen stakeholder engagement and trust in research through the HealthStreet Program and enhance collaboration with policy stakeholders from Florida Medicaid, Florida surgeon general and others; and (4) strengthen regional and national collaborations to accelerate the collective impact of the CTSA network through continued work with ACT, PCORnet, genomic medicine, aging and metabolomics. Throughout this important work, the UF-FSU hub will remain dedicated to supporting the recruitment, retention and career development of underrepresented minority and disabled trainees 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) clinical informatics, (3) clinician and stakeholder engagement, and (4) strong support from implementation and improvement science expertise.

PUBLICATIONS**2022**

- 1. 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
<https://doi.org/10.1128/aac.00563-22> | PMID: 35699444 | PMCID: PMC9295596
Citations: | AltScore: NA
- 2. 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
<https://doi.org/10.1089/sur.2021.152> | PMID: 34958257 | PMCID: PMC8892986
Citations: | AltScore: NA
- 3. 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
Neurobiol Pain, 2022 Jan-Jul, 11: 100086
<https://doi.org/10.1016/j.ynpai.2022.100086> | PMID: 35243180 | PMCID: PMC8885563
Citations: | AltScore: 13.3
- 4. 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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[pii: 3061. https://doi.org/10.3390/s22083061](https://doi.org/10.3390/s22083061) | PMID: 35459045 | PMCID: PMC9032589
Citations: 1 | AltScore: 1.75
- 5. Characterizing Expiratory Respiratory Muscle Degeneration in Duchenne Muscular Dystrophy Using MRI.**
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Citations: | AltScore: 13.45
- 6. Longitudinal changes in cardiac function in Duchenne muscular dystrophy population as measured by magnetic resonance imaging.**
Batra A, Barnard AM, Lott DJ, Willcocks RJ, Forbes SC, Chakraborty S, Daniels MJ, Arbogast J, Triplett W, Henricson EK, Dayan JG, Schmalfluss C, Sweeney L, Byrne BJ, McDonald CM, Vandenborne K, Walter GA
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<https://doi.org/10.1186/s12872-022-02688-5> | PMID: 35681116 | PMCID: PMC9185987
Citations: | AltScore: 1.5
- 7. Multicomponent intervention to prevent mobility disability in frail older adults: randomised controlled trial (SPRINTT project).**

Bernabei R, Landi F, Calvani R, Cesari M, Del Signore S, Anker SD, Bejuit R, Bordes P, Cherubini A, Cruz-Jentoft AJ, Di Bari M, Friede T, Gorostiaga Ayestar?n C, Goyeau H, J?nsson PV, Kashiwa M, Lattanzio F, Maggio M, Mariotti L, Miller RR, Rodriguez-Ma?as L, Roller-Wirnsberger R, R?znarov? I, Scholpp J, Schols AMWJ, Sieber CC, Sinclair AJ, Skalska A, Strandberg T, Tchalla A, Topinkov? E, Tosato M, Vellas B, von Haehling S, Pahor M, Roubenoff R, Marzetti E, SPRINTT consortium.

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<https://doi.org/10.1136/bmj-2021-068788> | PMID: 35545258 | PMCID: PMC9092831

Citations: 2 | AltScore: 584.63

8. **A wrinkle in time: circadian biology in pulmonary vascular health and disease.**

Bryant AJ, Ebrahimi E, Nguyen A, Wolff CA, Gumz ML, Liu AC, Esser KA

Am J Physiol Lung Cell Mol Physiol, 2022 Jan 1, 322(1): L84-L101

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9. **Chronic Critical Illness in Patients With Sepsis is Associated With Persistent Anemia, Inflammation, and Impaired Functional Outcomes.**

Carmichael ED, Apple CG, Kannan KB, Gardener A, Anton S, Efron PA, Moldawer LL, Moore FA, Brakenridge SC, Mohr AM

Am Surg, 2022 May 20 31348221104252

<https://doi.org/10.1177/00031348221104252> | PMID: 35593749

Citations: | AltScore: 0.25

10. **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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Citations: | AltScore: NA

11. **Relationships Between Cognitive Screening Composite Scores and Pain Intensity and Pain Disability in Adults With/At Risk for Knee Osteoarthritis.**

Crowley S, Mickle AM, Wiggins ME, Cardoso J, Lai S, Tanner JJ, Staud R, Fillingim RB, Price CC, Sibille KT

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<https://doi.org/10.1097/AJP.0000000000001042> | PMID: 35514280 | PMCID: PMC9210870

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12. **Exosomes in Age-Related Cognitive Decline: Mechanistic Insights and Improving Outcomes.**

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13. **SEX DIFFERENCES ASSOCIATE WITH LATE MICROBIOME ALTERATIONS AFTER MURINE SURGICAL SEPSIS.**

Efron PA, Darden DB, Li EC, Munley J, Kelly L, Fenner B, Nacionales DC, Ungaro RF, Dirain ML, Rincon J, Mankowski RT, Leeuwenburgh C, Moore FA, Brakenridge SC, Foster TC, Laitano O, Casadesus G, Moldawer LL, Mohr AM, Thomas RM

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<https://doi.org/10.1097/TA.0000000000003599> | PMID: 35324554 | PMCID: PMC9323556

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14. **Animal Models for Studies of Alcohol effects on the Trajectory of Age-Related Cognitive Decline.**

Foster TC

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[pii: S0741-8329\(22\)00035-0. https://doi.org/10.1016/j.alcohol.2022.04.005](https://doi.org/10.1016/j.alcohol.2022.04.005) | PMID: 35504438

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15. **Avoidance-Endurance Model in Older Black Men with Low Back Pain: Exploring Relationships.**

Fullwood D, Means S, Paxton R, Wells B, Riley JL 3rd, Stickley Z, Tucker C, You L, Elie M, Thomas C, Anton S, Pahor M, Wilkie DJ

J Racial Ethn Health Disparities, 2022 May 2

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16. **Biopsychosocial influence on shoulder pain: results from a randomized pre-clinical trial of exercise-induced muscle injury.**

George SZ, Bishop MD, Wu SS, Staud R, Borsa PA, Wallace MR, Greenfield WH 3rd, Dai Y, Fillingim RB

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17. **Unexplained anemia of aging: Etiology, health consequences, and diagnostic criteria.**

Guralnik J, Ershler W, Artz A, Lazo-Langner A, Walston J, Pahor M, Ferrucci L, Evans WJ

J Am Geriatr Soc, 2022 Mar, 70(3): 891-899

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Citations: 2 | AltScore: 40.4

18. **Reuniting the Body \Neck Up and Neck Down\ to Understand Cognitive Aging: The Nexus of Geroscience and Neuroscience.**

Hernandez AR, Hoffman JM, Hernandez CM, Cortes CJ, Jumbo-Lucioni P, Baxter MG, Esser KA, Liu AC, McMahan LL, Bizon JL, Burke SN, Buford TW, Carter CS

J Gerontol A Biol Sci Med Sci, 2022 Jan 7, 77(1): e1-e9

<https://doi.org/10.1093/gerona/glab215> | PMID: 34309630 | PMCID: PMC8751793

Citations: 3 | AltScore: 18.2

19. **Analysis of US Household Catastrophic Health Care Expenditures Associated With Chronic Disease, 2008-2018.**

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21. **Sociodemographic and Clinical Characteristics Associated With Worst Pain Intensity**

Among Cancer Patients.

Joseph V, Huo J, Cook R, Fillingim RB, Yao Y, Egziabher-Kiros G, Villarreal EV, Chen X, Molokie R, Wilkie DJ

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J Am Dent Assoc, 2022 Mar, 153(3): 241-250.e10

<https://doi.org/10.1016/j.adaj.2021.08.008> | PMID: 34952681

Citations: | AltScore: 13.7

23. Methods for Phenotyping Adult Patients in Sepsis and Septic Shock: A Scoping Review.

Li H, Markal A, Balch JA, Loftus TJ, Efron PA, Ozrazgat-Baslanti T, Bihorac A

Crit Care Explor, 2022 Apr, 4(4): e0672

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24. Gait subgroups among older adults with chronic pain differ in cerebellum and basal ganglia gray matter volumes.

Lipat AL, Clark DJ, Hass CJ, Cruz-Almeida Y

Exp Gerontol, 2022 Jun 15, 163: 111773

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25. Decreased cognitive function is associated with impaired spatiotemporal gait performance in community dwelling older adults with chronic musculoskeletal pain.

Lipat AL, Peterson JA, Clark DJ, Cruz-Almeida Y

Brain Cogn, 2022 Jun, 159: 105862

<https://doi.org/10.1016/j.bandc.2022.105862> | PMID: 35358922

Citations: | AltScore: NA

26. Aligning Patient Acuity With Resource Intensity After Major Surgery: A Scoping Review.

Loftus TJ, Balch JA, Ruppert MM, Tighe PJ, Hogan WR, Rashidi P, Upchurch GR Jr, Bihorac A

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Citations: | AltScore: 2.5

27. Interventions for Informal Caregivers of Stroke Survivors: Is There Racial and Ethnic Representation in Stroke Caregiver Studies?

Lopez J, Stacciarini JM, Scarton L, Uphold CR

Rehabil Nurs, 2022 Jan-Feb 01, 47(1): 3-11

<https://doi.org/10.1097/RNJ.0000000000000315> | PMID: 33560779

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Madushani RWMA, Patel V, Loftus T, Ren Y, Li HJ, Velez L, Wu Q, Adhikari L, Efron P, Segal M, Ozrazgat-Baslanti T, Rashidi P, Bihorac A, Sepsis and Critical Illness Research Center Investigators.

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<https://doi.org/10.1016/j.jss.2022.04.052> | PMID: 35569215

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Montesino-Goicolea S, Valdes-Hernandez PA, Cruz-Almeida Y

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Nair VD, Vasoya M, Nair V, Smith GR, Pincas H, Ge Y, Douglas CM, Esser KA, Sealton SC
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Citations: | AltScore: 1.5

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Nmezi NA, Turkson-Ocran RA, Tucker CM, Commodore-Mensah Y

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Citations: | AltScore: NA

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O'Neal LJ, Perri MG, Befort C, Janicke DM, Shankar MN, Bauman V, Daniels MJ, Dhara K, Ross KM

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Patel M, Johnson AJ, Booker SQ, Bartley EJ, Palit S, Powell-Roach K, Terry EL, Fullwood D, DeMonte L, Mickle AM, Sibille KT

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Citations: | AltScore: NA

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Peterson JA, Meng L, Rani A, Sinha P, Johnson AJ, Huo Z, Foster TC, Fillingim RB, Cruz-Almeida Y

Exp Gerontol, 2022 May 29, 166: 111861

<https://doi.org/10.1016/j.exger.2022.111861> | PMID: 35640781

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Picca A, Guerra F, Calvani R, Romano R, Coelho-Junior HJ, Bucci C, Leeuwenburgh C, Marzetti E

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[pii: S1084-9521\(22\)00095-7. https://doi.org/10.1016/j.semcdb.2022.03.023](https://doi.org/10.1016/j.semcdb.2022.03.023) | PMID: 35367122

Citations: 1 | AltScore: 7.6

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Powell-Roach KL, Yao Y, Wallace MR, Chamala S, Cruz-Almeida Y, Jhun E, Molokie RE, Wang ZJ, Wilkie DJ

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Rani A, Barter J, Kumar A, Stortz JA, Hollen M, Nacionales D, Moldawer LL, Efron PA, Foster TC

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39. **Weight Loss Strategies.**

Roberts SB, Anton S, Dao MC

Handb Exp Pharmacol, 2022, 274: 331-348

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Citations: | AltScore: NA

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Ross KM, Carpenter CA, Arroyo KM, Shankar MN, Yi F, Qiu P, Anthony L, Ruiz J, Perri MG

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Ryan TE, Kim K, Scali ST, Berceli SA, Thome T, Salyers ZR, O'Malley KA, Green TD, Karnekar R, Fisher-Wellman KH, Yamaguchi DJ, McClung JM

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Citations: 1 | AltScore: 4

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Saini SK, Singh A, Saini M, Gonzalez-Freire M, Leeuwenburgh C, Anton SD

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43. **Vulnerable Dispositional Traits and Chronic Pain: Predisposing but not**

Predetermining.

Sambuco N, Mickle AM, Garvan C, Cardoso J, Johnson AJ, Kusko DA, Addison A, Glover TL, Staud R, Redden D, Goodin B, Fillingim RB, Sibille KT

J Pain, 2022 Apr, 23(4): 693-705

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Sanders AE, Weatherspoon ED, Ehrmann BM, Soma PS, Shaikh SR, Preisser JS, Ohrbach R, Fillingim RB, Slade GD

J Pain, 2022 Jun 10

pii: S1526-5900(22)00335-2. <https://doi.org/10.1016/j.jpain.2022.05.008> | PMID: 35697285

Citations: | AltScore: 0.25

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Schroder EA, Burgess DE, Johnson SR, Ono M, Seward T, Elayi CS, Esser KA, Delisle BP

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Tanner JJ, Cardoso J, Terry EL, Booker SQ, Glover TL, Garvan C, Deshpande H, Deutsch G, Lai S, Staud R, Addison A, Redden D, Goodin BR, Price CC, Fillingim RB, Sibille KT

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Citations: 2 | AltScore: 4

49. Associations between pain catastrophizing and resting-state functional brain connectivity: Ethnic/race group differences in persons with chronic knee pain.

Terry EL, Tanner JJ, Cardoso JS, Sibille KT, Lai S, Deshpande H, Deutsch G, Price CC, Staud R, Goodin BR, Redden DT, Fillingim RB

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Citations: | AltScore: 1.5

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Vouri SM, Morris EJ, Usmani SA, Reise R, Jiang X, Pepine CJ, Manini TM, Malone DC,

Winterstein AG

Pharmacoepidemiol Drug Saf, 2022 Jan, 31(1): 72-81

<https://doi.org/10.1002/pds.5362> | PMID: 34553438 | PMCID: PMC8688319

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Wade FE, Kellaher GK, Pesquera S, Baudendistel ST, Roy A, Clark DJ, Seidler RD, Ferris DP, Manini TM, Hass CJ

J Biomech, 2022 Jun, 138: 111130

<https://doi.org/10.1016/j.jbiomech.2022.111130> | PMID: 35569430 | PMCID: PMC9284670

Citations: | AltScore: NA

52. **Gestational weight change and childhood body composition trajectories from pregnancy to early adolescence.**

Widen EM, Burns N, Daniels M, Backlund G, Rickman R, Foster S, Nichols AR, Hoepner LA, Kinsey EW, Ramirez-Carvey J, Hassoun A, Perera FP, Bukowski R, Rundle AG

Obesity (Silver Spring), 2022 Mar, 30(3): 707-717

<https://doi.org/10.1002/oby.23367> | PMID: 35137558 | PMCID: PMC8957403

Citations: | AltScore: 255.3

53. **Associations between Vitamin D, Omega 6:Omega 3 Ratio, and Biomarkers of Aging in Individuals Living with and without Chronic Pain.**

Wijayabahu AT, Mickle AM, Mai V, Garvan C, Glover TL, Cook RL, Zhao J, Baum MK, Fillingim RB, Sibille KT

Nutrients, 2022 Jan 9, 14(2):

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Citations: | AltScore: 1.25

54. **Experimental Pain Phenotype Profiles in Community-dwelling Older Adults.**

Wilson AT, Johnson AJ, Laffitte Nodarse C, Hoyos L, Lysne P, Peraza JA, Montesino-Goicolea S, Valdes-Hernandez PA, Somerville J, Bialosky JE, Cruz-Almeida Y
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<https://doi.org/10.1097/AJP.0000000000001048> | PMID: 35656805 | PMCID: PMC9202441

Citations: | AltScore: 0.5

55. **Autonomic Nervous System Dysregulation and Osteoarthritis Pain: Mechanisms, Measurement, and Future Outlook.**

Yeater TD, Cruz CJ, Cruz-Almeida Y, Allen KD

Curr Rheumatol Rep, 2022 Jun, 24(6): 175-183

<https://doi.org/10.1007/s11926-022-01071-9> | PMID: 35420372 | PMCID: PMC9189055

Citations: | AltScore: 52.75

56. **Operationally defining cognitive reserve genes.**

Yegla B, Foster TC

Neurobiol Aging, 2022 Feb, 110: 96-105

<https://doi.org/10.1016/j.neurobiolaging.2021.08.015> | PMID: 34565615

Citations: 2 | AltScore: NA

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Zhang D, Leeuwenburgh C, Zhou D, Gong Y, Pahor M, Licht JD, Braithwaite D
JAMA Netw Open, 2022 Jun 1, 5(6): e2218183

<https://doi.org/10.1001/jamanetworkopen.2022.18183> | PMID: 35731518 | PMCID: PMC9218849

Citations: | AltScore: 13.5

58. Frailty and risk of mortality in older cancer survivors and adults without a cancer history: Evidence from the National Health and Nutrition Examination Survey, 1999-2014.

Zhang D, Mobley EM, Manini TM, Leeuwenburgh C, Anton SD, Washington CJ, Zhou D, Parker AS, Okunieff PG, Bian J, Guo Y, Pahor M, Hiatt RA, Braithwaite D
Cancer, 2022 Aug 1, 128(15): 2978-2987

<https://doi.org/10.1002/cncr.34258> | PMID: 35608563

Citations: | AltScore: 12.85

2021

1. Application of social cognitive theory in weight management: Time for a biological component?

Anton S, Das SK, McLaren C, Roberts SB
Obesity (Silver Spring), 2021 Dec, 29(12): 1982-1986

<https://doi.org/10.1002/oby.23257> | PMID: 34705335 | PMCID: PMC8612961

Citations: | AltScore: 0.5

2. The effects of intermittent fasting regimens in middle-age and older adults: Current state of evidence.

Anton S, Ezzati A, Witt D, McLaren C, Vial P
Exp Gerontol, 2021 Dec, 156: 111617

<https://doi.org/10.1016/j.exger.2021.111617> | PMID: 34728336

Citations: 1 | AltScore: 5.9

3. Machine Learning Applications in Solid Organ Transplantation and Related Complications.

Balch JA, Delitto D, Tighe PJ, Zarrinpar A, Efron PA, Rashidi P, Upchurch GR Jr, Bihorac A, Loftus TJ

Front Immunol, 2021, 12: 739728

<https://doi.org/10.3389/fimmu.2021.739728> | PMID: 34603324 | PMCID: PMC8481939

Citations: 1 | AltScore: 12.35

4. Adulthood systemic inflammation accelerates the trajectory of age-related cognitive decline.

Barter J, Kumar A, Bean L, Ciesla M, Foster TC
Aging (Albany NY), 2021 Sep 29, 13(18): 22092-22108

<https://doi.org/10.18632/aging.203588> | PMID: 34587117 | PMCID: PMC8507275

Citations: 3 | AltScore: NA

5. Elevated IL-6 and CRP Levels Are Associated With Incident Self-Reported Major Mobility Disability: A Pooled Analysis of Older Adults With Slow Gait Speed.

Beavers DP, Kritchevsky SB, Gill TM, Ambrosius WT, Anton SD, Fielding RA, King AC, Rejeski WJ, Lovato L, McDermott MM, Newman AB, Pahor M, Walkup MP, Tracy RP, Manini TM

J Gerontol A Biol Sci Med Sci, 2021 Nov 15, 76(12): 2293-2299

<https://doi.org/10.1093/gerona/glab093> | PMID: 33822946 | PMCID: PMC8598983

Citations: | AltScore: 4.5

6. Study Protocol Modeling Evoked Pain in Older African Americans With Knee Osteoarthritis.

Booker SQ, Starkweather A, Manini TM, Staud R, Fillingim RB

Nurs Res, 2021 Set/Oct 01, 70(5): 391-398

<https://doi.org/10.1097/NNR.0000000000000520> | PMID: 33951704 | PMCID: PMC8405558

Citations: | AltScore: 1.5

7. **Cannabidiol as prophylaxis for SARS-CoV-2 and COVID-19? Unfounded claims versus potential risks of medications during the pandemic.**

Brown JD

Res Social Adm Pharm, 2021 Jan, 17(1): 2053

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Citations: 9 | AltScore: 15

8. **Three-Year, Postintervention, Follow-up Comparison of Health Care Resource Utilization and Costs in the Lifestyle Interventions and Independence for Elders (LIFE) Study.**

Brown JD, Wang CY, Groessl EJ, Pahor M, Manini TM

J Gerontol A Biol Sci Med Sci, 2021 Jan 18, 76(2): 272-276

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Citations: 1 | AltScore: 3.35

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Budamagunta V, Foster TC, Zhou D

Aging (Albany NY), 2021 Aug 12, 13(15): 19920-19941

<https://doi.org/10.18632/aging.203405> | PMID: 34382946 | PMCID: PMC8386533

Citations: 6 | AltScore: 26.458

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Budamagunta V, Manohar-Sindhu S, Yang Y, He Y, Traktuev DO, Foster TC, Zhou D

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Citations: 6 | AltScore: 31.358

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Cardoso J, Apagueno B, Lysne P, Hoyos L, Porges E, Riley JL, Fillingim RB, Woods AJ, Cohen R, Cruz-Almeida Y

Pain Med, 2021 Aug 6, 22(8): 1776-1783

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Citations: 3 | AltScore: NA

12. **Ratings of Perceived Exertion During Walking: Predicting Major Mobility Disability and Effect of Structured Physical Activity in Mobility-Limited Older Adults.**

Cenko E, Chen H, Gill TM, Glynn NW, Henderson RM, King AC, Pahor M, Qiu P, Rego A, Reid KF, Tudor-Locke C, Valiani V, You L, Manini TM

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Citations: | AltScore: 3.25

13. **The impact of sarcopenia and acute muscle mass loss on long-term outcomes in critically ill patients with intra-abdominal sepsis.**

Cox MC, Booth M, Ghita G, Wang Z, Gardner A, Hawkins RB, Darden DB, Leeuwenburgh C, Moldawer LL, Moore FA, Efron PA, Anton S, Brakenridge SC

J Cachexia Sarcopenia Muscle, 2021 Jun 30, 12(5): 1203-1213

<https://doi.org/10.1002/jcsm.12752> | PMID: 34196134 | PMCID: PMC8517344

Citations: 9 | AltScore: 17.2

14. **Pain differences in neurite orientation dispersion and density imaging measures among community-dwelling older adults.**

Cruz-Almeida Y, Coombes S, Febo M

Exp Gerontol, 2021 Oct 15, 154: 111520

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15. **Preliminary investigation of interactive associations of sleep and pain with cognition in sedentary middle-aged and older adults.**

Curtis AF, Dzierzewski JM, Buman MP, Giacobbi PR, Roberts BL, Aiken-Morgan AT, Marsiske M, McCrae CS

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Citations: 1 | AltScore: 6.3

16. **A Novel Single Cell RNA-seq Analysis of Non-Myeloid Circulating Cells in Late Sepsis.**

Darden DB, Dong X, Brusko MA, Kelly L, Fenner B, Rincon JC, Dirain ML, Ungaro R, Nacionales DC, Gauthier M, Kladden M, Brusko TM, Bihorac A, Moore FA, Loftus T, Bacher R, Moldawer LL, Mohr AM, Efron PA

Front Immunol, 2021, 12: 696536

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Citations: | AltScore: 2.5

17. **The Effect of Sensor Placement and Number on Physical Activity Recognition and Energy Expenditure Estimation in Older Adults: Validation Study.**

Davoudi A, Mardini MT, Nelson D, Albinali F, Ranka S, Rashidi P, Manini TM

JMIR Mhealth Uhealth, 2021 May 3, 9(5): e23681

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Citations: 4 | AltScore: NA

18. **Functional connectivity of key resting state networks and objectively measured physical activity in older adults with joint pain: A pilot study.**

Dion C, Tanner JJ, Crowley SJ, Wiggins ME, Mareci T, Ding M, Price CC, Manini TM

Exp Gerontol, 2021 Oct 1, 153: 111470

<https://doi.org/10.1016/j.exger.2021.111470> | PMID: 34246732

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Erickson ML, Esser KA, Kraus WE, Buford TW, Redman LM

Exerc Sport Sci Rev, 2021 Jan, 49(1): 35-41

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Citations: 4 | AltScore: 69.1

20. **Age and intranasal oxytocin effects on trust-related decisions after breach of trust: Behavioral and brain evidence.**

Frazier I, Lin T, Liu P, Skarsten S, Feifel D, Ebner NC

Psychol Aging, 2021 Feb, 36(1): 10-21

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Citations: 3 | AltScore: 1

21. **Elevated lymphotoxin-a (TNF?) is associated with intervertebral disc degeneration.**

Guo Z, Qiu C, Mecca C, Zhang Y, Bian J, Wang Y, Wu X, Wang T, Su W, Li X, Zhang W, Chen B, Xiang H

BMC Musculoskelet Disord, 2021 Jan 13, 22(1): 77

<https://doi.org/10.1186/s12891-020-03934-7> | PMID: 33441130 | PMCID: PMC7807514

Citations: 1 | AltScore: NA

22. **Resveratrol and exercise combined to treat functional limitations in late life: A pilot randomized controlled trial.**

Harper SA, Bassler JR, Peramsetty S, Yang Y, Roberts LM, Drummer D, Mankowski RT, Leeuwenburgh C, Ricart K, Patel RP, Bamman MM, Anton SD, Jaeger BC, Buford TW
Exp Gerontol, 2021 Jan, 143: 111111

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Hu H, Zheng Y, Wen X, Smith SS, Nizomov J, Fische J, Hogan WR, Shenkman EA, Bian J
Sci Total Environ, 2021 May 10, 768: 144832

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Citations: 7 | AltScore: 3.75

24. **Vascular dysfunction as a potential culprit of sarcopenia.**

Jeon YK, Shin MJ, Saini SK, Custodero C, Aggarwal M, Anton SD, Leeuwenburgh C, Mankowski RT

Exp Gerontol, 2021 Mar, 145: 111220

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Citations: 7 | AltScore: 12.15

25. **Transcriptomic Changes Within Human Bone Marrow After Severe Trauma.**

Kelly LS, Apple CG, Darden DB, Kannan KB, Pons EE, Fenner BP, Parvataneni HK, Hagen JE, Brakenridge SC, Efron PA, Mohr AM

Shock, 2021 Jun 24, 57(1): 24-30

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Citations: 1 | AltScore: 2.1

26. **Multi-ethnic GWAS and meta-analysis of sleep quality identify MPP6 as a novel gene that functions in sleep center neurons.**

Khoury S, Wang QP, Parisien M, Gris P, Bortsov AV, Linnstaedt SD, McLean SA, Tungate AS, Sofer T, Lee J, Louie T, Redline S, Kaunisto MA, Kalso EA, Munter HM, Nackley AG, Slade GD, Smith SB, Zaykin DV, Fillingim RB, Ohrbach R, Greenspan JD, Maixner W, Neely GG, Diatchenko L

Sleep, 2021 Mar 12, 44(3):

[pii: zsaa211. https://doi.org/10.1093/sleep/zsaa211](https://doi.org/10.1093/sleep/zsaa211) | PMID: 33034629 | PMCID:

PMC7953222

Citations: | AltScore: 4.75

27. **Older adults demonstrate biomarker evidence of the persistent inflammation, immunosuppression and catabolism syndrome (PICS) after sepsis.**

Mankowski RT, Anton SD, Ghita GL, Brumback B, Darden DB, Bihorac A, Moldawer LL, Efron PA, Brakenridge SC, Moore FA

J Gerontol A Biol Sci Med Sci, 2021 Mar 15, 77(1): 188-196

[pii: glab080. https://doi.org/10.1093/gerona/glab080](https://doi.org/10.1093/gerona/glab080) | PMID: 33721883 | PMCID:

PMC8751807

Citations: 4 | AltScore: 5.45

28. **Age Differences in Estimating Physical Activity by Wrist Accelerometry Using Machine Learning.**

Mardini MT, Bai C, Wanigatunga AA, Saldana S, Casanova R, Manini TM

Sensors (Basel), 2021 May 12, 21(10):

[pii: 3352. https://doi.org/10.3390/s21103352](https://doi.org/10.3390/s21103352) | PMID: 34065906 | PMCID: PMC8150764

Citations: 1 | AltScore: NA

29. **The Temporal Relationship Between Ecological Pain and Life-Space Mobility in Older**

Adults With Knee Osteoarthritis: A Smartwatch-Based Demonstration Study.

Mardini MT, Nerella S, Kheirkhahan M, Ranka S, Fillingim RB, Hu Y, Corbett DB, Cenko E, Weber E, Rashidi P, Manini TM

JMIR Mhealth Uhealth, 2021 Jan 13, 9(1): e19609

<https://doi.org/10.2196/19609> | PMID: 33439135 | PMCID: PMC7840291

Citations: 5 | AltScore: NA

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McQuail JA, Dunn AR, Stern Y, Barnes CA, Kempermann G, Rapp PR, Kaczorowski CC, Foster TC

Front Aging Neurosci, 2020, 12: 607685

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Citations: 8 | AltScore: 15.4

31. Sesquiterpene Alcohol Cedrol Chemosensitizes Human Cancer Cells and Suppresses Cell Proliferation by Destabilizing Plasma Membrane Lipid Rafts.

Mishra SK, Bae YS, Lee YM, Kim JS, Oh SH, Kim HM

Front Cell Dev Biol, 2020, 8: 571676

<https://doi.org/10.3389/fcell.2020.571676> | PMID: 33585438 | PMCID: PMC7874189

Citations: 2 | AltScore: 0.5

32. Differences in Health-Related Quality of Life Among Adults with a Potential Dihydropyridine Calcium Channel Blocker-Loop Diuretic Prescribing Cascade.

Morris EJ, Brown JD, Manini TM, Vouri SM

Drugs Aging, 2021 Jun 7, 38(7): 625-632

<https://doi.org/10.1007/s40266-021-00868-0> | PMID: 34095980

Citations: | AltScore: 3.85

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Ronan EA, Xiao R, Xu XZS

Cell Calcium, 2021 Sep, 98: 102446

<https://doi.org/10.1016/j.ceca.2021.102446> | PMID: 34303264 | PMCID: PMC8419106

Citations: | AltScore: 6.6

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Rouzaud Laborde C, Cenko E, Mardini MT, Nerella S, Kheirkhahan M, Ranka S, Fillingim RB, Corbett DB, Weber E, Rashidi P, Manini T

JMIR Aging, 2021 Jul 14, 4(3): e24553

<https://doi.org/10.2196/24553> | PMID: 34259638 | PMCID: PMC8319786

Citations: 3 | AltScore: 3.1

35. Safety and tolerability of chronic intranasal oxytocin in older men: results from a randomized controlled trial.

Rung JM, Horta M, Tammi EM, Perez E, Ojeda MC, Lin T, Harris G, Somerville J, Salmeron D, Beltz SE, Sandesara B, Feifel D, Ebner NC

Psychopharmacology (Berl), 2021 May 12, 238(9): 2405-2418

<https://doi.org/10.1007/s00213-021-05862-3> | PMID: 33982141 | PMCID: PMC8115997

Citations: 2 | AltScore: 7.35

36. Exercise mitigates sleep-loss-induced changes in glucose tolerance, mitochondrial function, sarcoplasmic protein synthesis, and diurnal rhythms.

Saner NJ, Lee MJ, Kuang J, Pitchford NW, Roach GD, Garnham A, Genders AJ, Stokes T,

Schroder EA, Huo Z, Esser KA, Phillips SM, Bishop DJ, Bartlett JD

Mol Metab, 2021 Jan, 43: 101110

<https://doi.org/10.1016/j.molmet.2020.101110> | PMID: 33137489 | PMCID: PMC7704425

Citations: 5 | AltScore: 293.35

37. **Safety signals for QT prolongation or Torsades de Pointes associated with azithromycin with or without chloroquine or hydroxychloroquine.**

Sarayani A, Cicali B, Henriksen CH, Brown JD

Res Social Adm Pharm, 2021 Feb, 17(2): 483-486

<https://doi.org/10.1016/j.sapharm.2020.04.016> | PMID: 32327397 | PMCID: PMC7166303

Citations: 27 | AltScore: 32.3

38. **A novel role of the mitochondrial iron-sulfur cluster assembly protein ISCU-1/ISCU in longevity and stress response.**

Sheng Y, Yang G, Casey K, Curry S, Oliver M, Han SM, Leeuwenburgh C, Xiao R

Geroscience, 2021 Feb 1, 43(2): 691-707

<https://doi.org/10.1007/s11357-021-00327-z> | PMID: 33527323 | PMCID: PMC8110660

Citations: 3 | AltScore: 0.75

39. **Distinct temporal actions of different types of unfolded protein responses during aging.**

Sheng Y, Yang G, Markovich Z, Han SM, Xiao R

J Cell Physiol, 2021 Jul, 236(7): 5069-5079

<https://doi.org/10.1002/jcp.30215> | PMID: 33345326 | PMCID: PMC8026671

Citations: 1 | AltScore: 6.25

40. **The Relationship Between Plasma BDNF and Pain in Older Adults With Knee Osteoarthritis.**

Sorkpor SK, Galle K, Teixeira AL, Colpo GD, Ahn B, Jackson N, Miao H, Ahn H

Biol Res Nurs, 2021 Oct, 23(4): 629-636

<https://doi.org/10.1177/10998004211012479> | PMID: 33910384 | PMCID: PMC8726424

Citations: 2 | AltScore: NA

41. **Changes in Brain-derived Neurotrophic Factor From Active and Sham Transcranial Direct Current Stimulation in Older Adults With Knee Osteoarthritis.**

Suchting R, Teixeira AL, Ahn B, Colpo GD, Park J, Ahn H

Clin J Pain, 2021 Dec 1, 37(12): 898-903

<https://doi.org/10.1097/AJP.0000000000000987> | PMID: 34757341 | PMCID: PMC8589111

Citations: | AltScore: NA

42. **An evaluation of co-use of chloroquine or hydroxychloroquine plus azithromycin on cardiac outcomes: A pharmacoepidemiological study to inform use during the COVID19 pandemic.**

Vouri SM, Thai TN, Winterstein AG

Res Social Adm Pharm, 2021 Jan, 17(1): 2012-2017

<https://doi.org/10.1016/j.sapharm.2020.04.031> | PMID: 32409150 | PMCID: PMC7190482

Citations: 9 | AltScore: 112.8

43. **Function of Mitogen-Activated Protein Kinases in Hepatic Inflammation.**

Westenberger G, Sellers J, Fernando S, Junkins S, Han SM, Min K, Lawan A

J Cell Signal, 2021, 2(3): 172-180

PMID: 34557866 | PMCID: PMC8457364

Citations: | AltScore: NA

44. **Temperature Sensation: From Molecular Thermosensors to Neural Circuits and Coding Principles.**

Xiao R, Xu XZS

Annu Rev Physiol, 2021 Feb 10, 83: 205-230

<https://doi.org/10.1146/annurev-physiol-031220-095215> | PMID: 33085927 | PMCID: PMC7932759

Citations: 2 | AltScore: 3.75

45. **Partial microglial depletion is associated with impaired hippocampal synaptic and cognitive function in young and aged rats.**

Yegla B, Boles J, Kumar A, Foster TC

Glia, 2021 Jun, 69(6): 1494-1514

<https://doi.org/10.1002/glia.23975> | PMID: 33586813 | PMCID: PMC8278544

Citations: 9 | AltScore: 1

46. **Iron homeostasis and organismal aging.**

Zeidan RS, Han SM, Leeuwenburgh C, Xiao R

Ageing Res Rev, 2021 Dec, 72: 101510

<https://doi.org/10.1016/j.arr.2021.101510> | PMID: 34767974 | PMCID: PMC8620744

Citations: 2 | AltScore: 8.85

EXTERNAL ADVISORY BOARD MEMBERS

George Kuchel, MD
University of Connecticut
Serving since 2022 (0 years)

Joseph Takahashi, PhD
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Laura Niedernhofer, MD, PhD
University of Minnesota
Serving since 2022 (0 years)

Monty Montano, PhD
Harvard University
Serving since 2022 (0 years)

RECOGNITION AND AWARDS (2021-2022)

Carolyn Tucker, PhD (2021)

- Member, Academy of Science, Engineering and Medicine of Florida (ASEMFL), 2021

Marco Pahor, MD (2021)

- Fellow, Gerontological Society of America, 2021
- Editorial Board, Journal of Gerontology: Medical Sciences, 2004-present
- Consulting Editor, Aging Clinical and Experimental Research, 2000-present
- Editorial Board, Journal of Nutrition, Health and Aging, 2002-present
- Editorial Board, Journal of Frailty and Aging, 2016-present

MINORITY RESEARCH

General Brief Description of Minority Activities:

Steve Anton, PhD

- Co-PI R33 AG056540: “The University of Florida Jacksonville Aging Studies Center (JAXASCENT)
- Mentor for minority junior faculty member, Latoya O’Neal, Ph.D. (2017)

Yenisel Cruz-Almeida, MSPH, PhD

- Pedro Valdes Hernandez, PhD- T32 Mentor
- Soamy Montesino Goicolea, MD- Mentor
- Carolina Maciel, MD- Junior Pepper Scholar Mentor
- Desiree Lussier, PhD- Mentor
- Keesha Roach, BSN, PhD- T32 Mentor
- Sophia McCray- Honors Thesis Mentor
- Vanessa Davila- Honors Thesis Mentor
- Lorraine Hoyos- Medical Student, UCF, Research Mentor

Roger Fillingim, PhD

P30AG059297: “University of Florida Resource Center for Minority Aging Research

Todd Manini, PhD, Mentor

- Dottington Fullwood, PhD

Marco Pahor, MD

- Co-PI R33 AG056540: “The University of Florida Jacksonville Aging Studies Center (JAXASCENT)

Carolyn Tucker, PhD

- Human Foundation: “Health-Smart, Holistic Health and Wellness Centers Program to Promote Social Connection and Food Security among Minority, Underserved, and/or Low- Income Jacksonville Seniors”
- PCORI: “Culturally Sensitive Primary Care Clinic-Based Interventions”

Minority Trainee(s):

- M. Dottington Fullwood, PhD, Postdoctoral Fellow

Dr. Fullwood is a rising scientist who is enthusiastic to expand his research focus to include aging, specifically understanding the connection between multidimensional impacts of chronic low back pain and mobility decline using mobile health technology in older minority adults. His research plan to assess the extent to assessment of behavioral interventions delivered to underserved older adult populations explains low back pain and mobility decline that leads to better ways to maintain and restore physical function to older adults. These objectives are directly aligned with the objective of the our JAX-ASCENT, which will provide excellent resources for him to pursue and achieve his research and training goals. Most importantly, he will work closely with JAX-ASCENT investigators who are invested in promoting an interdisciplinary academic environment by building lasting collaborations with clinical, behavioral and epidemiology scientists. His primary mentor—Dr.

Anton—exemplifies this characteristic through his many collaborative research initiatives (see Biosketch). Moreover, Dr. Fullwood has assembled a mentoring team that contains experts in behavioral interventions to promote healthy aging, mobile health technology and multidimensional aspects of pain. His advisement from each mentor will vary in activities ranging from one-on-one individual meetings to directed readings and group discussion with his dream team of expert mentors. Dr. Fullwood will also participate in the many activities offered through the Claude D. Pepper Older Americans Independence Center (OAIC: P30AG028740) and Research Career Development Core (RCDC). He will follow specific training plans outlined by the RCDC co-leaders that will provide him clear benchmarks for meeting his career and research goals. He will attend weekly seminars focused on pain and aging and round table meetings with other more senior scholars.

- Pedro Valdes Hernandez , PhD, Postdoctoral Fellow

Over the 22-months of the supplement, the research and career development plan for Pedro is designed to promote his transition to independence as a researcher at the intersection of the fields of pain and aging. Results from a recent paper submitted by Dr. Valdes Hernandez revealed that chronic musculoskeletal pain in older adults may negatively impact specific cerebral circuits related to memory, language, motor planning, mobility and physical function (see Figure 1). These findings fueled Pedro's avidity to delve into the fields of pain and aging, specifically investigating the mechanisms mediating the impact of pain on mobility and physical function in older adults. This critical gap in knowledge aligns quite well with the scientific theme of the UF OAIC. Pedro came to UF 18 months ago with no previous background in pain or aging research. His preliminary research training experiences have provided a foundation of knowledge and skills in these areas, enabling him to develop and implement innovative mechanism-based research protocols investigating pain in older adults. This Administrative Supplement would provide the opportunity for Pedro to pursue advanced training in pain, aging and mobility research in a more structured manner, allowing him the time to develop research interests and expertise, expediting his transition to research independence. His mid-term goal is to submit a K01 award by February 2021. His long-term goals are to: 1) excel in an academic institution as an independent translational neuroscientist with expertise in the fields of pain and aging; and 2) to contribute to the biomedical research community through scholarship and education with the ultimate goal of improving the life of older populations. The proposed research and career development plan is designed to help him achieve these career goals. Specifically, we propose a combination of experiential,

training, pain and aging dedicated research and grant-writing activities. This will provide Pedro with hands-on research experience and increased knowledge in aging and pain. As a result of this training program, Pedro will be prepared to continue pain and geriatric research as a faculty member to greatly enhance his ability to pursue his long-term goal of an independent academic research career.

Minority Grant(s):

UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO

Claude D. Pepper Older Americans Independence Center

Nicolas Musi, M.D. Principal Investigator	210 562 6140	Musi@uthscsa.edu
Sara Espinoza, M.D. Co-PI	210 617 5197	espinozas2@uthscsa.edu
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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: Nicolas Musi, MD musi@uthscsa.edu

Leader 2: Sara Espinoza, MD espinozas2@uthscsa.edu

Leader 3: 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

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: Robert A. Clark, MD clarkra@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: Sara Espinoza, MD, MS espinozas2@uthscsa.edu

Leader 2: Nick Musi, MD musi@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
<p>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.</p>	2021-2023 / 34 (total) 12 (1st/Sr)
<p>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></p>	2021-2023 / 32 (total) 10 (1st/Sr)
<p>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></p>	2021-2023 / 11 (total) 2 (1st/Sr)
<p>Gustavo Almeida Assistant Professor / UT Health San Antonio <u>Effect of prehabilitation blood-flow restriction training on muscle function in older adults with knee osteoarthritis awaiting total knee replacement: A Pilot Randomized Controlled Trial</u> The proposed project aims to evaluate the effect of a prehabilitation program (before surgery) using blood-flow restriction training (BFRT) on quadriceps muscle function in older adults (60+) with knee osteoarthritis (KOA) awaiting total knee replacement (TKR). Results from this study will elucidate how tolerable and efficacious prehabilitation BFRT is and early on after TKR as well. We predict that BFRT will be highly acceptable and feasible before and after TKR. BFRT will produce significant positive changes in muscle function, joint inflammation, physical function and physical activity. This pilot study will allow better understanding of this novel intervention in older adults with KOA awaiting TKR and will provide pivotal preliminary support for a large-scale randomized trial.</p> <ul style="list-style-type: none"> • School of Health Professions Pilot Seed Grant Program – UT Health San Antonio, Role: PI • Foundation for Physical Therapy's Center of Excellence in Health Services Research, Role: Co-Investigator 	2020-2022 / 42 (total) 8 (1st/Sr)
<p>Christopher Shannon Assistant Professor / Department of Medicine, UT Health San Antonio <u>Effects of SGLT2 Inhibition on Liver Fat and Plasma Lipidome in Older Adults</u> Dr. Shannon will study hepatic metabolism in older adults with insulin resistance. Pilot trials at the San Antonio Pepper Center are currently exploring whether the pleiotropic effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors, a glucose-lowering class of drugs for the treatment of type 2 diabetes, can be repurposed to improve biomarkers of aging in humans. As part of these efforts, Dr. Shannon's project will evaluate the impact of SGLT2 inhibition on hepatic and plasma lipids in an aging population at high risk of developing metabolic liver disease.</p>	2020-2022 / 9 (total) 5 (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)

PILOT/EXPLORATORY PROJECTS (6 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 \leq 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 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- γ co-activator-1 α (PGC-1 α), 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 α , 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.

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 (<5 yrs.) and older (5-15 yrs.) marmosets previously treated with rapamycin (or placebo) for up to 3.5 years. RC3 will carry out the required statistical analyses. If positive, findings from this study will lay the foundation for a clinical trial in older adults with heart failure with preserved ejection fraction, a growing population with few treatment options.

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/senomorphing 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/senomorphing 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 early phase 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 (8 Projects Listed)**1. Project Title: ALZHEIMER'S DISEASE-ASSOCIATED TAU TOXICITY INDUCES CELLULAR SENESCENCE IN THE BRAIN.**

Leader(s): ORR, MIRANDA ETHEL
SOUTH TEXAS VETERANS HEALTH CARE SYSTEM
VA IK2BX003804 / (2017 - 2022)

Core(s):

Tau protein aggregation is the most common pathology among neurodegenerative diseases, which collectively are termed tauopathies. These diseases encompass over 15 distinct disorders that greatly affect Veterans, including Alzheimer's disease (AD) and traumatic brain injury. As the most common cause of dementia in the United States, AD affects more than 5 million Americans, including 600,000 military personnel and costs \$200 billion per year. Effective treatment strategies remain elusive. We are applying fresh perspectives from different disciplines and are investigating cellular senescence as a novel cell stress response involved in tau-associated neurodegeneration. Large insoluble tau-containing aggregates, neurofibrillary tangles (NFTs), are the closest histopathological correlate with neuron loss and cognitive decline in AD. However, because NFT-containing neurons do not die, their role in neurodegeneration remains unclear. We suggest that NFTs may evoke toxicity through secondary, non-cell autonomous mechanisms. Specifically, we propose that NFT-containing cells may contribute to tissue destruction by secreting toxic soluble factors in a mechanism similar to cellular senescence. Cellular senescence is generally characterized by a permanent cell cycle arrest and alterations in gene expression, metabolic state, morphology, and cytokine secretion. In neurons, senescence has been used to describe age-associated changes that include swelling of the soma, loss of dendritic spines, and progressive choking of cytoplasmic space with abnormal material; phenotypes in good agreement with NFT-containing neurons. While there is no single unifying marker that defines the complex senescence stress response, robust phenotypes include elevated gene expression of tumor suppressor p16INK4a (p16) and inflammatory cytokines. Studies have illustrated that senescent cells contribute to tissue damage and functional decline with age. Recently, we found that transgenic mice with NFTs have a significant elevation in senescence markers in the brain, including p16. The increase in p16 was associated with an elevation in brain cytokines, Tnf α and Il1. Only mice with NFTs, but not age-matched controls with high levels of soluble tau, expressed senescence-associated factors. Collectively, these data suggest that pathogenic tau and cellular senescence are interconnected. The research goal is to elucidate whether tau-associated pathogenesis induces a senescence-like phenotype that reciprocally contributes to brain pathology and behavioral deficits in tau-associated neurodegenerative diseases. Ongoing studies with transgenic mice will focus on molecular mediators of cellular senescence in the brain, specific cell types involved and the mechanistic interplay among cellular senescence, tau pathology, neurodegeneration and cognitive decline. Through the activities proposed in this CDA-2, I will achieve my ultimate career goal: to become an independent investigator dedicated to the pursuit of understanding AD while improving the health and wellbeing of Veterans and their families. I have developed a comprehensive program, guided by an outstanding mentoring team. They represent leaders within the VA and in the research of AD, senescence and inflammation. Through the planned activities, I will acquire new technical skills to achieve my research goals and lay the foundation for my independent career. My mentoring team will advocate for my career development within the VA, including providing me opportunities for leadership and supporting my greater community outreach activities. The exceptional training opportunities at the South Texas Veterans Health Care System in San Antonio, and community involvement in Military City, USA, provide an ideal environment for my ambitions as a well-rounded scientist. By the completion of the CDA-2 I expect to be fully prepared to (1) lead an independent research program focused on AD; (2) have generated sufficient data to compete for Merit Review Award funding; (3) and joined the VA scientific workforce.

2. 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 ABSTRACT This Beeson Emerging Leaders in Aging Career Development Award (K76) seeks to equip Dr. Lisa Kilpela with the expertise and professional skill set needed to become a leading gerontological expert in disordered eating and 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 disorder pathology, which constitutes a group of complex psychiatric disorders characterized by dysregulated and abnormal 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 eating disorder symptoms are surprisingly prevalent in older women. Dr. Kilpela's preliminary research as a Pepper Center 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 women aged 60+ reporting at least weekly BE episodes. BE is closely linked to obesity and depression and, even independent of these comorbidities, is associated with metabolic dysfunction, sleep problems, disability, and poorer quality of life. Therefore, BE appears to represent a significant health problem for older women with greater 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 in younger 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 tailored for older women with BE and pilot implementation to determine its feasibility, and (3) integrate work completed in 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 an R01 application for a full-scale trial. Complementary to the proposed research, Dr. Kilpela will complete a program of career development to gain the scientific and professional development skills to transition to an independent investigator. This proposal is supported by a mentorship team of renowned scientists in aging research (Drs. Musi and Espinoza), women's health (Dr. LaCroix), and eating disorders (Dr. Keel), and advisors in geriatric medicine education (Dr. Sanchez-Reilly) and biostatistics (Dr. Gelfond). This team, along with resources available through the San Antonio Pepper Center and Barshop Institute for Longevity and Aging Studies, comprise an ideal environment for Dr. Kilpela to successfully reach her goal to promote healthy aging in older women by addressing disordered eating and nutrition pathology.

3. 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-Bykovskiy, 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-Bykovskiy is in an ideal environment to complete the proposed research and pursue advanced training relevant to her career goals. Dr. Gilmore-Bykovskiy'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-Bykovskiy to lead an independent research program in clinical AD research.

4. Project Title: METFORMIN FOR PREVENTING FRAILTY IN HIGH RISK OLDER ADULTS

Leader(s): ESPINOZA, SARA ELYSE
UNIVERSITY OF TEXAS HLTH SCI CTR SAN ANT
NIH R01AG052697 / (2017 - 2022)

Core(s):

ABSTRACT Frailty is a geriatric syndrome which leads to poor health outcomes in older adults, such as falls, disability, hospitalization, institutionalization, and death. Due to the dramatic growth in the U.S. aging population and the health care costs associated with frailty (estimated at more than \$18 billion per year), frailty is a major healthcare problem. There has been little research into potential pharmacologic interventions that would delay or reduce the incidence of frailty. Thus, the major goal of this study is to test metformin as a novel intervention for the prevention of frailty. We propose that diabetes/insulin resistance and inflammation are major contributors to frailty, and that the use of metformin to modulate diabetes/insulin resistance and inflammation will prevent and/or ameliorate the progression of frailty. The rationale for testing metformin for frailty prevention is based on the following: 1) Insulin resistance has been linked to the pathogenesis of frailty and our own research shows that diabetes is a significant predictor of frailty onset or worsening in community-dwelling older adults; 2) Several studies have shown that frail older subjects (compared with non-frail) are under a state of chronic low grade sterile inflammation, as evidenced by increased plasma concentration of inflammatory markers; 3) In addition to frailty, inflammation also plays a key role in the pathogenesis of insulin resistance; 4) Metformin has both insulin sensitizing and anti-inflammatory properties, and; 5) Our analyzed clinical administrative data from 2,415 adult veterans with diabetes shows that those who were taking metformin as monotherapy were at 34% reduced risk of becoming frail compared to patients taking sulfonylureas. We hypothesize that metformin will lead to reduced inflammation and insulin resistance present in older glucose-intolerant subjects and that these changes will consequently prevent the onset and/or progression of frailty in this sub-population of older adults. We propose to study glucose intolerant subjects, a population which encompasses approximately one-third of older adults, and is most likely to benefit from metformin. To our knowledge, this research will be the first to study a potential intervention targeted toward a central mechanism involved in the etiology of frailty. We will also assess potential molecular mechanisms (insulin signaling, AMPK signaling, etc.) as potential cellular defects in frailty that are alleviated by metformin. Because of the enormous costs associated with frailty (both personal and economic), a treatment that prevents or delays frailty, even in a sub-population of older adults, would have a major positive impact in our society.

5. Project Title: PRIMARY FIBROBLAST RESILIENCY AS A PREDICTOR OF HEALTH AND LIFESPAN IN MICE

Leader(s): SALMON, ADAM
UNIVERSITY OF TEXAS HLTH SCI CTR SAN ANT
NIH R01AG057431 / (2017 - 2022)

Core(s):

In response to RFA-AG-17-040, Short-term Measurements of Physical Resilience as a Predictor of Healthspan in Mice, we propose testing primary fibroblast resilience with a panel of different cellular insults as a means to predict individual mouse longevity and healthspan. As outlined by the funding announcement for this RFA, there is a need to develop these standardized tests for use among the aging community to accelerate research towards revealing mechanisms that underlie the physiological decline of aging. We previously have shown that primary fibroblasts isolated from the tail skin of mice likely retain characteristics of the in vivo environment of the mouse (or other species) from which they were established. For example, we showed in a series of studies that skin-derived primary fibroblasts isolated from long-lived mice with deficiencies in growth hormone/insulin-like growth factor 1 levels are resilient to multiple cytotoxic and metabolic insults. These differences persist even after numerous population doublings in culture using identical conditions as fibroblast lines from control mice. In addition, we have shown in this fibroblast model that resiliency to one form of insult predicts resiliency to multiple other forms of insult in an individual cell line. Our overall hypothesis is that cellular resiliency of skin-derived

primary fibroblasts represents the vitality of an individual in vivo and predicts both healthspan and longevity of individual mice. We have designed this study to test this hypothesis and meet the goals outlined by this RFA. In our first aim, we test whether fibroblast resiliency is predictive of individual longevity and healthspan in a normally aging group of genetically heterogeneous mice. Because of the unique fibroblast resiliency panel of tests we have outlined, we can test physical resiliency of mice with little to no effect on the overall health and longevity of the animals. That is, in an individual mouse we will measure fibroblast resilience (including repeated assessments throughout middle age) and longevity and use these data to develop a predictive model. In our second aim, we test the effect on fibroblast resiliency of interventions in mice known to alter longevity and/or healthspan. This will test whether this model can predict novel interventions that may alter these parameters within a population. Because we currently lack standardized research tools to probe resiliencies at the cellular level, this marker of resilience has the potential to be a highly important marker of healthspan and longevity in mouse studies.

6. 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 to attack by reactive oxygen species to result in lipid peroxidation. Lipid peroxidation is increased in AD brains and is believed to play a key role in driving neurodegeneration of AD. However, supplementation of lipid soluble antioxidants yields only mixed results in clinical trials. So the importance of lipid peroxidation in AD remains unproven. Glutathione peroxidase 4 (Gpx4) is a glutathione peroxidase that can suppress lipid peroxidation by directly reducing phospholipid hydroperoxides in membranes. Therefore, Gpx4 suppresses lipid peroxidation through a mechanism distinct from that of lipid antioxidants. Gpx4's role in reducing phospholipid hydroperoxides in 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 health and survival of neurons in adult animals, such as forebrain neurons that are severely afflicted in AD. In preliminary studies, we obtained data indicating that there is a Gpx4 dysfunction in AD brains that could lead to exacerbated pathogenesis and that enhanced Gpx4 function retards cognitive impairment of AD mouse models. In this project, we will determine whether increased membrane lipid peroxidation induced by Gpx4 deficiency aggravates disease pathogenesis such as neurodegeneration, and determine the efficacy of Gpx4 overexpression in retarding cognitive impairment and neurodegeneration in AD mice. The overall hypothesis tested in this project is: Membrane lipid peroxidation aggravates neurotoxicity in vivo, and augmentation of Gpx4 function to suppress membrane lipid peroxidation will retard AD pathogenesis. The hypothesis will be tested by three specific aims. Aim 1 is to determine the effect of membrane lipid peroxidation induced by Gpx4 deficiency on AD pathogenesis. Aim 2 is to determine whether overexpression of Gpx4 can suppress neurodegeneration and improve cognition in AD mice. Aim 3 is to determine whether Gpx4 overexpression via transduction with viral vector can retard progression of disease in AD mice at different disease stages. Our study will establish the importance of membrane lipid peroxidation in neurodegeneration of AD and provide proof-of-concept evidence for the efficacy of Gpx4 as a target of intervention to retard progression of AD.

7. 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, comprising approximately 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, more than 40% of seniors regularly experience loneliness. Loneliness is thought to accelerate cognitive decline in older adults, possibly mediated through rising glucocorticoid levels and increasing inflammation. There is a great unmet therapeutic need for the development of cognitive therapeutics for the treatment of neurocognitive disorders associated with aging including dementias and Alzheimer's disease. Identifying characteristics of animal models that may contribute to the development of such a cognitive therapeutic would have significant impact. Common marmosets are poised to become an important nonhuman primate model in the study of age-related disease. The focus of this research is healthy brain aging, and the social, neuroendocrine, and vascular contributions associated with normal aging rather than disease states. The population will be characterized using standardized cognitive assessments to define those that have good vs poor cognitive aging. The likelihood of the following variables as determinants of cognitive aging outcomes will be modeled: sex, social history, current housing condition, cerebral blood flow (imaging assessments), and myelination. Aim 1 will focus on assessing whether social support buffers the effects of stress on cognitive and neuroendocrine function during aging. An experimental manipulation of a period of separation of a long-term pair, then reunion, will allow us to investigate the role of social buffering on cognition and 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 cognitive performance and cerebral blood flow (CBF) by arterial spin labeling in aged and geriatric marmosets. We expect cognitive outcomes will be positively correlated with CBF and brain vascular density. Aim 3 will determine whether changes in white matter integrity are associated with cognitive dysfunction. The results of this study will contribute novel insights and deeper understanding of the role of social stress and neuroendocrine disruption in age-associated cognitive dysfunction. We anticipate that identifying these links will fundamentally advance research in the study of aging, and may advance the establishment of the marmoset as a highly translational model of these conditions.

8. Project Title: HARNESSING THE POWER OF CTSA-CDRN DATA NETWORKS: USING SOCIAL DETERMINANTS OF HEALTH, FRAILTY AND FUNCTIONAL STATUS TO IDENTIFY AT-RISK PATIENTS AND IMPROVE RISK ADJUSTMENT

**Leader(s): SHIREMAN, PAULA K
UNIVERSITY OF TEXAS HLTH SCI CTR SAN ANT
NIH U01TR002393 / (2018 - 2022)**

Core(s):

Postoperative complications and readmissions rates are higher in minority and low socioeconomic status (SES) patients. Low SES is associated with frailty, one of the best predictors of 30-day postoperative complications and early hospital readmission. Despite their influence on health outcomes, frailty and social risk factors are not considered in risk adjustment for reimbursement and quality measures. CMS developed financial incentive-based programs to improve quality of care. Yet this strategy disproportionately penalizes minority-serving, major teaching and safety net hospitals (SNH), further constraining resources for the care of vulnerable populations. Our long-term goal is to use frailty and social risk factors to identify at-risk patients to design more effective clinical care pathways. Frailty can be derived retrospectively using the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) dataset. Data networks are powerful research tools that can be used to answer important questions. However, extracting data from EHR is challenging. The Patient-Centered Outcomes Research Institute (PCORI) developed 13 Clinical Data Research Networks (CDRN) that have considerable overlapping membership with Clinical Translational Science Award (CTSA) institutions. While steady progress has been made, multiple barriers exist to efficiently access and use data. We will engage 3 CTSA hubs, each members of a different CDRN, to locally merge identified datasets developing data accessing and linking strategies at diverse institutions for dissemination across sites within CDRNs and to ultimately perform similar studies across CDRNs. We will use the SMART IRB reliance platform to harmonize the regulatory approval process as much as possible for each step of this project to identify barriers to use in data networks. We propose the following Aims: 1) Determine the predictive power of ethnicity, race, SES, and frailty for postoperative complications, mortality and readmissions to improve risk adjustment at 3 CTSA/CDRNs 2) Estimate postoperative functional status using natural language processing (NLP) and machine learning algorithms on inpatient physical therapy (PT), occupational therapy (OT) and nursing notes for ACS NSQIP patients to predict long-term functional status 3) Develop methods to predict long-term loss of independence after major surgery 4) Determine hospital resource utilization stratified by SES, frailty and minority status The significance of our study is the incorporation of social risk factors, frailty and functional status in risk adjustment forming the basis for future interventions by targeting patients at the highest risk for postoperative complications and reducing health care disparities. Our innovative approach harnesses data sources at diverse institutions with the goal of disseminating these methods across 3 CDRNs and the

CTSA network.

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<https://doi.org/10.1111/accel.13407> | PMID: 34118180 | PMID: PMC8282273
Citations: 2 | AltScore: 3.35
11. **Exercise Intolerance in Older Adults With?Heart?Failure With Preserved Ejection?Fraction: JACC State-of-the-Art Review.**

Pandey A, Shah SJ, Butler J, Kellogg DL Jr, Lewis GD, Forman DE, Mentz RJ, Borlaug BA, Simon MA, Chirinos JA, Fielding RA, Volpi E, Molina AJA, Haykowsky MJ, Sam F, Goodpaster BH, Bertoni AG, Justice JN, White JP, Ding J, Hummel SL, LeBrasseur NK, Taffet GE, Pipinos II, Kitzman D

J Am Coll Cardiol, 2021 Sep 14, 78(11): 1166-1187

<https://doi.org/10.1016/j.jacc.2021.07.014> | PMID: 34503685 | PMCID: PMC8525886

Citations: 9 | AltScore: 19.3

12. **Circulating microRNA profile in humans and mice with congenital GH deficiency.**

Saccon TD, Schneider A, Marinho CG, Nunes ADC, Nouredine S, Dhahbi J, Nunez Lopez YO, LeMunyan G, Salvatori R, Oliveira CRP, Oliveira-Santos AA, Musi N, Bartke A, Aguiar-Oliveira MH, Masternak MM

Aging Cell, 2021 Jul, 20(7): e13420

<https://doi.org/10.1111/accel.13420> | PMID: 34118183 | PMCID: PMC8282278

Citations: 2 | AltScore: 2.5

13. **Insulin resistance is mechanistically linked to hepatic mitochondrial remodeling in non-alcoholic fatty liver disease.**

Shannon CE, Ragavan M, Palavicini JP, Fourcaudot M, Bakewell TM, Valdez IA, Ayala I, Jin ES, Madesh M, Han X, Merritt ME, Norton L

Mol Metab, 2021 Mar, 45: 101154

<https://doi.org/10.1016/j.molmet.2020.101154> | PMID: 33359401 | PMCID: PMC7811046

Citations: 9 | AltScore: NA

14. **Comparison of rectal swab, glove tip, and participant-collected stool techniques for gut microbiome sampling.**

Short MI, Hudson R, Besasie BD, Reveles KR, Shah DP, Nicholson S, Johnson-Pais TL, Weldon K, Lai Z, Leach RJ, Fongang B, Liss MA

BMC Microbiol, 2021 Jan 14, 21(1): 26

<https://doi.org/10.1186/s12866-020-02080-3> | PMID: 33446094 | PMCID: PMC7809826

Citations: 1 | AltScore: 0.75

15. **Responses to acute infection with SARS-CoV-2 in the lungs of rhesus macaques, baboons and marmosets.**

Singh DK, Singh B, Ganatra SR, Gazi M, Cole J, Thippeshappa R, Alfson KJ, Clemmons E, Gonzalez O, Escobedo R, Lee TH, Chatterjee A, Goetz-Gazi Y, Sharan R, Gough M, Alvarez C, Blakley A, Ferdin J, Bartley C, Staples H, Parodi L, Callery J, Mannino A, Klaffke B, Escareno P, Platt RN 2nd, Hodara V, Scordo J, Gautam S, Vilanova AG, Olmo-Fontanez A, Schami A, Oyejide A, Ajithdoss DK, Copin R, Baum A, Kyratsous C, Alvarez X, Ahmed M, Rosa B, Goodroe A, Dutton J, Hall-Ursone S, Frost PA, Voges AK, Ross CN, Sayers K, Chen C, Hallam C, Khader SA, Mitreva M, Anderson TJC, Martinez-Sobrido L, Patterson JL, Turner J, Torrelles JB, Dick EJ Jr, Brasky K, Schlesinger LS, Giavedoni LD, Carrion R Jr, Kaushal D

Nat Microbiol, 2021 Jan, 6(1): 73-86

<https://doi.org/10.1038/s41564-020-00841-4> | PMID: 33340034 | PMCID: PMC7890948

Citations: 79 | AltScore: 210.58

16. **The treatment of neurogenic lower urinary tract dysfunction in persons with spinal cord injury: An open label, pilot study of anticholinergic agent vs. mirabegron to evaluate cognitive impact and efficacy.**

Trbovich M, Romo T, Polk M, Koek W, Kelly C, Stowe S, Kraus S, Kellogg D

Spinal Cord Ser Cases, 2021 Jun 10, 7(1): 50

<https://doi.org/10.1038/s41394-021-00413-6> | PMID: 34112758 | PMCID: PMC8192499

Citations: 2 | AltScore: 2.75

17. **Tailoring a dissonance-based body image intervention for adult women in a proof of concept trial: The Women's Body Initiative.**

Verzijl CL, Duan J, Wilfred SA, Becker CB, Kilpela LS

Body Image, 2021 Mar, 36: 269-275

<https://doi.org/10.1016/j.bodyim.2021.01.001> | PMID: 33486295 | PMCID: PMC8995137

Citations: | AltScore: NA

18. **Binge eating among older women: prevalence rates and health correlates across three independent samples.**

Wilfred SA, Becker CB, Kanzler KE, Musi N, Espinoza SE, Kilpela LS

J Eat Disord, 2021 Oct 19, 9(1): 132

<https://doi.org/10.1186/s40337-021-00484-8> | PMID: 34666821 | PMCID: PMC8524882

Citations: 2 | AltScore: 4.1

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RECOGNITION AND AWARDS (2021-2022)

Carolina Solis-Herrera (2021)

- Doris Duke Charitable Foundation (DDCF) Clinical Scientist Development Award

MINORITY RESEARCH

General Brief Description of Minority Activities:

Not defined.

Minority Trainee(s):

- Nothing to report, Nothing to report
Nothing to report

Minority Grant(s):

UNIVERSITY OF TEXAS MEDICAL BRANCH (UTMB) Claude D. Pepper Older Americans Independence Center

Elena Volpi, M.D.
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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 blasmus@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

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: 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 blasmus@utmb.edu

Leader 2: Stanley J. Watowich, PhD sjwatowi@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

Leader 2: Heidi Spratt, PhD hespratt@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**

Huiwen Xu, PhD, MHA (Phase I)

Assistant Professor / Population Health & Health Disparities

Aging; cancer rehabilitation; long-term care

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)

Neil Mehta, PhD (Phase I)

Associate Professor / Epidemiology

Identifying the Causes of the Stagnation in National U.S. Cardiovascular Disease

Mortality

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

Implementation science; Hip Fracture; Osteoporosis; Malnutrition; eHealth

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 (4 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 an “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.

DEVELOPMENT PROJECTS (4 Development Projects Listed)**1. Project Title: Integrate behavioral methodologies to improve retention and intervention fidelity in clinical studies****Leader: Elizabeth Lyons, PhD****Core(s): Clinical Research Resource Core (CRRC)**

The QuinteT (qualitative research integrated into trials) approach is a mixed-method strategy to understand barriers to clinical trial recruitment and intervene upon them as the trial proceeds. This strategy has demonstrated clear benefits to trial recruitment rates, but it has not yet been implemented to improve retention and intervention fidelity. We propose to build upon this framework by integrating specific behavior change techniques into the action plan, using the Behavior Change Wheel model to match issues discovered during the QuinteT process to theory- and evidence-based strategies to overcome them. The specific aims for this project are:

1. Conduct focus groups with Pepper Center coordinators and leadership to refine a set of support tools and checklists for conducting a QuinteT-based analysis and intervention; Conduct focus groups with local older adults to investigate the acceptability of several methods for implementing each behavior change technique pertinent to trial retention (e.g., yearly presentation of research results, monthly newsletters, social media posts, branded accessories, etc.); Evaluate retention rates in a pilot trial of the full QuinteT plus behavior change technique process as used in an ongoing clinical trial. Approach: Focus groups will be conducted iteratively, with materials refined between each group. Groups will continue until data saturation is reached; we anticipate 20–30 participants each for Aims 1 and 2. Two trained coders will perform thematic analysis on the transcripts to identify themes. Once materials are finalized, we will pilot test the procedure as part of the STEP-HI study (EP16). We will 1) interview study Principal and Co-investigators; 2) interview coordinators who interact with participants; 3) audio record participant interactions; 4) interview participants who drop out; and 5) analyze recruitment and attrition logs. We will use this information as a needs assessment for the Behavior Change Wheel program planning model, which will facilitate matching behavior change techniques to the identified needs. We will compare recruitment, attrition, and compliance rates in all participants before and after the intervention. Dr. Lyons, highly experienced in use of the Behavior Change Wheel to develop interventions, conducting process evaluations, and implementing pilot clinical trials, will oversee this process with the qualitative data analysis expert Dr. Pappadis. Expected results: We expect to create a systematic methodology for intervening to improve retention during a clinical trial. We plan to disseminate manuscripts that detail the methodology and discuss the pilot evaluation results, then move on to implementation in additional trials being conducted by OAIC investigators.

2. Project Title: Develop best practices to increase recruitment of Hispanic older adults**Leader: Rafael Samper-Ternent, MD, PhD****Core(s): Clinical Research Resource Core (CRRC)**

19% of adults 65 yr and older living in our area (Galveston-Houston) are Hispanic, yet Hispanics make up only 7% of the volunteers in our Registry. Recruitment strategies that work in other populations do not necessarily translate to Hispanic participants. There are also significant language and cultural differences among Hispanics of different national/regional origin (e.g. US, Mexico, Central America, South America, Caribbean). Thus, different groups

may call for different strategies. We propose to develop best practices in recruiting Hispanic research participants. The specific aims of this project are: 1. Conduct a systematic review the existing literature to identify strategies used in the past; 2. Conduct qualitative studies within our local Hispanic community to identify barriers and preferences for participation in clinical research; 3. Develop recruitment materials and strategies that are culturally and linguistically appropriate for each specific target Hispanic population. Approach: We will engage the Hispanic Council on Aging (see LAC) for the systematic review. Results will be presented to the OAIC PSC. Hispanic investigative team members will interview Hispanic seniors from the most common national origin found in our area (US, Mexico, El Salvador, Venezuela, ~20/group until data saturation) using the structured qualitative interview model. Two experts in qualitative analysis will oversee thematic analysis of interview transcripts to identify major themes and sub-themes using NVivo qualitative analysis software. Best practices and culturally sensitive materials will be developed to increase the number of Hispanic participants in clinical trials and pilot-tested in our hospital (EP11) and clinic-based (EP4) trials. Expected results. We expect to identify specific barriers and facilitators to recruitment for each group of Hispanic seniors interviewed and develop tailored strategies for successful recruitment. We will disseminate the best practices nationally (e.g. publications, OAIC Coordinating Center, RCMAR, RCCN).

3. Project Title: Novel therapeutics to alleviate anabolic resistance in aging

Leader: Stanley Watowich, PhD

Core(s):

In this DP, Dr. Watowich will develop new oral drugs that greatly improve anabolic and insulin sensitivity in peripheral muscles and metabolic function in white adipose tissue, thereby restoring normal glucose homeostasis aged mice. Dr. Watowich has developed drug-like inhibitors of nicotinamide N-methyltransferase (NNMT), a recently identified modulator of cell metabolism, bioenergetics, and epigenetic gene regulation. Importantly, NNMT expression is increased in both aged tissues and expanded white adipose tissues. The hypothesis of this project is since IMCL levels increase with age and correlate with insulin resistance, we hypothesize that translationally-relevant animal models of anabolic resistance (i.e., diet-induced obese C57Bl/6 mice) will show age-dependent improvements in metabolic disease markers when treated with potent NNMT inhibitor drug candidates. There will be two specific aims for this project: 1) characterize and compare improvements in muscle insulin sensitivity and glycemic response in young (6-mo), middle-aged (12-mo), and aged (24-mo) animal models of anabolic resistance treated with NNMT inhibitor drug candidates. 2) characterize and compare improvements in liver and adipose tissue chronic inflammation in young, middle-aged, and aged animal models of anabolic resistance treated with NNMT inhibitor drug candidates. This developmental project will enhance the muscle biology of aging component of the UTMB OAIC and allow other researchers to collaborate in genetic and therapeutic methods to define the biological pathways that lead to sarcopenia and functional loss.

4. 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.

RESEARCH (15 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/ABSTRACT I am an assistant professor in the Division of Rehabilitation Sciences at the University of Texas Medical Branch in 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 funded research program that advances the quality of post-acute care for older adults, in particular for those with cognitive impairment, Alzheimer's disease and related dementias. My K01 application is focused on skilled nursing facilities (SNFs) because they are the most frequent post-acute care site for older adults. My training in gerontology has focused on analyzing cognitive data and using large data sets to identify potentially modifiable risk factors for cognitive impairment and dementia. During the K01 period, I will receive training in four areas that build upon my prior training in gerontology and expertise on the epidemiology of dementia: (1) Health characteristics, assessment process, quality outcomes and follow-up needs associated with older adults receiving SNF care; (2) Operational standards and regulatory (decision making) policies of SNFs; (3) Statistical skills for studying post-acute care outcomes using claims data; and (4) Career advancement and leadership development. Training in these areas will include coursework, shadowing interdisciplinary teams in clinical settings, and experiences accessing, managing, and analyzing Medicare files. This training will make me a researcher with a highly-informed view of healthcare policy and clinical context. My training activities have been integrated with a research project in which I will use national Medicare data files (2012-2014) to complete the following specific aims: (A) Evaluate the change in cognitive status during a SNF stay for older adults with impaired cognition on admission; (B) Examine the variation across SNFs in the percentage of patients with impaired cognition on admission whose cognitive status improves during a SNF stay; and (C) Assess the relationship between cognitive status on admission, improvement in cognitive status during a SNF stay, and performance on SNF quality measures. The expected findings of this research can inform clinical interventions that target patient- and facility-level characteristics associated with improved cognitive status. The findings can also 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 skills necessary to develop a program of research that will advance the quality of post-acute care for older adults, in particular for older adults with cognitive impairment, Alzheimer's disease and related dementias.

2. Project Title: REHABILITATION RESEARCH CAREER DEVELOPMENT PROGRAM

Leader(s): OTTENBACHER, KENNETH J.
UNIVERSITY OF TEXAS MEDICAL BR GALVESTON
NIH K12HD055929 / (2007 - 2022)

Core(s):

ABSTRACT In response to RFA-HD-17-021, we propose the Rehabilitation Research Career Development Program (RRCD), a renewal of our current grant (K12 HD-055929) to train rehabilitation scientists who are occupational and physical therapists. The goal of the RRCD Program is to increase the number of rigorously trained, extramurally competitive, and scientifically competent rehabilitation scientists who will conduct translational investigations, lead clinical research teams, and eventually mentor the next generation of occupational and physical therapy scientists. The University of Texas Medical Branch (UTMB), the University of Florida (UF) and the University of Southern California (USC) will function as a research consortium to achieve this goal. The consortium includes senior rehabilitation investigators (Lead Mentors) who provide Scholars with the skills and knowledge necessary to become independent investigators and future leaders in rehabilitation science. The training program is comprised of two phases. Phase 1 (years 1-3) is designed to provide Scholars with the foundation needed for a productive career in interdisciplinary rehabilitation research. Scholars will conduct research at one of the consortium institutions under the supervision of a Lead Mentor and collaborate with members of an interdisciplinary translational team in their area of research interest. Each Scholar will prepare an Individualized Career Development Plan based on their past training and recommendations from the Lead Mentor and research team. The plan will consist of

structured didactic training involving research methodology, specialized courses and seminars, and mentored grant writing experiences. In Phase 1, Scholars will acquire research experience, generate, analyze, present and publish research data, and become equipped to compete for independent external funding (e.g., NIH R21, R34, or R01 grants). In Phase 2 (years 4-5), RRCD Scholars will transition to independent researcher positions. Scholars will continue to devote 50-75% effort to research and remain associated with the Lead Mentor and members of the research team, but will no longer receive salary support from the K12 award per the RFA instructions. The mentor-based training model takes advantage of the excellent resources at the consortium institutions (e.g., NIH and NIDILRR career development programs, NIH-funded research centers, and Clinical and Translational Science Awards). Eighty percent of the RRCD Scholars who are currently in Phase 2, or completed the program, have obtained external funding from federal, foundation, or industry sources as an independent investigator.

**3. 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 is currently 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 a competing renewal for our P01, originally funded as AADCRC AI46004 and subsequently through two P01 cycles (9/1/2005-present). Work in our P01 has elucidated mechanisms by which RSV infection produces a rapid epithelial oxidative stress response, triggering innate signaling and resulting in cytokine secretion that triggers and shapes adaptive immunity. More recently, we have developed additional compelling evidence supporting the central theme of this P01 that innate inflammation produced by infection with the ubiquitous viral pathogen RSV impairs antioxidant capacity, producing disease and triggering long-term airway remodeling. Our projects are developed from original discoveries by our internationally recognized project leaders (PLs) expert in innate inflammation, oxidative stress, and the DNA damage response. Our renewal includes three major research projects (RPs): 1) RP1 (Epigenetic regulation of innate inflammation-driven airway remodeling) will focus on the role of the NF- κ 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 in downregulation of the airway antioxidant response during paramyxovirus infection) will focus on how RSV causes disease mediated by unbalanced ROS production via a progressive decrease in NF-E2-related factor 2 (NRF2); and 3) RP3 (Linkage of the oxidant-induced OGG1-DNA complex to airway inflammation and remodeling) will test the hypothesis that RSV-induced epigenetic modification via oxidation of guanine to oxoG in gene regulatory regions controls acute/chronic inflammation and airway remodeling via the N κ B pathway. This P01 is guided by regular and sustained interactions with our Internal and 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). Translational advances include applications of BRD4 inhibitors, NRF2 agonists, and OGG1 inhibitors that in preclinical studies show promise to interfere with RSV-induced inflammation and remodeling. Upon completion, this P01 will have identified mechanisms of innate signaling-induced remodeling and developed strategies for reversing remodeling and restoring defective innate immunity in allergic airway diseases.

**4. 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 their caregivers, many of whom were interviewed in 2016 (Wave 9) and/or in 2010-11 (Wave 7). We propose the new field work for 2019-20. The baseline was conducted during 1993-94 when a representative sample of 3,050 Mexican Americans aged >65 residing in Texas, New Mexico, Colorado, Arizona, and California were interviewed. At Wave 5 (2004-05), a new cohort of 902 subjects aged >75 was added. The proposed contact will be our tenth for the original subjects plus the third contact for most of the caregivers whom we interviewed in 2010-11 and 2016. At our last contact in 2016 we interviewed 480 subjects that were aged >88 plus 460 informants, most of whom were family caregivers. Our specific aims below are based on our key findings from the 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 2.5 years 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 plan to interview their caregivers (N=300) most of whom were interviewed in 2016 and some of them also interviewed in 2010-11. The Hispanic EPESE has been a multipurpose study with contributions to numerous aspects of aging in the Mexican American population. The proposed application will also have multiple aims mostly centered on the health and health care needs of the oldest old Mexican Americans with special attention to their caregiving needs and caregiving arrangements. Also of interest are factors that contribute to survival to such advanced ages. Our primary aims are: Aim 1. Assess the dynamics of caregiving and living arrangements of very old Mexican Americans over a nine-year period (2010-2011 to 2016 and to 2019-2020) by obtaining information from 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. Also examined are factors influencing changes in caregiving arrangements, as well as changes in living arrangements including institutionalization. Aim 3. Identify predictors of survival, change in disability, change in cognitive function, 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 oldest old subjects and examine their association with caregiver arrangements, caregiver burden and quality of life of their caregivers (N=300). Aim 5. Archive proposed Wave 10 data with NACDA (the National Archive of Computerized Data in Aging). Waves 1 to 8 have been archived with NACDA and Wave 9 collected in 2016 will be archived this year.

5. Project Title: **MEXICAN HEALTH AND AGING STUDY - MHAS**
Leader(s): **WONG, REBECA**
UNIVERSITY OF TEXAS MEDICAL BR GALVESTON
NIH R01AG018016 / (1999 - 2022)

Core(s):

The proposed project aims to design and field two more waves of survey data collection in Mexico, extending and improving the Mexican Health and Aging Study (MHAS). This is a national, multi-purpose, community-based, longitudinal cohort study of adults aged 50 and older. The two new waves will be fielded in 2018 and 2021, completing a cycle of 20 years since the first wave was fielded in 2001. Funds are also sought to continue to archive, document, and disseminate for public use the new waves as well as the resulting integrated data base containing all six waves. Since its inception, MHAS aimed to create a longitudinal prospective study of Mexican aging, starting with a national sample (n=15,000), using study protocols and survey instruments that were highly comparable to the U.S. Health and Retirement Study. In addition, the study design sought to facilitate the examination of long term implications for health and aging of the massive Mexico-U.S. migration flows. Thus, the sample design included an over-sample in states of Mexico with historically high levels of migration to the United States. The new waves will replicate and improve these and other unique features of previous rounds. New emphasis areas will be: environmental health; life histories; health literacy; evaluation of losses and deaths in the panel. We will also continue an emphasis on the culture of multi-generational Mexico-U.S. migration and its consequences for aging; and the impact for older adults of structural changes in Mexico such as the health sector reform that started in 2003 and the economic recession of 2009. Our aims are: 1) To carry out Waves 5 and 6 retaining the original substance of MHAS and adding new content, following the survivors of Waves 1 through 4, and refreshing the sample in Wave 5 to yield again a representative cross section of the Mexican population aged 50 and over; and 2) To enhance data linkages, data distribution, dissemination, and outreach activities and to expand knowledge about and use of the datasets and products of the resulting six waves of the MHAS. We will continue the user-friendly web-based platforms and educational materials whose enhanced public access to the data and project documentation have stimulated cross-country and other studies. The analytical significance of the new MHAS data will be exceptional, producing a national longitudinal study of aging that span over twenty years, which is unique for a developing country. The data platform will enhance research on aging and related population changes: of physical and mental health, physical and cognitive functionality, environmental risks, health behaviors and health care use, family support, aging and the life course, wealth, income, labor and retirement, migration and old age, and mortality, in a

developing country aging fast with limited institutional support for individuals in old age, and with close social and economic ties to the United States. The data will enable cross-period and cross-cohort analyses of health and aging, and will continue to be highly comparable with other similar studies in developed and developing countries, enhancing the study of aging and health with a cross-national perspective.

6. Project Title: COMBINING TESTOSTERONE THERAPY AND EXERCISE TO IMPROVE FUNCTION POST HIP FRACTURE

**Leader(s): BINDER, ELLEN F; KIEL, DOUGLAS P. ; MAGAZINER, JAY ; ORWIG, DENISE L ; SCHECHTMAN, KENNETH B. ; SCHWARTZ, ROBERT S ; VOLPI, ELENA ; WASHINGTON UNIVERSITY
NIH R01AG051647 / (2017 - 2022)**

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: 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 SUMMARY In the United States, an estimated 5.5 million persons are affected by Alzheimer's disease, the most common type 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 the patient 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 needs of patients and their caregivers, including those based within health care systems and those based in the community. These programs have been implemented at either single sites or on a relatively small scale; none has 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 pragmatic clinical trial to compare the effectiveness of health-systems-based care (based on the UCLA Alzheimer's and Dementia Care program) with community-based care (based on the Benjamin Rose Institute Care Consultation program) on patient- and caregiver-reported outcome measures, including behavioral symptoms and caregiver distress (co-primary outcomes), and secondary outcomes of caregiver strain, unmet needs, and depression over 18-months. Because of PCORI's mandate, neither intervention will be compared to usual care (thus, only relative 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 active treatment arms. It will also allow evaluation of whether paying for such care will offset the costs and determination of which intervention is more cost effective. The study will also conduct exploratory analyses of tertiary outcomes of both interventions versus usual care including mortality, time spent at home, long-term nursing home placement, physician and patient/caregiver satisfaction and comparing all three groups on several types of utilization and out-of-pocket expenses. The study's questions are fundamental to planning for the clinical care of persons with dementia. They address both clinical effectiveness and cost-effectiveness. By answering these questions, clinicians, health systems, and insurers can make decisions about which programs to promote, scale and disseminate.

8. 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 SUMMARY Older adult women are at unique risk for negative outcomes of insufficient physical activity (PA). Mobile health interventions using wearable activity monitors have shown promise for increasing walking for PA, but adherence to PA recommendations declines sharply over time. To improve adherence in this at-risk population, we propose to test an innovative method of framing mobile health devices and apps. As opposed to the more typical corrective frame, a celebratory frame focuses on positive aspects of the target behavior. This approach is rooted in Self-Determination Theory, which posits that autonomous regulations (motivations related 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 enjoyable and related to older women's identity and values, thus increasing their autonomous regulation for PA and in turn PA adherence. The CHALLENGE study (Challenges for Healthy Aging: Leveraging Limits for Engaging Networked Game-based Exercise) will consist of an initial sub-study followed by a large randomized controlled intervention trial. During the sub-study, we will conduct cognitive interviews among 20 older women to ensure that refinements to the game after our pilot trials are acceptable. Then, we will randomize 300 women (aged 65-85,

9. 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 changes in 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 historically neglected research demographic who present with a largely youthful phenotype, but are at risk of accelerated disuse 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 function outcomes. This project will address critical knowledge gaps that limit the efficacy of current strategies to restore muscle health following periods of disuse. Current strategies, while well intentioned, are largely inconsistent with the practice of evidence-based medicine and place a financial and human resource burden on our health care delivery system. By characterizing changes in the molecular, morphologic and functional landscape of skeletal muscle 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 in clinical populations with comorbid conditions.

10. 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.

11. Project Title: HEALTH OF OLDER MINORITIES

**Leader(s): WONG, REBECA
UNIVERSITY OF TEXAS MEDICAL BR GALVESTON
NIH T32AG000270 / (1999 - 2022)**

Core(s):

ABSTRACT This application seeks funds for 5 years, to continue the current NIH-funded T32 program for Hispanic and other Minority Health and Aging at the University of Texas Medical Branch (UTMB), to support 3 pre-doctoral and 1 post-doctoral trainees per year. The program aims to increase and improve the pool of researchers with relevant expertise to help address challenges raised by the growing diversity in aging of the United States population. Given our strengths in the areas of Hispanic/Latino aging with a multi-disciplinary, population based perspective, we focus on factors related to health disparities involving these populations as well as minorities in general. The pre-doctoral students benefit by interacting with PhD students in other Population Health Science programs, funded by the Graduate School of Biomedical Sciences. The post-doctoral fellows as well as the pre-doctoral students are housed in the Sealy Center on Aging. Our faculty have had a long history of epidemiological, social and behavioral research on aging with particular strengths in Hispanic population aging. UTMB is currently the home of two large population-based, longitudinal, cohort studies funded by the National Institute on Aging, the Hispanic Established Population for the Epidemiological Study of the Elderly (Hispanic EPESE) and the Mexican Health and Aging Study (MHAS), and hosts multi-disciplinary research grants on aging. The current faculty in the affiliated programs have strengths in sociology, demography, anthropology, social epidemiology, medicine, public health, rehabilitation sciences, and geriatrics. Our plan is to build on our strengths and train scientists in social/behavioral and epidemiological factors related to aging in Hispanic/Latino aging as well as health disparities in general. As is the case in our current program, special efforts will be made to recruit students from underrepresented backgrounds, and all our trainees will focus their research on the health of Hispanic and other minority older adults. Compared to our previous grant, new in our proposed program are: a) new leadership in the training program and new key faculty, b) a strengthened recruitment approach, and c) one new area of thematic emphasis.

12. 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/SUMMARY This new T32 program for Health Service Research at the University of Texas Medical Branch (UTMB) seeks funds for 5 years to support 3 predoctoral trainees per year. The program aims to increase and improve the pool of health service researchers with clinical background to help address complex issues in health care delivery in the US. Given our strengths in the areas of health service research, we focus on using cutting edge methodology to study the patterns and trends of health care delivery, to assess the impact of health policy, and to examine the effectiveness of various care models. The trainees are PhD or MD-PhD students in the Population Health Science program, Clinical Science program, or Rehabilitation Science program of the Department of Preventive Medicine and Community Health. UTMB has an excellent record in conducting health service research. We were funded by an R24 on Health Service Research in Underserved Population between 2001 and 2006 from the Agency for Healthcare Research and Quality (AHRQ). Since then, we have continuously developed health service research with two R01s and an R24 on Patient Centered Outcomes Research in the Elderly, currently funded by AHRQ. Besides funding from AHRQ and several additional health service research R01s from the NIH, we also have a P2C grant for the Center for Large Data Research and Data Sharing in Rehabilitation funded by the National Institute of Child Health & Human Development and another Multi-Investigator Research Award on Comparative Effectiveness Research on Cancer in Texas funded by the Cancer Prevention & Research Institute 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 our strengths and train health care professionals in health service research in different populations. As is the case in our other programs, special efforts will be made to recruit students from diverse clinical backgrounds, and all our trainees will focus their health service research in their clinical field. The Graduate School of Biomedical Sciences and Provost's Office have made significant commitments in the past 5 years to enhance the excellence of graduate education at UTMB. These commitments include the President's Scholars Program to recruit outstanding graduate students and the establishment of an Office of Postdoctoral Affairs that includes organized training and opportunities in career development and mentoring. We have developed a formal structure and related activities to enhance recruitment and facilitate the placement of our trainees regionally and nationally. We believe that our health care profession trainees will be competitive for leadership positions among the next generation of health service researchers in their clinical area.

13. Project Title: University of Texas Adult Clinical Center
Leader(s): RASMUSSEN, BLAKE B
UNIVERSITY OF TEXAS MED BR GALVESTON

NIH U01AR071150 / (2016 - 2022)**Core(s):**

PROJECT SUMMARY The University of Texas Medical Branch at Galveston (UTMB) and the University of Texas Health Science Center at San Antonio (UTHSCSA) jointly propose the creation of a University of Texas Adult Clinical Center (UTACC) for the Molecular Transducers of Physical Activity Consortium (MoTrPAC). We will integrate resources and combine our expertise to provide a state-of-the-art center for comprehensive studies on physical activity in adults. The Specific Aims of the UTACC are: 1) To participate in the planning of the multi-center trial; 2) To enroll 450 participants in the acute and chronic exercise training studies, conduct physiological assessments, and collect biospecimens (muscle, adipose, and blood); and 3) To analyze and interpret outcome data and disseminate findings to the scientific community. We will use innovative tools to maximize participant retention and enhance fidelity and adherence to the exercise training protocols. The UTACC will have a significant impact on the MoTrPAC and advance the field of exercise science based on our strengths, feasibility of the proposed study, and expected outcomes: The strengths of the UTACC include our long-track record of performing human studies on molecular transducers of exercise; shared resources and years of networking through the Claude D. Pepper Older Americans Independence Center network and the Texas Regional CTSA Consortium; and our success with enrolling understudied populations such as older individuals and Hispanics-Latinos. The feasibility for the UTACC is high due to our experience with clinical trials on physical activity; our substantial expertise in collecting muscle and adipose biopsies in humans undergoing exercise studies; and our access to outstanding clinical research facilities in which to conduct human research in a safe environment. Expected outcomes of this program include the determination of baseline molecular signatures associated with metabolic health and physical performance; the integration of multi-omic data for the elucidation of molecular networks that control metabolic responses to exercise and how they influence physical performance; and discovery of novel mediators (proteins, metabolites, miRNAs) of the beneficial effects of exercise.

14. 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.

15. 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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<https://doi.org/10.1093/gerona/glaa205> | PMID: 32822475 | PMCID: PMC8087272

Citations: 3 | AltScore: 2.6

21. Important-performance analysis to conceptualize goal priorities in community dwelling stroke survivors.

Hay CC, Pappadis MR, Sander AM, Weller SC, Wang W, Reistetter TA

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<https://doi.org/10.1080/10749357.2021.1928838> | PMID: 34009101 | PMCID: PMC8602464

Citations: | AltScore: 2.25

22. Development of a physical function outcome measure to harmonize comparisons between three Asian adult populations.

Hong I, Hreha KP, Hilton CL, Lee MJ

Qual Life Res, 2021 Jun 12, 31(1): 281-291

<https://doi.org/10.1007/s11136-021-02909-y> | PMID: 34120274 | PMCID: PMC8858009

Citations: | AltScore: 0.5

23. Social Engagement and Cognitive Function of Older Adults in Mexico and the United States: How Universal Is the Interdependence in Couples?

Howrey B, Avila JC, Downer B, Wong R

J Gerontol B Psychol Sci Soc Sci, 2021 Jun 8, 76(Suppl 1): S41-S50

<https://doi.org/10.1093/geronb/gbaa025> | PMID: 34101812 | PMCID: PMC8186856

Citations: 1 | AltScore: 5.2

24. **Association between vision impairment and cognitive decline in older adults with stroke: Health and Retirement Study.**

Hreha KP, Downer B, Ehrlich JR, Howrey B, Taglialatela G

Aging Clin Exp Res, 2021 Jan 11, 33(9): 2605-2610

<https://doi.org/10.1007/s40520-020-01776-w> | PMID: 33428171 | PMCID: PMC8272742

Citations: 3 | AltScore: NA

25. **Effect of Protein Intake on Visceral Abdominal Fat and Metabolic Biomarkers in Older Men with Functional Limitations: Results from a Randomized Clinical Trial.**

Huang G, Pencina K, Li Z, Apovian CM, Trivison TG, Storer TW, Gagliano-Juc? T, Basaria S, Bhasin S

J Gerontol A Biol Sci Med Sci, 2021 Jan 8, 76(6): 1084-1089

pii: glab007. <https://doi.org/10.1093/gerona/glab007> | PMID: 33417663 | PMCID:

PMC8140050

Citations: 3 | AltScore: 29.35

26. **Nurse Practitioner Involvement in Medicare Accountable Care Organizations: Association With Quality of Care.**

Huang N, Raji M, Lin YL, Chou LN, Kuo YF

Am J Med Qual, 2021 May-Jun 01, 36(3): 171-179

<https://doi.org/10.1177/1062860620935199> | PMID: 32715726 | PMCID: PMC8108822

Citations: 1 | AltScore: 1.5

27. **Muscle damaging eccentric exercise attenuates disuse-induced declines in daily myofibrillar protein synthesis and transiently prevents muscle atrophy in healthy men.**

Jameson TSO, Kilroe SP, Fulford J, Abdelrahman DR, Murton AJ, Dirks ML, Stephens FB, Wall BT

Am J Physiol Endocrinol Metab, 2021 Nov 1, 321(5): E674-E688

<https://doi.org/10.1152/ajpendo.00294.2021> | PMID: 34632796 | PMCID: PMC8791791

Citations: | AltScore: 19.1

28. **Mobility and Self-Care are Associated With Discharge to Community After Home Health for People With Dementia.**

Knox S, Downer B, Haas A, Ottenbacher KJ

J Am Med Dir Assoc, 2021 Jan 19, 22(7): 1493-1499.e1

pii: S1525-8610(20)31064-1. <https://doi.org/10.1016/j.jamda.2020.12.014> | PMID: 33476569

| PMCID: PMC8496773

Citations: | AltScore: 0.25

29. **Overdose deaths from nonprescribed prescription opioids, heroin, and other synthetic opioids in Medicare beneficiaries.**

Kuo YF, Baillargeon J, Raji MA

J Subst Abuse Treat, 2021 May, 124: 108282

<https://doi.org/10.1016/j.jsat.2021.108282> | PMID: 33771281 | PMCID: PMC8004556

Citations: 3 | AltScore: 0.5

30. **Functional Status Across Post-Acute Settings is Associated With 30-Day and 90-Day Hospital Readmissions.**

Li CY, Haas A, Pritchard KT, Karmarkar A, Kuo YF, Hreha K, Ottenbacher KJ

J Am Med Dir Assoc, 2021 Dec, 22(12): 2447-2453.e5

<https://doi.org/10.1016/j.jamda.2021.07.039> | PMID: 34473961 | PMCID: PMC8627458

Citations: | AltScore: 0.25

- 31. A Cohort Study of Anticholinergic Medication Burden and Incident Dementia and Stroke in Older Adults.**
Lockery JE, Broder JC, Ryan J, Stewart AC, Woods RL, Chong TT, Cloud GC, Murray A, Rigby JD, Shah R, Storey E, Ward SA, Wolfe R, Reid CM, Collyer TA, Ernst ME, ASPREE Investigator Group, ASPREE Investigator Group listed on www.aspree.org.
J Gen Intern Med, 2021 Mar 22, 36(6): 1629-1637
<https://doi.org/10.1007/s11606-020-06550-2> | PMID: 33754317 | PMCID: PMC8175463
Citations: 4 | AltScore: 16.55
- 32. Trends and variation in benzodiazepine use in nursing homes in the USA.**
Malagaris L, Mehta HB, Goodwin JS
Eur J Clin Pharmacol, 2021 Nov 2, 78(3): 489-496
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Citations: | AltScore: 1
- 33. Racial and ethnic differences in the improvement in daily activities during a nursing home stay.**
Mathuba W, Deer R, Downer B
J Am Geriatr Soc, 2021 Dec 9, 70(4): 1244-1251
<https://doi.org/10.1111/jgs.17600> | PMID: 34882305 | PMCID: PMC8986583
Citations: | AltScore: 22.55
- 34. Effect of Aspirin on Cancer Incidence and Mortality in Older Adults.**
McNeil JJ, Gibbs P, Orchard SG, Lockery JE, Bernstein WB, Cao Y, Ford L, Haydon A, Kirpach B, Macrae F, McLean C, Millar J, Murray AM, Nelson MR, Polekhina G, Reid CM, Richmond E, Rodr?guez LM, Shah RC, Tie J, Umar A, Londen GJV, Ronaldson K, Wolfe R, Woods RL, Zalcborg J, Chan AT, ASPREE Investigator Group.
J Natl Cancer Inst, 2021 Mar 1, 113(3): 258-265
<https://doi.org/10.1093/jnci/djaa114> | PMID: 32778876 | PMCID: PMC7936068
Citations: 29 | AltScore: 428.64
- 35. Time Trends in Opioid Use by Dementia Severity in Long-Term Care Nursing Home Residents.**
Mehta HB, Kuo YF, Raji M, Li S, Westra J, Goodwin JS
J Am Med Dir Assoc, 2021 Jan, 22(1): 124-131.e1
<https://doi.org/10.1016/j.jamda.2020.04.029> | PMID: 32605815 | PMCID: PMC7765734
Citations: 4 | AltScore: 0.75
- 36. State Variation in Chronic Opioid Use in Long-Term Care Nursing Home Residents.**
Mehta HB, Kuo YF, Raji MA, Westra J, Boyd C, Alexander GC, Goodwin JS
J Am Med Dir Assoc, 2021 Dec, 22(12): 2593-2599.e4
<https://doi.org/10.1016/j.jamda.2021.04.016> | PMID: 34022153 | PMCID: PMC9000974
Citations: | AltScore: 7
- 37. Risk Factors Associated With SARS-CoV-2 Infections, Hospitalization, and Mortality Among US Nursing Home Residents.**
Mehta HB, Li S, Goodwin JS
JAMA Netw Open, 2021 Mar 1, 4(3): e216315
<https://doi.org/10.1001/jamanetworkopen.2021.6315> | PMID: 33787905 | PMCID: PMC8013796
Citations: 26 | AltScore: 101.85
- 38. Gender Differences in Neuropsychiatric Symptoms Among Community-Dwelling Mexican Americans Aged 80 and Older.**
Milani SA, Cantu PA, Berenson AB, Kuo YF, Markides KS, Raji MA

Am J Alzheimers Dis Other Demen, 2021 Jan-Dec, 36: 15333175211042958

<https://doi.org/10.1177/15333175211042958> | PMID: 34565200 | PMCID: PMC8641300

Citations: | AltScore: 6.25

39. **Gender differences in activity-limiting pain trajectories over a 17-year period in the Mexican Health and Aging Study.**

Milani SA, Howrey B, Rodriguez MA, Samper-Ternent R, Wong R

Pain, 2021 Apr 7, 163(2): e285-e292

<https://doi.org/10.1097/j.pain.0000000000002292> | PMID: 33863866 | PMCID: PMC8494819

Citations: 1 | AltScore: 6.7

40. **Trends in the Use of Benzodiazepines, Z-Hypnotics, and Serotonergic Drugs Among US Women and Men Before and During the COVID-19 Pandemic.**

Milani SA, Raji MA, Chen L, Kuo YF

JAMA Netw Open, 2021 Oct 1, 4(10): e2131012

<https://doi.org/10.1001/jamanetworkopen.2021.31012> | PMID: 34694388 | PMCID:

PMC8546497

Citations: 6 | AltScore: 71.63

41. **Health-related quality of life and all-cause mortality among older healthy individuals in Australia and the United States: a prospective cohort study.**

Phyo AZZ, Ryan J, Gonzalez-Chica DA, Woods RL, Reid CM, Nelson MR, Murray AM, Gasevic D, Stocks NP, Freak-Poli R, ASPREE Investigator Group.

Qual Life Res, 2021 Apr, 30(4): 1037-1048

<https://doi.org/10.1007/s11136-020-02723-y> | PMID: 33389487 | PMCID: PMC8005489

Citations: 5 | AltScore: 29.2

42. **Association of Occupational and Physical Therapy With Duration of Prescription Opioid Use After Hip or Knee Arthroplasty: A Retrospective Cohort Study of Medicare Enrollees.**

Pritchard KT, Baillargeon J, Raji MA, Chou LN, Downer B, Kuo YF

Arch Phys Med Rehabil, 2021 Feb 19, 102(7): 1257-1266

pii: S0003-9993(21)00157-X. <https://doi.org/10.1016/j.apmr.2021.01.086> | PMID: 33617862

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Citations: 2 | AltScore: 8.2

43. **Challenges in defining Long COVID: Striking differences across literature, Electronic Health Records, and patient-reported information.**

Rando HM, Bennett TD, Byrd JB, Bramante C, Callahan TJ, Chute CG, Davis HE, Deer R, Gagnier J, Korashy FM, Liu F, McMurry JA, Moffitt RA, Pfaff ER, Reese JT, Relevo R, Robinson PN, Saltz JH, Solomonides A, Sule A, Topaloglu U, Haendel MA

medRxiv, 2021 Mar 26

pii: 2021.03.20.21253896. <https://doi.org/10.1101/2021.03.20.21253896> | PMID: 33791733 |

PMCID: PMC8010765

Citations: | AltScore: 58.5

44. **Cyclooxygenase inhibitor use is associated with increased COVID-19 severity.**

Reese JT, Coleman B, Chan L, Blau H, Callahan TJ, Cappelletti L, Fontana T, Bradwell KR, Harris NL, Casiraghi E, Valentini G, Karlebach G, Deer R, McMurry JA, Haendel MA, Chute CG, Pfaff E, Moffitt R, Spratt H, Singh J, Mungall CJ, Williams AE, Robinson PN

medRxiv, 2021 Apr 20

pii: 2021.04.13.21255438. <https://doi.org/10.1101/2021.04.13.21255438> | PMID: 33907758 |

PMCID: PMC8077581

Citations: | AltScore: 232.64999999999999

45. **Understanding Variation in Postacute Care: Developing Rehabilitation Service Areas Through Geographic Mapping.**
Reistetter TA, Eschbach K, Prochaska J, Jupiter DC, Hong I, Haas AM, Ottenbacher KJ
Am J Phys Med Rehabil, 2021 May 1, 100(5): 465-472
<https://doi.org/10.1097/PHM.0000000000001577> | PMID: 32858537 | PMCID: PMC8262929
Citations: | AltScore: 1
46. **Using the Behaviour Change Wheel Program Planning Model to Design Games for Health: Development Study.**
Robertson MC, Baranowski T, Thompson D, Basen-Engquist KM, Swartz MC, Lyons EJ
JMIR Serious Games, 2021 Dec 3, 9(4): e29964
<https://doi.org/10.2196/29964> | PMID: 34870604 | PMCID: PMC8686484
Citations: 1 | AltScore: 3.2
47. **Factors associated with pain at the end-of-life among older adults in Mexico.**
Samper-Ternent R, Gonzalez-Gonzalez C, Zazueta JD, Wong R
Public Health, 2021 Feb, 191: 68-77
<https://doi.org/10.1016/j.puhe.2020.11.025> | PMID: 33540186 | PMCID: PMC8765468
Citations: | AltScore: 2.85
48. **Primary Language and Participation Outcomes in Hispanics With Traumatic Brain Injury: A Traumatic Brain Injury Model Systems Study.**
Sander AM, Ketchum JM, Lequerica AH, Pappadis MR, Bushnik T, Hammond FM, Sevigny M
J Head Trauma Rehabil, 2021 Feb 22, 36(4): E218-E225
<https://doi.org/10.1097/HTR.0000000000000655> | PMID: 33656477 | PMCID: PMC8249338
Citations: | AltScore: 3.85
49. **Association of co-prescribing of opioid and benzodiazepine substitutes with incident falls and fractures among older adults: a cohort study.**
Shah R, Raji MA, Westra J, Kuo YF
BMJ Open, 2021 Dec 30, 11(12): e052057
<https://doi.org/10.1136/bmjopen-2021-052057> | PMID: 35476819 | PMCID: PMC8719209
Citations: 1 | AltScore: NA
50. **Non-pharmacological sleep interventions for pediatric cancer patients and survivors: a systematic review protocol.**
Stavinoha PL, Olsthoorn IM, Swartz MC, Nowakowski S, Wells SJ, Hicklen RS, Sheikh I, Jang HJ
Syst Rev, 2021 Jun 4, 10(1): 166
<https://doi.org/10.1186/s13643-021-01724-3> | PMID: 34088350 | PMCID: PMC8176735
Citations: 1 | AltScore: 5.33
51. **Association Between Cognitive Status and Falls With and Without Injury During a Skilled Nursing Facility Short Stay.**
Tzeng HM, Downer B, Haas A, Ottenbacher KJ
J Am Med Dir Assoc, 2021 Jul 5, 23(1): 128-132.e2
[pii: S1525-8610\(21\)00575-2. https://doi.org/10.1016/j.jamda.2021.06.017](https://doi.org/10.1016/j.jamda.2021.06.017) | PMID: 34237256
| PMCID: PMC8712356
Citations: | AltScore: 18.95
52. **Neuropsychiatric Symptoms by Cognitive Status for Mexican-Americans Aged 85 and Older.**
Vu LH, Markides KS, Downer B
Gerontol Geriatr Med, 2021 Jan-Dec, 7: 23337214211002724

<https://doi.org/10.1177/23337214211002724> | PMID: 33796630 | PMCID: PMC7983470

Citations: 1 | AltScore: 3.35

53. **Decomposing Differences in Risk-Adjusted Rates of Emergency Department Visits Between Micropolitan and Urban Nursing Homes.**

Xu H, Bowblis JR, Caprio TV, Li Y, Intrator O

J Am Med Dir Assoc, 2021 Dec 16

[pii: S1525-8610\(21\)00987-7. https://doi.org/10.1016/j.jamda.2021.11.017](https://doi.org/10.1016/j.jamda.2021.11.017) | PMID: 34919837

| PMCID: PMC9200897

Citations: | AltScore: 4.45

54. **Changing landscape of nursing homes serving residents with dementia and mental illnesses.**

Xu H, Intrator O, Culakova E, Bowblis JR

Health Serv Res, 2021 Nov 7, 57(3): 505-514

<https://doi.org/10.1111/1475-6773.13908> | PMID: 34747498 | PMCID: PMC9108080

Citations: 1 | AltScore: 5.95

EXTERNAL ADVISORY BOARD MEMBERS

Stephen Kritchevsky, PhD
Wake Forest School of Medicine
Serving since 2011 (11 years)

Thomas M. Gill, MD
Yale School of Medicine
Serving since 2019 (3 years)

Karen Bandeen-Roche, PhD
Johns Hopkins Bloomberg School of Public Health
Serving since 2022 (0 years)

RECOGNITION AND AWARDS (2021-2022)**Blake Rasmussen, PhD (2021)**

- Texas American College of Sports Medicine Honor Award

Chih-Ying (Cynthia) Li, PhD, OTR (2021)

- AOTF Early Career Research Excellence Award

Elizabeth J. Lyons, PhD (2021)

- Member of the Health Promotion in Communities Study Section, Center for Scientific Review (2021-2025)
- Grace Bucksch Gnitzinger Distinguished Professorship in Aging (2019)

Heidi Spratt, PhD (2021)

- Distinguished Faculty Award (Graduate School of Biomedical Sciences)

Huiwen Xu, PhD, MHA (2021)

- Best Abstract Award, China Health Policy and Management Society 2021 Annual Symposium

Monique Pappadis, PhD, MEd (2021)

- American Congress of Rehabilitation Medicine (ACRM) Early Career Outstanding Mentor Award (2021)
- Elite Reviewer for the Archives of Physical Medicine and Rehabilitation (2020)
- Dr. Suzanne Kneuper Linder Research Award in Excellence in Patient-Centered Outcomes Research (2019)

Monique Pappadis, PhD, MEd (2022)

- Elite Reviewer – Archives of Physical Medicine and Rehabilitation (2021)

Monique Pappadis, PhD, MEd (2021)

- NIH-NIMHD Loan Repayment Program Award

Monique Pappadis, PhD, MEd (2021)

- Career Development Networking Group's 2021 Outstanding Mentor Award - American Congress of Rehabilitation Medicine

Rafael Samper-Ternent, MD, PhD (2022)

- Maribel Sanchez Ayala Award from the Latin American Academy of Geriatric Medicine

Rafael Samper-Ternent, MD, PhD (2022)

- MCC Scholar - HCSRN-OAICs Aging Initiative

Rafael Samper-Ternent, MD, PhD (2021)

- Butler-Williams Scholar - National Institute on Aging

Rebeca Wong, PhD (2021)

- Member of NIH Working Group of the Council on Behavioral & Social Sciences Research (BSSR) Integration (2021)
- NICHD Advisory Council Member

Sadaf Milani, PhD (2022)

- Early Career Investigator Award from the Diversity and Disparities Professional Interest Area - International Society to Advance Alzheimer's Research and Treatment

Soham Al Snih, MD, PhD (2021)

- Distinguished Teacher Award (Graduate Student Organization)

Xiaoying Yu, PhD (2021)

- 2nd place - Steve Wallace Poster Award; 2021 International Conference on Aging in the Americas (ICAA)

MINORITY RESEARCH

General Brief Description of Minority Activities:

Research (Pilot Projects):

The role of urological factors, testosterone deficiency and testosterone therapy prescription in the risk of mortality among U.S. Hispanic men

Investigators: David S. Lopez, DrPH, MS, MPH

Mentors: Drs. Kyriakos Markides and Jacques Baillargeon

Racial and ethnic differences in mortality rates, including cardiovascular and cancer-specific, remains a public health concern in the United States. Similar disparities are reported for the incidence of those cancers related to obesity such as kidney, bladder and prostate cancer (herein we use the term obesity-related cancers). Disparities on obesity-related cancers are suggested to be due, in part, to the high prevalence of obesity, diabetes and metabolic syndrome in minority populations. The Non-Hispanic Black and Hispanic population are disproportionately affected by rates of mortality (all-cause, cardiovascular and cancer-specific) and incidence of obesity-related cancers. There is a paucity of research about the role of lifestyle (e.g. diet, obesity), epidemiological and clinical factors in the risk of mortality (all-cause, cardiovascular and cancer-specific) and incidence of obesity-related cancers in minority populations. The public health significance of this investigation is that we will address these research gaps in non-Hispanic White (NHW), non-Hispanic Black (NHB) and Hispanic men.

Specific Aims: 1) To determine prospective associations between T deficiency and all-cause, cardiovascular, cancer-specific mortality among Hispanic adult men aged 40+ in the NHANES. We will also explore interrelations of T deficiency, obesity, urological and dietary factors with all-cause, cardiovascular and cancer-specific mortality. 2) To investigate prospective associations of T therapy with risk of obesity-related cancers (prostate, bladder and kidney) and cancer-specific mortality among Hispanic adult men aged 65+ in the SEER Medicare.

Disparities in Non-Cancer Pain, Use of Opioids and Health Outcomes for Older Adults in the United States

Investigator: Sapna Kaul, PhD

Mentors: Drs. Yong-Fang Kuo and Mukaila Raji

Background: About 20% of the U.S. adult population reports chronic pain. In 2016, 14.4 million Medicare Part D beneficiaries received opioids, 5 million used opioids for ≥ 3 months, and over 500,000 non-cancer and non-Hospice beneficiaries used opioids that exceeded the recommended doses. Yet, because of negative stereotyping and lower access to health care, older adults belonging to racial and ethnic minority groups may be less likely to receive pain management via opioids compared with non-Hispanic whites. Further, these disparities may have consequences for pain management and related health outcomes.

Specific Aims: To examine race and ethnicity-related disparities in non-cancer pain, opioid use and resulting-health outcomes among a nationally representative sample of older adults in the U.S. Our aims include: (1) examine self-reported pain and opioid use among older adults and determine disparities for Hispanics and non-Hispanic blacks compared with non-Hispanic whites, and (2) identify if patient outcomes (ADLs, general physical and mental health, pain) are associated with

opioid use and race and ethnicity.

Household composition and cognitive change among older adults in Mexico Investigator: Jacqueline Torres, PhD

Mentors: Drs. Rebeca Wong and Kyriakos Markides

Background: As the burden of Alzheimer's disease and related dementias (ADRDs) increases worldwide, there is growing interest in identifying key population-level drivers of cognitive outcomes in global settings, including social and family-level determinants of cognitive aging. However, research on the social determinants of cognitive aging in high-income countries often focuses on the effects of social factors like living alone or social isolation, which typically have low prevalence in low and middle-income country (LMIC) settings. Other features of social and family life may serve as important drivers of cognitive outcomes global settings. For example, while older adults in LMICs exhibit high overall prevalence of co-residence, including with adult children, there may be changes in the underlying composition of the household due to the internal or international out-migration of adult children and residential moves among older adults themselves (e.g. to the home of an adult child). These changes may influence cognitive outcomes by adversely impacting the availability of social interaction and support for older adults and by contributing to greater risk for health conditions (e.g. depression). Conversely, changes in household composition may have positive impacts on cognitive outcomes by contributing to increased opportunity for social interaction and improvements in health conditions that may contribute to cognitive function.

Specific Aims: 1. Evaluate the feasibility of constructing meaningful variables to capture the change in household composition over time, including respondent and family-member moves in mid to late-life. 2. Examine the effect of changes in household composition on cognitive decline for older respondents.

Publications:

Garcia MA, Downer B, Chiu CT, Saenz JL, Rote S, Wong R. (2019) Racial/Ethnic and Nativity Differences in Cognitive Life Expectancies Among Older Adults in the United States. *Gerontologist*, 59(2), 281-289. doi: 10.1093/geront/gnx142. PMID: 28958071 / PMCID: PMC6417765

Downer, B., Al Snih, S., Raji, M., Chou, L. N., Kuo, Y. F., Markides, K. S., & Ottenbacher, K. J. (2020). Healthcare utilization of Mexican-American Medicare beneficiaries with and without Alzheimer's disease and related dementias. *PloS one*, 15(1), e0227681. doi:10.1371/journal.pone.0227681

Downer, B., Milani, S., & Wong, R. The Sequence of Physical and Cognitive Impairment and the Association with Mortality among Unimpaired Older Mexican Adults (2019). *Journal of Gerontology: Medical Sciences*, 75(7), 1386-1392. doi:10.1093/gerona/glz238

Downer, B., Al Snih, S., Chou, L. N., Kuo, Y. F., Markides, K. S., & Ottenbacher, K. J. (2019). Differences in hospitalizations, emergency room admissions, and outpatient visits among Mexican-American Medicare beneficiaries. *BMC geriatrics*, 19(1), 136. doi:10.1186/s12877-019-1160-9.

Milani, SA, Marsiske, M, Striley, CW. (2019). Discriminative ability of Montreal Cognitive Assessment subtests and items in racial and ethnic minority groups. *Alzheimer Dis Assoc Disord.* 2019;33(3):226-232. <https://doi.org/10.1097/WAD.0000000000000310>. PMID: 31058685; PMCID: PMC6710139 [Available on 2020-07-01]

Downer, B, Milani, SA, Wong, R. (2019). The Sequence of Physical and Cognitive Impairment and the Association with Mortality among Unimpaired Older Mexican Adults. *Journal of Gerontology: Medical Sciences.* 2020;75(7):1386-1392. PMID: 31639186. PMCID: PMC7302177

Other:

Rafael Samper-Ternent, MD PhD - Dissertation Committee member for Jacob Moran in the MD/PhD program at UTMB. Title of Dissertation "The Roles of Estate Planning and Social Support in Racial/Ethnic Disparities in Advance Care Planning and End-of-Life Care"

Rafael Samper-Ternent, MD PhD - K08 submitted to NIA and received score of 37. Title of proposal "Caring for a spouse with dementia: the well-being of Hispanic caregivers". The proposal compares Hispanic caregivers to non-Hispanics. Awaiting comments.

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 diabetes, 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.

Minority Grant(s):

WAKE FOREST UNIVERSITY SCHOOL OF MEDICINE

Claude D. Pepper Older Americans Independence Center

Stephen Kritchevsky, Ph.D.
Principal Investigator

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Dalane Kitzman, MD
Co-Principal Investigator

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Kimberly Kennedy, MS, CCRC
Program Administrator

336-713-8567

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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 5 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 Usuh, 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 jdjing@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 llechik@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
<p>Lindsay Reynolds, PhD Assistant Professor / Department of Epidemiology and Prevention <u>Dietary Patterns and Biological Aging in the Women's Health Initiative</u></p>	2022-2024 / 0 (total) 0 (1st/Sr)
<p>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></p>	2022-2024 / 0 (total) 0 (1st/Sr)
<p>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></p>	2022-2024 / 0 (total) 0 (1st/Sr)
<p>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></p> <ul style="list-style-type: none"> • Wake Forest Pepper Pilot award: Monkeys, muscle, and mobility: a multi-omic approach to understanding the biology of muscle aging (1/22 – 12/22) 	2021-2023 / 0 (total) 0 (1st/Sr)
<p>Atalie Thompson, MD, MPH Assistant Professor / Department of Ophthalmology, Section on Glaucoma <u>Exploring visual impairment and physical dysfunction in older adults</u></p>	2021-2023 / 0 (total) 0 (1st/Sr)

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 (8 Pilot Projects Listed)

1. Project Title: **PESC 2018.1 Evaluation of Blood-Based Biomarkers of Biological Aging in Heart Failure with preserved Ejection Fraction (HFpEF).**

Leader: Jamie Justice, PhD (Geriatrics)

A new generation of clinical trials is being designed to test the Geroscience Hypothesis: that targeting the biology of aging will help maintain function and prevent or delay the onset of age-related chronic diseases, including heart failure with preserved ejection fraction (HFpEF). Biomarkers serve critical roles in clinical trials as surrogate endpoints and by providing evidence that the intervention is appropriately influencing the underlying biology. A utility set of blood-based biomarkers of aging for use in geroscience-guided clinical trials targeting incidence of age-related chronic disease and death has been identified, and includes IL-6, CRP, TNF-Receptor II, GDF15, IGF-1, Insulin, Cystatin C, NT-proBNP, and HbA1c. However, this biomarker set has not yet been tested; this limits development, analysis, and clinical trial planning. Further, no study has examined the intervention effects on broad multi-system biomarkers of biological aging in HFpEF. Such an investigation could provide insights into potential mechanisms and future therapeutic targets in HFpEF while providing crucial evaluation of blood-based biomarkers proposed for clinical trials targeting biological aging.

The research aims of this Pepper Pilot are to 1) measure differences in biomarkers of biological aging in HFpEF patients compared with age-similar healthy adults; 2) determine if the biomarkers of biological aging are associated with physical and cardiovascular function, adjusting for age, sex, adiposity; 3) estimate changes in biomarkers of biological aging over time (controls) and following a diet and exercise intervention in overweight and obese adults with HFpEF. The research aims will leverage a specimen repository from the WFSM Aging Center: de-identified patient records and cryopreserved samples in HFpEF patients previously enrolled in SECRET (100 at baseline, 76 at follow-up), and 64 adults in the Healthy Aging cross-sectional cohort. Well-justified biomarkers of biological aging (IL-6, TNFa-Receptor II, CRP, GDF15, insulin, IGF1, cystatin-C, NT-proBNP, and HbA1c) will be measured. In conjunction with this we have organized a Pepper OAIC Biomarkers Working Group that cuts across multiple Wake Forest OAIC cores to evaluate study progress, inform rigorous measurements, balance resource use, develop an analytic approaches and biomarker indices, and offer scientific consultation and engagement of local studies involving biomarkers of biological aging.

We leveraged the WF OAIC biorepository to measure a consensus-derived panel of blood-based biomarkers of aging and constructed a geroscience-guided biomarker index (TAME-BI) for the first time in a clinical trial. We measured IL-6, TNF-a-receptor-I, growth differentiating factor-15, cystatin C, and N-terminal pro-b-type natriuretic peptide in a 20-week randomized trial of caloric restriction (CR), aerobic exercise (EX), CR+EX, or attention-control in 88 patients (67 ± 5 years) with heart failure with preserved ejection fraction (HFpEF). We calculated TAME-BI (analyte levels ranked, binned by quintile, and summed) and found a time \times treatment interaction for improved TAME-BI with intervention ($p=0.05$) and detected associations between change in TAME-BI and change in six-minute walk distance ($r=-0.24$), usual walk speed ($r=-0.23$), and left ventricular relative wall thickness ($r=0.31$). In sum, CR+EX intervention improves TAME-BI and changes in TAME-BI are associated with changes in functional measures in older HFpEF patients.

2. Project Title: PESC.2019.1 Isolation and molecular characterization of exosomes secreted by visceral adipose tissue.**Leader: Gagan Deep, PhD (Cancer Biology)**

The goal of this project is to isolate and characterize visceral adipose tissue (VAT) specific exosomes based on their unique surface markers from blood plasma/serum. Dr. Deep's laboratory has developed novel techniques and tools to identify tissue specific exosomes, and these established methods will be used to identify VAT-specific exosomes as outlined in following specific aims: Specific Aim I. To identify unique proteins on the surface of exosomes isolated from visceral adipose tissue in mouse and nonhuman primate (NHP) models. Specific Aim II. To isolate and characterize VAT-derived exosomes (VATExo) from blood in mouse and NHP models. Specific Aim III. To isolate and characterize VATExo from the blood of NHP and humans. The long term objective is to develop blood based VAT-specific exosomal biomarkers to allow noninvasive evaluation of visceral adipose tissue depot to provide novel molecular insights into the biology of this important tissue as well as help us to better understand VAT's role in various diseases. The successful identification of VAT-derived exosomes from this study will be used as proof of concept for major NIH grants where we will functionally characterize the VAT exosomes in more detail for their "cargo" (including protein, lipids, metabolites, mRNA and miRNA) in order to explore relationships with physical function, frailty, heart failure with preserved ejection fraction, and other phenotypes as well as responses to exercise, diet modification, and other interventions. Novel methods have been developed that will be useful for several studies.

3. Project Title: PESC.2019.2 Is Restoring Protein Homeostasis A Viable Therapy For Age-Related Osteoarthritis?**Leader: Raghunatha Yammani, PhD (Internal Medicine, Molecular Medicine)**

This Pepper pilot's overall goal is to determine the role of proteostasis in age-related OA. To achieve our aim, we will administer a small molecule chemical chaperone 4-phenyl butyric acid (PBA) to 18 months -old mice to restore proteostasis and examine age-linked severity osteoarthritis. There was a delay in starting the project on time due to COVID 19 related shut down of research activities. Yet, good progress has been made in accomplishing the goals described in the pilot application. Eighteen months old (10 male and 10 female) C57BL6 mice were divided into two groups. Group 1 mice receive (0.5mg/kg body) of phenyl butyric acid (PBA) in drinking water, and Group 2 mice received just water. We plan to administer PBA to mice for 20 weeks and collect their knee joint and analyze for cartilage lesion and OA. We also plan to collect tissues other than knee joints, including heart, lung, brain, liver, and blood from mice for tissue bank available to other investigators. Mice on the PBA showed decreased cartilage lesions and improved matrix production compared to the untreated group, evidenced by the ACS score and SafarinO staining. qPCR analysis showed that treatment with decreased mRNA expression of CHOP, an ER stress marker, and pro-apoptotic molecule and increased expression of ATG5, a key component of autophagy system. Additionally, PBA also modulated the gut microbiomes including increased microbiome diversity indices and phylogenetic abundance of beneficial bacteria. These results demonstrate that ER stress plays a significant role in primary OA, and PBA reduces OA by reducing ER stress and beneficially modulating the microbiome. This study demonstrates that alleviating ER stress improved autophagy, matrix production, and decreased cartilage lesions in aged mice. Treatment with PBA also beneficially modulated the microbiome. Taken together, our study demonstrated that targeting ER stress

could be a therapeutic approach for primary OA. This data has been submitted as an abstract to international scientific meeting (OARSI 2022, Berlin, Germany). Additionally, we are planning to submit our finding to the journal of Osteoarthritis and cartilage.

4. 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 D3Cr muscle 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 D3Cr muscle 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).

5. Project Title: PESC.2020.2 Development of a Nonhuman Primate Model of Age-Related Sleep Changes & Physical Decline

Leader: Carol Shively, PhD, Brett Frye, (Pathology/Comparative Medicine, Primate Center)

Physical decline, poor sleep, and social isolation are characteristics of many older Americans, and these conditions are linked to increased morbidity and mortality. While associations are observed between all three, whether they have causal relationships is poorly understood. Poor sleep and physical decline have been associated in several cross sectional studies, whereas prospective/longitudinal studies are rare and often based on self-reports of sleep quality. Social isolation predicts poor sleep, but recent evidence suggests that disrupted sleep may lead to social withdrawal. Increasing evidence also suggests that social isolation may result in physical decline, but loss of physical function also may be socially isolating. Given the potential negative impacts of poor sleep, social isolation and physical decline on the health of older adults, longitudinal studies using objective, physiologic data are needed to understand the relationships between these variables. Unfortunately, it is difficult and expensive to characterize these variables in longitudinal clinical studies. Preclinical translational studies enable comprehensive phenotyping repeatedly across the life course. This application addresses important gaps in knowledge by investigating the relationships between social isolation, sleep quality, and physical function (i.e., gait speed, strength, activity) in a prospective longitudinal study of 25 vervets (*Chlorocebus aethiops sabaeus*) which range in age from middle-age to end of life. These nonhuman primates (NHPs) recapitulate many aging-related neurocognitive and physical declines and, unlike rodents, exhibit sleep/wake patterns that closely resemble those of humans. In addition to measures of physical function, we will develop a NHP Frailty Index based on the Fried Model of Frailty (i.e., weight loss, muscle strength, physical activity, and

gait speed). We will accomplish our goals by leveraging a currently available dataset (one-time measures of sleep and social integration, plus annual physical function and frailty measurements), and add new longitudinal measurements of sleep, social integration, and physical performance to allow assessment of change with aging. Overall, we hypothesize that decline in any one of these domains may result in decrements in the other two domains which ultimately results in loss of the ability for independent living. The primary goals of this project is to establish the feasibility of a longitudinal study to determine the nature of the relationships between poor sleep, social isolation, and physical function, and generate key data necessary to support extramural grant applications to understand the biological mechanisms linking poor sleep to social and physical impairment. Characterization of these relationships will identify targets for intervention to prolong health span and independent living into advanced age.

Overall, we have successfully recorded ECG, 24-hour activity, metrics of NHP frailty, and social behavior using the proposed in this application. We were unable to determine sleep stages using the proposed methodology. Data organization and analyses are ongoing. We successfully recorded ECGs and 24 hour heart rates in N=20 female vervet monkeys (9-29 years of age). In addition to measures of heart rates, measured as successive inter beat intervals (R-R intervals), we have collaborated with Dr. Hossam Shaltout (Obstetrics and Gynecology, Wake Forest School of Medicine) to determine several measures of heart-rate variability (HRV) including: (1) the standard deviation of successive IBIs (SDNN), (2) the root-mean square of successive differences (RMSSD), (3) very low frequency (VLF) power, (4) low frequency (LF) power, (5) high frequency (HF) power, and (6) the LF/HF ratio. We are currently determining to what degree age is associated with changes in HRV in the aging vervet monkey. These data are relevant to the goals of the WF Pepper OAIC PESC, as impaired cardiac autonomic control (indicated by HRV) may predict cardiovascular risk, frailty, and all-cause mortality in aging human populations. Activity levels were recorded continuously for 24-hour bouts in the same N=20 animals. These measures will contribute to our construction of a NHP index of frailty (see below). We have also measured normal gait speed in the population.

Development of a NHP Frailty Index: We have successfully collected most of the data necessary to develop a NHP index of frailty, including (1) time spent hanging from the sides of the chain link enclosure with all four feet off the ground (measure of weakness), (2) gait speed, and (3) 24-hour activity levels. We are in the process of conducting bi-annual assessments of weight to determine patterns in unintentional weight loss. We are now poised to generate the frailty index and subsequently test the index's utility in predicting morbidity and mortality. Specifically, morbidity will be based on clinical diagnoses gathered from the NHP electronic medical records (EMR) in CARS (Computerized Animal Record System), and mortality will be characterized as animals becoming sick or reach end of life over the next months and years.

Social Behavior: We have successfully collected data of social integration for the aging vervet cohort. Analyses are ongoing to determine the relationship between age and social isolation. Moreover, we are in the process of analyzing data to determine whether social integration predicts declines in physical function or vice versa. Additionally, given that several of aging vervets have reached their end of natural life (N=), our comprehensive, integrative approach will enable us to determine the utility of the experimental variables in predicting all-causes mortality. We have yet to accurately determined sleep stages - awake, rapid-eye-movement sleep (REM), and non-REM) in the NHPs using our proposed analytic approach (machine learning from combined actigraphy and heart rate telemetry). Thus, our determination of sleep is limited to distinguishing wakefulness from resting via actigraphy alone.

6. 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: 38 participants have completed baseline insole assessment: 26 of those have been randomized, 15 participants have completed at-home wear, and 5 have completed follow up assessment. Limb loading metrics (cumulative loading, loading rate, peak loading) are being processed and analyzed as data collection is on-going. Subject specific FE models of the dominant leg for all randomized subjects (n=26) have been generated. Work is underway to determine how insole loading correlates to loading at the mid-femur to define a translation value for appropriate application of the insole forces to the isolated femoral FE model. This test will be performed with a well-validated full human body FE model in loading phase, midstance, and terminal stance.

7. 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 detectable 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 predictive 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.

8. 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.

DEVELOPMENT PROJECTS (2 Development Projects Listed)**1. Project Title: Development of Automated Approaches to Obtaining Age-Related Body Composition Phenotypes from Routine Computed Tomography (CT) Examinations****Leader: Leon Lenchik, MD****Core(s):** Pilot and Exploratory Studies Core (PESC)
BioImaging (BioImaging)

This project aims to develop automated approaches to CT segmentation of muscle using machine learning methods. The long-term objective is to create a widely available, automated image analysis algorithm, which will extract measures of body composition and structure from clinical image repositories in data warehouses and hospital-based image archive systems. These analyses could identify predictors of age-related decline in physical performance across multiple hospital health-care delivery systems. This project resulted in a successful R21 application, (funding to begin in 7/21) This study received ancillary funding to support acquiring CTs in the SOMMA study so this automation can be incorporated into the analyses of these scans. This project has led to 2 peer-reviewed publications and an R21 application to MrOS, Novel Computed Tomography (CT) Imaging Biomarkers in Older Men for Predicting Adverse Geriatric Health Outcomes.

2. Project Title: Novel Big Data Processing Algorithms and Summary Metrics to Enhance our Understanding of Health and Mobility (PepperMINT)**Leader: Michael E Miller, PhD; W. Jack Rejeski, PhD, Jason Fanning, PhD, Shyh-Huei Chen, PhD****Core(s):** Clinical Research Core (CRC)
Biostatistical Design and Analysis Core (BIC)

An important step in advancing accelerometry lies in first cross-calibrate core monitoring devices using direct observation in order to leverage data produced in existing datasets derived from large multisite trials (e.g., Look AHEAD; LIFE). Once complete, these data can be used to generate sophisticated metrics that better capture both amount and variability in sedentary and physical activity behaviors. Eligible participants will be older adults (aged = 65) who are overweight or obese (BMI=30-45 kg/m²), and low-active (i.e., engaging in less than 2 days/wk of structured physical activity for at least 20 minutes). We will aim to recruit an even number of males and females (i.e., 15 each) and within each sex, we will aim to recruit at least 7 individuals with a short physical performance battery (SPPB) score >9, and at least 7 with an SPPB score = 9. Excluded individuals will be unable to walk without assistive devices or will have cognitive impairment as indicated by a Montreal Cognitive Assessment score of less than 22. This study consists of two phases. During the first phase, a sample of low-active older adults (N = 30) will be guided through a series of 13 tasks while wearing two Actigraph accelerometers, one ActivPAL, one Fitbit, and one RT3. The main purpose of this phase is to identify how each monitor captures movement at low, moderate, and vigorous intensities, sitting and lying still, and transitioning for sitting to standing. Additional activities of daily living (e.g., folding laundry, sweeping) will be included to assess the potential influence of these tasks on the accelerometer data. Participants will spend one week wearing the monitors, and then return to repeat the task list. Following completion of this period, the analytic team (Miller, Chen) will utilize the data to identify effective means of devices calibration using

metrics such as cadence (steps/minute) or energy expenditure (MET/h). This study has completed and data analysis is underway.

RESEARCH (8 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 an independent investigator who can advance interventions that extend healthy lifespan to randomized, controlled trials in older persons. Specifically, cellular senescence is a biologic hallmark of aging that emerging preclinical evidence indicates could have profound consequences on aging-related disease and function, and removal of senescent cells results in robust improvements in healthspan in rodents. Translation of these interventions to clinical trial has been proposed, yet health consequences of cell senescence and therapeutic potential has not been evaluated in humans. Dr. Justice's preliminary data in a small number of older women are the first to show that cells expressing tumor suppressor protein and senescence biomarker p16INK4a are present in adipose tissue from older adults and related to worse physical function, but exercise and weight loss by caloric restriction may mitigate this burden. The proposed research project represents a critical next step by examining 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 reduction will be related to improvement in functional and metabolic outcomes. This will be accomplished by capitalizing on a recent NIH-funded RCT (VEGGIE, R01DK103531) and the candidate's engaged inter-disciplinary primary mentoring team (Drs. Nicklas, Ding, Kritchevsky, Kirkland). VEGGIE will determine the effects of CR designed to achieve 10% weight loss vs. health education control in 200 men and women aged 40-65 years with obesity (BMI 30-45 kg/m²), to characterize epigenetic and transcriptomic effects of CR in adipocytes and peripheral blood monocytes and T cells, and associations with physical and metabolic function. We propose an ancillary investigation in a subset of 90 participants (50-65 years, n=45 per group) to determine the effects of CR on senescent cell burden (Aim 1): a) proportion of p16INK4a expressing senescent cells (immunohistochemistry) in subcutaneous abdominal adipose tissue; b) expression of senescence biomarkers in isolated adipocytes and monocytes (RNAseq) and T cells (p16INK4a expression); and c) SASP biomarkers in plasma (cytokine/chemokine panel). We will also examine cross-sectional associations of age and obesity with cell senescence (Aim 2), and relationships between changes in senescence biomarkers and physical function and metabolic outcomes (Aim 3). The research proposed is aligned with an approved NIA concept to develop markers of aging-related biologic mechanisms for human studies. Additionally, it will provide essential training for the candidate, who will establish expertise in cell senescence and translational research, and develop competencies in leading clinical trials with biological outcomes. This approach provides the ideal platform to advance the candidate's career as an independent investigator, and provide the foundation to establish the role of cell senescence in human age-related functional decline.

2. Project Title: IDENTIFYING FRAILITY IN PRIMARY CARE: IMPLEMENTATION OF AN ELECTRONIC MEDICAL RECORD-BASED FRAILITY 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 an independent 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 with negative outcomes, including hospitalizations, mobility disability, admission to skilled nursing facilities, and mortality. Despite efforts to define and quantify frailty, time and resource constraints limit the feasibility of frailty measures in clinical practice. Dr. Callahan's preliminary work supports the feasibility of translating an EMR-based Frailty Index, or eFI into the Wake Forest Baptist Health (WFBH) EMR, and demonstrates an initial association between eFI score and hospitalizations and mortality. The proposed research project represents critical next steps: (1) to adapt and refine the eFI using ambulatory care data, (2) assess its predictive value for healthcare 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 data regarding feasibility, acceptability, and effectiveness. The scientific goal is to develop and implement an index to 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 and costly health outcomes for frail older adults. We hypothesize that self-report and functional data from Annual Wellness Visits (AWVs) in the EMR will further refine the predictive value of the eFI; and that implementation of the eFI will be feasible and acceptable. This project is supported by engaged mentors (Drs. Williamson and Boustani) 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 adaptation and 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 this population. We will then conduct a pilot study implementing the adapted eFI score in six MSSP/Next Gen ACO primary care practices, and follow health outcomes. The research proposed aligns with an NIA priority to improve the health, well-being, and independence of adults as they age. It will also provide essential training for 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 to advance the candidate's career as an independent investigator and provides the foundation to establish frailty metrics in practice, leveraging the learning health system to implement interventions to improve health and function.

3. Project Title: BRAIN NETWORKS AND MOBILITY FUNCTION: B-NET
Leader(s): KRITCHEVSKY, STEPHEN B.; LAURIENTI, PAUL ;
WAKE FOREST UNIVERSITY HEALTH SCIENCES
NIH R01AG052419 / (2017 - 2022)

Core(s):

- Leadership and Administrative Core (LAC)
- Clinical Research Core (CRC)
- BioImaging (BioImaging)
- Biostatistical Design and Analysis Core (BIC)

Project Summary/Abstract Declining mobility function is a common age-related phenomenon that is associated with reduced quality of life and high societal costs. Recently, the brain's critical role in mobility function has been recognized using imaging approaches assessing white matter characteristics. A new paradigm considering the brain as a complex network uses MRI to directly characterize the brain as a functional network. Brain Networks and Mobility Function: B-NET brings together national leaders in brain network science, neurology and mobility assessment to apply this innovative network paradigm to elucidate the aging brain's role in declining mobility. We propose that functional connectivity within and between the sensorimotor cortex -- community structure (SMC-CS) -- predicts declining mobility; and that SMC-CS will be associated with mobility independent of known relationships between white matter integrity and mobility function. B-Net will establish a cohort of 240 community-dwelling older adults (age range 70-85) and measure mobility function at baseline, 6, 18 and 30 months using the extended short physical performance battery (eSPPB). The MRI will be repeated at 30 months. B-Net's specific aims are to: Specific Aim 1. Determine the baseline association between SMC-CS and eSPPB score. We hypothesize that SMC-CS will be associated with eSPPB performance independent of known correlates of mobility function and white matter integrity (i.e. fractional anisotropy and white matter lesions). Specific Aim 2. Determine whether baseline SMC-CS predicts mobility decline. We hypothesize that poorer baseline SMC-CS will predict declining eSPPB scores after accounting for known correlates of mobility impairment including white matter integrity, cardiovascular fitness, and muscle strength. Specific Aim 3. Repeat brain MRI imaging to determine the longitudinal association between changes in SMC-CS and changes in eSPPB score. We hypothesize that longitudinal declines in SMC-CS will be significantly associated with declining eSPPB performance independent of known correlates of lower extremity function decline and white matter integrity. B-NET tests a novel emerging paradigm regarding the CNS's role in age-related functional decline to support the development of innovative strategies to sustain mobility function in older adults, a critical public health need.

4. Project Title: LONG-TERM FUNCTION AND HEALTH EFFECTS OF INTENTIONAL WEIGHT LOSS IN OBESE ELDERS
Leader(s): HOUSTON, DENISE KATHRYN
WAKE FOREST UNIVERSITY HEALTH SCIENCES
NIH R01AG056418 / (2017 - 2022)

- Core(s):**
- Clinical Research Core (CRC)
 - BioImaging (BioImaging)
 - Biostatistical Design and Analysis Core (BIC)
 - Integrative Biology Core (Integrative Biology Core)

Project Summary/Abstract Obesity exacerbates age-related declines in function, is a strong determinant of mobility disability, and is associated with poorer clinical outcomes and quality of life. Given that over one-third of older adults are obese and the public health burden of age-related disability, identifying effective therapies that prevent obesity-related declines in function and health in older adults are urgently needed. Clinical trials by our group and others show that diet-induced weight loss interventions, particularly when combined with exercise, improve body composition and physical and metabolic function over the short-term (in the weight-reduced state) in obese older adults. However, the overall safety and long-term benefits of intentional weight loss in this population remain controversial and weight loss is often not recommended because of uncertainty of whether the benefits outweigh the risks (e.g., loss of muscle mass and bone). Furthermore, most individuals are not successful at long-term maintenance of weight loss. Thus, whether improvements in physical and metabolic function and other health parameters persist over time among older adults following intentional weight loss, particularly if weight regain occurs, is unknown. The overall goals of the proposed study are to determine if the short-term benefits of intentional weight loss on physical and metabolic function are sustained and to examine potential long-term benefits and risks of weight loss in older adults. We will determine the effects of randomization to diet-induced weight loss on physical function (primary outcome), body composition, bone mineral density, and cardiovascular risk factors (secondary aims) a minimum of 3 and a maximum of 10 years after intervention completion. Our general hypothesis is that randomization to weight loss will result in improved long-term physical and metabolic function compared to randomization to no weight loss. We will take advantage of our unique access to five NIH-supported randomized, controlled trials that enrolled overweight or obese (BMI=27kg/m²) older adults (mean age at randomization, 67.3 years) and randomized them to weight loss plus exercise (n=458) or exercise alone (n=396) at Wake Forest from 2005 to 2014, the pooling of which will provide sufficient sample size to definitively evaluate the long-term functional and health consequences of prior intentional weight loss. We will also explore the long-term effects of randomization to weight loss on quality of life (SF-36), obesity- and weight loss-related medical events (e.g., knee replacements, fractures, MI), hospitalizations, and mortality; and assess the role of current behaviors (e.g., dietary intake, physical activity) on weight loss maintenance, physical function, body composition, and cardiovascular risk factors. The proposed study will be the first randomized, controlled design to examine the long-term effects of intentional weight loss in older adults and builds on our Aging Center's collaborative research focus in geriatric obesity treatment to answer compelling and clinically important questions regarding the long-term efficacy and safety of weight loss interventions in older adults in an efficient and cost-effective manner.

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 SUMMARY Old age and obesity are prevalent risk factors for morbidity and mortality. Weight loss (WL) ameliorates many clinical consequences of obesity; yet despite its benefits, recommendation of intentional WL in older adults remains controversial. Reluctance stems, at least in part, from loss of bone mass known to accompany overall WL and the potential for exacerbation of age-related risk of osteoporosis and fracture. Addition of resistance exercise training (RT) to WL is an effective means to attenuate, but not stop, WL-associated reductions in bone mineral 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 may also preserve bone mass. Pilot data from our institution signal that weighted vest use (designed to mimic weight stability) during WL is both feasible and likely efficacious in reducing WL-associated hip BMD loss while increasing biomarkers of bone formation. If confirmed, the greater availability, ease of administration, and reduced cost of weighted vest use to offset WL-associated bone loss, as compared to RT, holds significant public health potential as a translatable strategy to maximize the cardiometabolic benefits of WL, while minimizing negative implications for the musculoskeletal system. The main goal of the proposed R01 study is to compare the effects of WL alone and with weighted

vest use or RT on several indicators of bone health and subsequent 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 targeting 10% 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, 10 exercises, 10-12 repetitions). Our primary study outcome is 12 month change in total hip trabecular volumetric BMD (vBMD) and we hypothesize that despite similar reductions in total body weight: (1) participants in the WL+VEST group will show attenuated losses of total hip trabecular vBMD versus WL, and (2) loss in total hip trabecular vBMD will be no greater in WL+VEST compared to WL+RT. Led by a talented New Investigator, this proposal is a natural extension of the work accomplished during the PI's current MRSDA (K01 AG047291), and confers public health impact by testing a translatable strategy aimed at optimizing intentional WL in older adults with obesity while elucidating mechanisms governing musculoskeletal response to WL.

6. Project Title: STUDY OF MUSCLE, MOBILITY AND AGING (SOMMA)

**Leader(s): CUMMINGS, STEVEN RON; HEPPLER, 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 disability with dependency, decreased quality of life, and enormous health care costs. The role of age-related biological changes in skeletal muscle on the decline in mobility is poorly understood. We hypothesize that muscle mass and the capacity to produce ATP are strong determinants of the mobility disability in older adults. Based on advances 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 risk of mobility disability. We will also use transcriptomic profiling by RNAseq to discover patterns of gene expression 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 and women 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 the loss of mobility with aging. We will measure quadriceps contractile volume by MRI and total muscle mass by ³creatine dilution. We will use ³¹P MRS 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 will be the first to quantify autophagic flux to assess the role of autophagy in the loss of mobility with aging. We use respirometry 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 oxidative damage and denervation, and understanding these relationships will guide the analysis and interpretation of our results. Furthermore, we will use unbiased RNA-sequencing (RNA-seq) to profile the entire transcriptome to discover new associations between clusters of genes and individual variation in rates of loss of fitness (peak VO₂), muscle mass, and risk of mobility disability. Field centers at Wake Forest and Pittsburgh, with exceptional track records for recruiting and retaining older 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 properties and the risk of mobility disability. SOMMA may identify and prioritize targets for new therapeutics and tailored exercise regimens. We also will create a unique archive of tissue, blood, with longitudinal data about important clinical outcomes that the scientific community can use to efficiently test new hypotheses about muscle and loss of mobility with aging.

7. 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.

8. 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, 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.

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Alzheimers Dement (Amst), 2021, 13(1): e12161

<https://doi.org/10.1002/dad2.12161> | PMID: 33816754 | PMCID: PMC8010479

Citations: | AltScore: 7

27. Vascular dysfunction as a potential culprit of sarcopenia.

Jeon YK, Shin MJ, Saini SK, Custodero C, Aggarwal M, Anton SD, Leeuwenburgh C, Mankowski RT

Exp Gerontol, 2021 Mar, 145: 111220

<https://doi.org/10.1016/j.exger.2020.111220> | PMID: 33373710 | PMCID: PMC8168450

Citations: 7 | AltScore: 12.15

28. Diet-Microbiota-Brain Axis in Alzheimer's Disease.

Kincaid HJ, Nagpal R, Yadav H

Ann Nutr Metab, 2021, 77 Suppl 2: 21-27

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Citations: 6 | AltScore: 20.78

29. Physical Rehabilitation for Older Patients Hospitalized for Heart Failure.

Kitzman DW, Whellan DJ, Duncan P, Pastva AM, Mentz RJ, Reeves GR, Nelson MB, Chen H, Upadhyya B, Reed SD, Espeland MA, Hewston L, O'Connor CM

N Engl J Med, 2021 May 16, 385(3): 203-216

<https://doi.org/10.1056/NEJMoa2026141> | PMID: 33999544 | PMCID: PMC8353658

Citations: 40 | AltScore: 595.5560000000001

30. Automated Muscle Measurement on Chest CT Predicts All-Cause Mortality in Older Adults From the National Lung Screening Trial.

Lenchik L, Barnard R, Boutin RD, Kritchevsky SB, Chen H, Tan J, Cawthon PM, Weaver AA, Hsu FC

J Gerontol A Biol Sci Med Sci, 2021 Jan 18, 76(2): 277-285

<https://doi.org/10.1093/gerona/glaa141> | PMID: 32504466 | PMCID: PMC7812435

Citations: 9 | AltScore: 5.45

31. **Rehabilitation Intervention in Older Patients With Acute Heart Failure With Preserved Versus Reduced Ejection Fraction.**
Mentz RJ, Whellan DJ, Reeves GR, Pastva AM, Duncan P, Upadhyya B, Nelson MB, Chen H, Reed SD, Rosenberg PB, Bertoni AG, O'Connor CM, Kitzman DW
JACC Heart Fail, 2021 Oct, 9(10): 747-757
<https://doi.org/10.1016/j.jchf.2021.05.007> | PMID: 34246602 | PMCID: PMC8487922
Citations: 5 | AltScore: 45.8
32. **Effect of High-Intensity Strength Training on Knee Pain and Knee Joint Compressive Forces Among Adults With Knee Osteoarthritis: The START Randomized Clinical Trial.**
Messier SP, Mihalko SL, Beavers DP, Nicklas BJ, DeVita P, Carr JJ, Hunter DJ, Lyles M, Guermazi A, Bennell KL, Loeser RF
JAMA, 2021 Feb 16, 325(7): 646-657
<https://doi.org/10.1001/jama.2021.0411> | PMID: 33591346 | PMCID: PMC7887656
Citations: 4 | AltScore: 349.568
33. **Changes in body weight and knee pain in adults with knee osteoarthritis 3.5 years after completing diet and exercise interventions.**
Messier SP, Newman JJ, Scarlett MJ, Mihalko SL, Miller GD, Nicklas BJ, DeVita P, Hunter DJ, Lyles MF, Eckstein F, Guermazi A, Loeser RF, Beavers DP
Arthritis Care Res (Hoboken), 2021 Aug 9, 74(4): 607-616
<https://doi.org/10.1002/acr.24765> | PMID: 34369105 | PMCID: PMC8825890
Citations: | AltScore: 23.75
34. **Association of Urine Biomarkers of Kidney Tubule Injury and Dysfunction With Frailty Index and Cognitive Function in Persons With CKD in SPRINT.**
Miller LM, Rifkin D, Lee AK, Kurella Tamura M, Pajewski NM, Weiner DE, Al-Rousan T, Shlipak M, Ix JH
Am J Kidney Dis, 2021 Oct, 78(4): 530-540.e1
<https://doi.org/10.1053/j.ajkd.2021.01.009> | PMID: 33647393 | PMCID: PMC8390569
Citations: 2 | AltScore: 21.83
35. **Incorporating Nutrition, Vests, Education, and Strength Training (INVEST) in Bone Health: Trial Design and Methods.**
Miller RM, Beavers DP, Cawthon PM, Crotts C, Fanning J, Gerosa J, Greene KA, Hsieh KL, Kiel J, Lawrence E, Lenchik L, Lynch SD, Nesbit BA, Nicklas BJ, Weaver AA, Beavers KM
Contemp Clin Trials, 2021 May, 104: 106326
<https://doi.org/10.1016/j.cct.2021.106326> | PMID: 33631359 | PMCID: PMC8180512
Citations: | AltScore: 3.45
36. **New Horizons in Microbiota and Metabolic Health Research.**
Mishra SP, Jain S, Taraphder S, Yadav H
J Clin Endocrinol Metab, 2021 Jan 23, 106(2): e1052-e1059
<https://doi.org/10.1210/clinem/dgaa769> | PMID: 33128374 | PMCID: PMC7823252
Citations: | AltScore: 22.35
37. **Effects of a Motor Imagery Task on Functional Brain Network Community Structure in Older Adults: Data from the Brain Networks and Mobility Function (B-NET) Study.**
Neyland BR, Hugenschmidt CE, Lyday RG, Burdette JH, Baker LD, Rejeski WJ, Miller ME, Kritchevsky SB, Laurienti PJ
Brain Sci, 2021 Jan 17, 11(1):
[pii: 118. https://doi.org/10.3390/brainsci11010118](https://doi.org/10.3390/brainsci11010118) | PMID: 33477358 | PMCID:

PMC7830141

Citations: 1 | AltScore: NA

38. Physical frailty in older patients with acute heart failure: From risk marker to modifiable treatment target.

Pandey A, Gilbert O, Kitzman DW

J Am Geriatr Soc, 2021 Jun 19, 69(9): 2451-2454

<https://doi.org/10.1111/jgs.17306> | PMID: 34146340 | PMCID: PMC8440358

Citations: | AltScore: 61.45

39. Searching for the Optimal Exercise Training Regimen in Heart Failure With Preserved Ejection Fraction.

Pandey A, Kitzman DW

JAMA, 2021 Feb 9, 325(6): 537-539

<https://doi.org/10.1001/jama.2020.26347> | PMID: 33560307 | PMCID: PMC8261711

Citations: 4 | AltScore: 51.75

40. Exercise Intolerance in Older Adults With Heart Failure With Preserved Ejection Fraction: JACC State-of-the-Art Review.

Pandey A, Shah SJ, Butler J, Kellogg DL Jr, Lewis GD, Forman DE, Mentz RJ, Borlaug BA, Simon MA, Chirinos JA, Fielding RA, Volpi E, Molina AJA, Haykowsky MJ, Sam F, Goodpaster BH, Bertoni AG, Justice JN, White JP, Ding J, Hummel SL, LeBrasseur NK, Taffet GE, Pipinos II, Kitzman D

J Am Coll Cardiol, 2021 Sep 14, 78(11): 1166-1187

<https://doi.org/10.1016/j.jacc.2021.07.014> | PMID: 34503685 | PMCID: PMC8525886

Citations: 9 | AltScore: 19.3

41. Characterizing the physical function decline and disabilities present among older adults with fecal incontinence: a secondary analysis of the health, aging, and body composition study.

Parker-Autry C, Leng I, Matthews CA, Thorne N, Kritchevsky S

Int Urogynecol J, 2021 Aug 11

<https://doi.org/10.1007/s00192-021-04933-5> | PMID: 34379165

Citations: | AltScore: NA

42. The geriatric incontinence syndrome: Characterizing geriatric incontinence in older women.

Parker-Autry C, Neiberg RH, Leng I, Colombo L, Kuchel GA, Kritchevsky SB

J Am Geriatr Soc, 2021 Nov, 69(11): 3225-3231

<https://doi.org/10.1111/jgs.17374> | PMID: 34519024

Citations: | AltScore: 8.1

43. The other striated muscle: The role of sarcopenia in older persons with heart failure.

Reeves GR, Pandey A, Kitzman DW

J Am Geriatr Soc, 2021 Apr 17, 69(7): 1811-1814

<https://doi.org/10.1111/jgs.17160> | PMID: 33864385

Citations: 1 | AltScore: 35.85

44. Six-month changes in ghrelin and glucagon-like peptide-1 with weight loss are unrelated to long-term weight regain in obese older adults.

Rejeski JJ, Fanning J, Nicklas BJ, Rejeski WJ

Int J Obes (Lond), 2021 Apr, 45(4): 888-894

<https://doi.org/10.1038/s41366-021-00754-0> | PMID: 33526855 | PMCID: PMC8005376

Citations: | AltScore: 4.35

45. Long-term, induced expression of Hand2 in peripheral sympathetic neurons

ameliorates sarcopenia in geriatric mice.

Rodrigues ACZ, Messi ML, Wang ZM, Bonilla HJ, Freeman WM, Delbono O

J Cachexia Sarcopenia Muscle, 2021 Dec, 12(6): 1908-1924

<https://doi.org/10.1002/jcsm.12790> | PMID: 34546662 | PMCID: PMC8718059

Citations: 1 | AltScore: 0.25

46. Heart and neural crest derivative 2-induced preservation of sympathetic neurons attenuates sarcopenia with aging.

Rodrigues ACZ, Wang ZM, Messi ML, Bonilla HJ, Liu L, Freeman WM, Delbono O

J Cachexia Sarcopenia Muscle, 2021 Feb, 12(1): 91-108

<https://doi.org/10.1002/jcsm.12644> | PMID: 33258279 | PMCID: PMC7890150

Citations: 5 | AltScore: 15.358

47. Robust demographically-adjusted normative data for the Montreal Cognitive Assessment (MoCA): Results from the systolic blood pressure intervention trial.

Sachs BC, Chelune GJ, Rapp SR, Couto AM, Willard JJ, Williamson JD, Sink KM, Coker

LH, Gaussoin SA, Gure TR, Lerner AJ, Nichols LO, Still CH, Wadley VG, Pajewski NM

Clin Neuropsychol, 2021 Sep 1 1-16

<https://doi.org/10.1080/13854046.2021.1967450> | PMID: 34470584 | PMCID: PMC8885785

Citations: 2 | AltScore: 7

48. Nonhuman primates at the intersection of aging biology, chronic disease, and health: An introduction to the American Journal of Primatology Special Issue on aging, cognitive decline, and neuropathology in nonhuman primates.

Shively CA, Lacreuse A, Frye BM, Rothwell ES, Moro M

Am J Primatol, 2021 Nov, 83(11): e23309

<https://doi.org/10.1002/ajp.23309> | PMID: 34403529 | PMCID: PMC8935964

Citations: 1 | AltScore: 1.75

49. Does the Impact of Intensive Lifestyle Intervention on Cardiovascular Disease Risk Vary According to Frailty as Measured via Deficit Accumulation?

Simpson FR, Pajewski NM, Beavers KM, Kritchevsky S, McCaffery J, Nicklas BJ, Wing RR, Bertoni A, Ingram F, Ojeranti D, Espeland MA

J Gerontol A Biol Sci Med Sci, 2021 Jan 18, 76(2): 339-345

<https://doi.org/10.1093/gerona/glaa153> | PMID: 32564066 | PMCID: PMC8444302

Citations: 2 | AltScore: 10.7

50. Left Atrial Stiffness Index Independently Predicts Exercise Intolerance and Quality of Life in Older, Obese Patients With Heart Failure With Preserved Ejection Fraction.

Singleton MJ, Nelson MB, Samuel TJ, Kitzman DW, Brubaker P, Haykowsky MJ, Upadhy B, Chen H, Nelson MD

J Card Fail, 2021 Nov 10, 28(4): 567-575

pii: S1071-9164(21)00436-X. <https://doi.org/10.1016/j.cardfail.2021.10.010> | PMID:

34774747 | PMCID: PMC9018494

Citations: | AltScore: 7.7

51. Effect of Intensive Blood Pressure Control on Aortic Stiffness in the SPRINT-HEART.

Upadhy B, Pajewski NM, Rocco MV, Hundley WG, Aurigemma G, Hamilton CA, Bates JT, He J, Chen J, Chonchol M, Glasser SP, Hung AM, Pisoni R, Punzi H, Supiano MA, Toto R, Taylor A, Kitzman DW, SPRINT Research Group.

Hypertension, 2021 May 5, 77(5): 1571-1580

<https://doi.org/10.1161/HYPERTENSIONAHA.120.16676> | PMID: 33775127 | PMCID:

PMC8035296

Citations: 2 | AltScore: 11.6

52. Incidence and Outcomes of Acute Heart Failure With Preserved Versus Reduced Ejection Fraction in SPRINT.

Upadhyia B, Willard JJ, Lovato LC, Rocco MV, Lewis CE, Oparil S, Cushman WC, Bates JT, Bello NA, Aurigemma G, Johnson KC, Rodriguez CJ, Raj DS, Rastogi A, Tamariz L, Wiggers A, Kitzman DW, SPRINT Research Group.

Circ Heart Fail, 2021 Dec, 14(12): e008322

<https://doi.org/10.1161/CIRCHEARTFAILURE.121.008322> | PMID: 34823375 | PMCID: PMC8692397

Citations: 3 | AltScore: 6.35

53. Effect of Dietary Protein Intake on Bone Mineral Density and Fracture Incidence in Older Adults in the Health, Aging, and Body Composition Study.

Weaver AA, Tooze JA, Cauley JA, Bauer DC, Tylavsky FA, Kritchevsky SB, Houston DK *J Gerontol A Biol Sci Med Sci*, 2021 Nov 15, 76(12): 2213-2222

<https://doi.org/10.1093/gerona/qlab068> | PMID: 33677533 | PMCID: PMC8599066

Citations: | AltScore: 47.65

54. Effect of Intensive Versus Standard Blood Pressure Control on Stroke Subtypes.

Wright CB, Auchus AP, Lerner A, Ambrosius WT, Ay H, Bates JT, Chen J, Meschia JF, Pancholi S, Papademetriou V, Rastogi A, Sweeney M, Willard JJ, Yee J, Oparil S *Hypertension*, 2021 Apr, 77(4): 1391-1398

<https://doi.org/10.1161/HYPERTENSIONAHA.120.16027> | PMID: 33583199 | PMCID: PMC8224947

Citations: | AltScore: 4.1

EXTERNAL ADVISORY BOARD MEMBERS

Nir Barzilai
Albert Einstein College of Medicine
Serving since 2012 (10 years)

Heather Whitson
Duke University
Serving since 2018 (4 years)

Kirk Erickson
University of Pittsburgh
Serving since 2018 (4 years)

Nathan LaBrasseur
Mayo Clinic
Serving since 2018 (4 years)

Roger Fielding
Tufts University
Serving since 2018 (4 years)

RECOGNITION AND AWARDS (2021-2022)Atalie Thompson (2021)

- American Glaucoma Society, MAPS award

Charles McCall, MD (2021)

- Society for Leukocyte Biology Legacy Award Recipient

Dalane Kitzman, MD (2021)

- Michael L. Pollock Established Investigator Award, American Association of Cardiovascular and Pulmonary Rehabilitation

Denise Houston, PhD (2021)

- Career Development for Women Leaders (CDWL) Program, Wake Forest School of Medicine
- Team Science Award (PREVENTABLE), Wake Forest School of Medicine

Gagan Deep (2021)

- Research Excellence Award, Wake Forest School of Medicine

Heidi Kleipin, MD (2021)

- Fellow, American Society of Clinical Oncology (FASCO)
- Nominee, Harrison Teaching Award, nominated by Internal Medicine Residents

Jaime Speiser, PhD (2022)

- Top 8 Cited Paper in the Past 3 Years, Expert Systems with Applications Journal (Publication #5, Speiser et al.)

Jamie Justice, PhD (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

Jeff Williamson, MD (2021)

- Wake Forest School of Medicine and Atrium Health Team Science Award - US POINTER
- Wake Forest School of Medicine and Atrium Health Team Science Award - PREVENTABLE

Leon Lenchik (2021)

- 2021 Honorable Mention: NIH Prize for Enhancing Faculty Gender Diversity in Biomedical and Behavioral Science. Tooze JA, Anthony EY, MD, Gesell SB, Danhauer SC, Emory CL, Danelson KA, Dressler E, Parker-Autry CY, Gwathmey TM, Criswell TL, Lenchik L, Barrett N, Whitley H.

Nicholas Pajewski, PhD (2021)

- Wake Forest School of Medicine Team Science Award, PRagmatic EValuation of evENTs And Benefits of Lipid-lowering in oldEr adults (PREVENTABLE) trial

Rita Bahkru, MD (2021)

- Wake Forest Research Excellence Award

Stephen Kritchevsky, PhD (2021)

- James Edwin Byrum Jr. Distinguished Faculty Mentoring Award

Stephen Kritchevsky, PhD (2021)

- Toby R. Alligood, MD Endowed Professor in Geroscience

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):

- Amber Brooks, MD, Assistant Professor, Department of Anesthesiology
Project Title: Revisiting A Mobile Intervention to Reduce Pain and Improve Health (MORPH2) Leaders: Amber Brooks, MD and Jason Fanning, PhD Dept of Anesthesiology and Wake Forest Health and Exercise Sciences, respectively Wells Fargo Faculty Scholar Award / 2020-2022 MORPH concluded with a two-group randomized controlled pilot trial (RCT) in obese (BMI=30-45 kg/m²), low-active, older (55-85 years) adults with chronic pain who were randomized to either 12-weeks of active intervention or a wait-list control. This study represents an extension of MORPH—hereafter MORPH II—with the intention of immediately addressing limitations in the original MORPH study. We will randomize 30 older, low-active, obese adults to the active intervention or to a standard control for 12 weeks. To build upon the last phase of MORPH, we will deliver this intervention fully remotely, providing cellular data-equipped tablet computers to protect participant safety and reduce technical issues that may arise due to lack of face-to-face orientation appointments. We are mindful of the current COVID-19 climate and have chosen to deliver the entire intervention remotely. We will include intensive individual coaching throughout the program and greater emphasis on frequent movement to drive better uptake of a day-long movement program and will transition participants to a 12-week no-contact follow-up to observe whether behavior change sustains following completion of the focused intervention. CRC trained the staff and oversee the physical performance testing and core battery. BIC supports the collection and data entry of the core battery data into the common database. REC Continues support for this previous scholar. Study Status: Recruitment and intervention are underway
- 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):

YALE UNIVERSITY
Claude D. Pepper Older Americans Independence Center

Thomas M. Gill, M.D. Principal Investigator	203-688-9423	thomas.gill@yale.edu
Mary Geda Program Administrator	203-737-1800	mary.geda@yale.edu

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)

Leader 1: Katy Araujo, MPH katy.araujo@yale.edu

Leader 2: Mary Geda, RN, BSN, MSN mary.geda@yale.edu

Leader 3: 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)

Leader 1: Denise Esserman, PhD denise.esserman@yale.edu

Leader 2: 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

Edward Manning

Instructor / Yale University

2021-2023 /

2 (total)

Aging of the Human Pulmonary Artery: Analyzing Gene Expression to Tissue

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

2021-2023 /

3 (total)

Development and validation of the Patient-Reported Outcome Measure – Older adult care Transitions from the Emergency Department (PROM-OTED) tool

1 (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

Gregory Ouellet

Assistant Professor / Yale University

Does it still help? Benefits, harms, and surrogates' perspectives about anticoagulation in patients with atrial fibrillation and advanced dementia

Specific Aims: Aim 1: To examine the association between oral anticoagulant use with mortality and stroke risk reduction in older adults with advanced dementia and atrial fibrillation. Aim 2: To examine the association between oral anticoagulant use and serious bleeding events in older adults with advanced dementia and atrial fibrillation. Aim 3. To understand how surrogate decision-makers of individuals with atrial fibrillation and dementia perceive decisions about anticoagulation when presented with the empiric evidence of benefits and harms generated by this project.

2020-2022 /

12 (total)

5 (1st/Sr)

Zachary Levine

Assistant Professor of Pathology and Molecular Biophysics and Biochemistry / Yale University

Deducing the Intersection between Type II Diabetes and Cellular Senescence

Cellular senescence is one of the major hallmarks of aging and is presumed to play a causal role in age-related pathogenesis. Given that cellular senescence is often accompanied by increased pro-inflammatory activity, the accumulation of senescent cells in the endocrine and central nervous system likely drives inflammation and neurodegeneration over the life course. Given that over 30 million Americans (roughly 10% of the US population) have diabetes, it is urgent to understand how diabetes affects human aging, especially since increased rates of aging are associated with shorter lifespans and staggering increases in morbidity. In order to test this association, a molecular understanding of how soluble amyloids form and interact with pancreatic β -cells must be established. In this proposal, Dr. Levine focuses on Islet Amyloid Polypeptide (IAPP), an endocrine amyloid protein co-secreted with insulin in T2D, and which contributes to β -cell death in its aggregated form.

2020-2022 /

11 (total)

0 (1st/Sr)

Past Scholars

Xi Chen, Yale University (2016-2020)

Guido Falcone, Yale University (2017-2020)

Morgan Levine, Yale University (2018-2020)

Joan Monin, Yale University (2018-2020)

Janice Hwang, Yale University (2018-2020)

Brienne Miner, Yale University (2019-2021)

Maor Sauler, Yale University (2019-2021)

PILOT/EXPLORATORY PROJECTS (10 Pilot Projects Listed)**1. Project Title: Does it still help? Benefits, harms, and surrogates' perspectives about anticoagulation in patients with atrial fibrillation and advanced dementia: REC (2020-2022)****Leader: Gregory Ouellet**

Dementia affects 5.5 million U.S. adults 65 and older; almost 20% of them have atrial fibrillation, which significantly increases stroke risk. A critical decision is whether to prescribe an oral anticoagulant to reduce this risk. Current guidelines, derived from trials that largely excluded individuals with dementia, recommend weighing the tradeoff between the risk of stroke without treatment using the CHA₂DS₂-VASc score and the risk of bleeding with treatment. Nearly all patients with both atrial fibrillation and dementia meet the threshold for anticoagulation due to their age and comorbidities. However, considering tradeoffs for individuals with dementia is more complex, both because of lack of evidence and the potential for dementia to modify the magnitude of the potential benefits and harms.

The balance of benefits and harms of anticoagulation likely shifts over the course of dementia. As dementia progresses, there is less function to lose and life expectancy shortens, attenuating potential benefits. Our preliminary data, however, suggests that many individuals with advanced dementia and atrial fibrillation receive anticoagulants in the last six months of life. At this point, no formal studies have quantified the benefits and harms associated with anticoagulation in this population. Furthermore, the factors that surrogate decision-makers consider important when deciding about anticoagulation are not known. This information is critical, as surrogates may place value on additional outcomes which are not easily quantified, or may consider very modest benefits, if found, to be important. As a first step in optimizing atrial fibrillation treatment in persons with dementia, this work will investigate two factors critical to anticoagulant prescribing decisions: 1) empiric evidence of outcomes in those most severely affected by dementia and 2) the perspectives of surrogate decision-makers.

To begin building evidence that quantifies changing benefits and harms of anticoagulation over the course of dementia, this study will investigate whether anticoagulation retains a net benefit even among those with advanced dementia. Linking data from the Minimum Data Set, an assessment of nursing home patients, and Medicare claims will facilitate tracking longitudinal associations between anticoagulant use and the outcomes of death, stroke, and bleeding. Our hypothesis is that bleeding harms will exceed measurable reductions in mortality and stroke. As persons with dementia often live with prolonged incapacity (i.e., they are unable to make healthcare decisions), it is also critical to investigate the perspectives of surrogate decision-makers, who may or may not change their perspectives on anticoagulation for their loved one based on the evidence generated by this study. To accomplish this goal, surrogate decision-makers will be recruited from a large academic dementia care practice and local nursing homes for in-depth qualitative interviews.

The results of this work are critical to improving anticoagulation prescribing for atrial fibrillation among individuals with dementia. A Pepper Scholar Award will provide Dr. Ouellet the necessary training and mentorship to complete this important work and to make continued progress towards an independent career focused on decision-making at the interface of dementia and multimorbidity.

2. Project Title: Deducing the Intersection between Type II Diabetes and Cellular Senescence: REC (2020-2022)

Leader: Zachary Levine

While there are multiple hallmarks of human aging that cover a wide variety of genomic, epigenomic, metabolomic, and proteomic changes, many of these hallmarks are likely interconnected to one another. The confluence of aging hallmarks has historically been unclear, however deducing common threads that drive multiple hallmarks of aging would be a significant asset for understanding and intervening in age-related diseases and dysfunction. Knowledge of these determinants could greatly enhance clinical diagnoses of older Americans and reduce the number of comorbidities that accompany human aging. In this proposal, we investigate two hallmarks of aging, namely a loss in proteostasis and cellular senescence. We propose that a putative driver of both these hallmarks includes the aggregation of soluble amyloid oligomers, but not insoluble fibrils. To do this, we focus on models of Type II Diabetes, where the misfolding and soluble aggregation of Islet Amyloid Polypeptides results in the degenerative loss of insulin secreting b-cells and pancreatic dysfunction. Soluble amyloid oligomers are also one of the primary drivers of cellular senescence in fibroblasts and mesenchymal stem cells, however their ability to induce cellular stress and pancreatic senescence is less well understood. Using a combination of molecular modeling, solution biophysics techniques (spectroscopy and fluorescence microscopy), and a combination of biomarker and epigenetic measures, we will investigate the intersection of Type II Diabetes-induced loss of proteostasis and cellular senescence in pancreatic b-cells. We hypothesize that the same soluble amyloid species that degrade pancreatic islet cells are also potent inducers of cellular senescence, identifying a common pharmacophore that affects multiple hallmarks of aging. Targeting of soluble amyloids through peptidomimetic compounds will also be tested, and the degree to which the soluble amyloids can be modulated in order to mitigate multiple age-related processes at once. Successful completion of this proposal would highlight the intersection of multiple hallmarks of aging from a biophysical, chemical, and biological point of view. These results would also inform clinical models of disease and could lead to the use of senolytics for mitigating diabetes, or diabetes medications (e.g. metformin) for slowing biological aging. These results could also extend to other age-related pathologies such as Alzheimer's Disease and Parkinson's Disease, which are also accompanied by soluble amyloid species that likely enhance cellular senescence and premature biological aging. The need to better understand multifactorial contributions to human aging is essential and represents a challenge that must be met in the 21st century. By bridging knowledge from complimentary fields in physics, biology, and medicine, a cohesive theory of aging can be constructed that transcends individual hallmarks of aging, leading to treatments that target the biology of aging itself versus latent phenotypes that are often beyond intervention or rescue.

3. Project Title: The Feasibility of the Voices Digital Health Tool for Elder Mistreatment Screening in the Primary Care Setting: PESC (2021-2022)

Leader: Fuad Abujarad

Elder mistreatment is a deeply problematic social and medical issue that has received inadequate attention. The Centers for Disease Control and Prevention defines elder mistreatment as “the intentional act, or failure to act, by a caregiver or trusted person that causes or creates a risk of harm to an adult age 60 or older”. There are six commonly reported categories of elder mistreatment: physical abuse, financial exploitation, emotional abuse, sexual abuse, neglect, and abandonment. The prevalence of mistreatment in the United States is estimated to be 10% of community-dwelling older adults. Elder mistreatment causes serious adverse outcomes for its victims including injury, increased service utilization, mental distress, and increased mortality. A major barrier in overcoming elder mistreatment is the inability to accurately identify victims. It is estimated that only 1 in 24 cases become known to authorities. This is problematic as older adults are not likely to report that they are being mistreated. Working with leading experts in elder mistreatment, geriatrics, user experience research, and digital health, our team developed the digital health tool VOICES to screen and identify suspicion of elder mistreatment. VOICES is a user-friendly, self-administrated, tablet-based tool used by older adults to screen for elder mistreatment. The VOICES tool utilizes virtual coaching, interactive multimedia libraries (e.g., graphics, video clips, animations, etc.), and brief motivational interviewing designed to enhance identifying mistreatment among older adults. We have completed the development of the VOICES tool and piloted it with older adults in a challenging and busy emergency department settings. We were able to successfully establish a proof of concept and feasibility of our tool. Among the 230 subjects who used VOICES so far, 18 older adults wanted to self-report EM after using VOICES and requested help from the social workers. There is an opportunity to expand and test VOICES in broader and wider-reaching healthcare settings, specifically in primary care. In this project we will conduct a feasibility study (N= 80) examining the use of the VOICES tool to screen for elder mistreatment by older adults in primary care settings. This pilot project, if funded, will allow us to examine the feasibility of our complex intervention in the primary care settings. We expect this project will lead to a future comparative effectiveness study comparing (VOICES + in-person screening) to the standard-of-care (in-person screening).

4. Project Title: Genetic Predisposition to Cardiovascular Disease and Risk of Death, Dementia and Disability in Older Persons: PESC (2021-2022)

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 high risk 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.

5. Project Title: Improving the Tolerability and Efficacy of Allogenic Hematopoietic Stem Cell Transplant by Metabolic Modulation in Mice: PESC (2021-2022)

Leader: Rachel Perry

Allogeneic hematopoietic stem cell transplant (ASCT) is the current curative standard of care for treatment of certain patients with leukemia. Leukemia is most commonly diagnosed in elderly individuals, with the mean age at diagnosis with leukemia between 60 and 70 years old. Unfortunately, elderly individuals are well-known to respond more poorly to ASCT than their younger counterparts, exhibiting both reduced immune reconstitution, and increased susceptibility to graft vs. host disease (GvHD). As aging is inextricably linked to an increased risk of leukemia, it is crucial to understand the mechanisms by which elderly individuals are predisposed to impaired immune reconstitution and to GvHD, in order to better facilitate their response to curative therapy. In this proposal, we will probe this mechanism, and test a novel approach to improve immune reconstitution using fibroblast growth factor-21 (FGF-21) analog PF-05231023 in aging mice. FGF-21 analogs have been shown effective at improving metabolic health in multiple clinical trials across the lifespan; however, to our knowledge, neither clinical nor preclinical studies have explored the impact of these agents on immune reconstitution or GvHD following ASCT. Therefore, this proposal will bring to bear the PI's longstanding expertise in metabolic physiology and pathophysiology in rodents, with the mentorship of Drs. Vishwa (Deep) Dixit (an expert in FGF-21 biology), and Stuart Seropian (a hematologist/oncologist with substantial clinical experience in ASCT, who will advise regarding the clinical implications of the studies), and could identify a new therapeutic target following ASCT in elderly patients. As FGF-21 analogs are already in advanced clinical development, these results could quickly be translated to the clinic as an adjunct before ASCT in collaboration with colleagues at the Yale Claude D. Pepper Center and the Yale Cancer Center

6. Project Title: Development and validation of the Patient-Reported Outcome Measure – Older adult care Transitions from the Emergency Department (PROM-OTED) tool: REC (2021-2023)

Leader: Cameron Gettel

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.

7. Project Title: Aging of the Human Pulmonary Artery: Analyzing Gene Expression to Tissue: REC (2021-2023)

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.

8. Project Title: Evaluating Antibiotic Prescribing in Homebound Veterans: small REC (2021-2022)

Leader: Rupak Datta

A growing number of older adults in the United States are homebound: they rarely leave home or leave home only with assistance or significant difficulty. Because such persons have limited mobility, multiple chronic conditions, and often repeated hospitalizations, homebound persons incur high risk of infection. Homebound persons also face unique challenges to the diagnosis and treatment of infection. Currently, it is unknown how often antibiotics are prescribed in homebound persons and to what extent prescribing decisions adhere to standards of care for common clinical syndromes such as urinary tract infection. There is a need to study antibiotic prescribing in homebound persons to reduce harms associated with antibiotics such as antibiotic resistance, one of the greatest health challenges of our time. Work by the candidate suggests that antimicrobial stewardship programs may offer guidance regarding antibiotic prescribing in older adults with complex illnesses. The current proposal seeks to evaluate antibiotic prescribing in homebound older adults using a national cohort of homebound Veterans. Veterans who are homebound may receive home-based primary care (HBPC), which is comprehensive primary care delivered in the Veteran's residential home by an interdisciplinary team of providers. Alternatively, homebound Veterans may receive office-based primary care (OBPC). The candidate envisions a pilot study involving peer-to-peer comparisons of antibiotic

prescribing across regional HBPC programs. This proposal will address key knowledge gaps that stand in the way of such a pilot study. Because little is known about antibiotic prescribing in homebound Veterans, Aim 1 will compare the prevalence of antibiotic prescriptions in Veterans who used HBPC with those who used OBPC. Aim 2 will take up the broader challenge of assessing adherence to standards of care indicating that a urinalysis should be collected during treatment of urinary tract infection. Among homebound Veterans with suspected urinary tract infection treated with an antibiotic, Aim 2 will compare the proportion of Veterans having an order for a urinalysis between those who used HBPC and those who used OBPC. The candidate, Dr. Datta, is an infectious diseases physician at the Yale School of Medicine and Assistant Hospital Epidemiologist at the Veterans Affairs Connecticut Healthcare System (VACHS). He has an active role on the VACHS Antimicrobial Stewardship Program and a track record of early success, including several high-impact original reports, professional awards, and support from Yale Pepper Center and NIH. His primary co-mentors, Dr. Manisha Juthani-Mehta and Dr. Terri Fried, are internationally-recognized authorities on urinary tract infections and medical decision-making, respectively, in older adults. He has recruited another mentor, Dr. Andrew Cohen, with expertise in HBPC. This mentorship team will contribute complementary perspectives and expertise both to the proposed research and to the career development plan. Dr. Datta has outlined a rigorous program of training that draws upon resources from Yale University and the Department of Veterans Affairs that focus on data use and information systems for quality improvement programs. Execution of the proposal will facilitate Dr. Datta's emergence as an independent investigator at the forefront of geriatric infectious diseases, antibiotic stewardship, and infection prevention.

9. Project Title: Caregivers of Parents with ADRD: The Relation of Recalled Experiences to Personal Health Preferences and Perceived Caregiving Efficacy: small REC (2021-2022)

Leader: Emily Mroz

Over 11 million adults currently provide unpaid, family care to close others with ADRD. Informal caregiving is an “essential feature of health care provision” in the US and worldwide (Schulz, 2013). Providing care for loved ones with Alzheimer's Disease and Related Dementias (ADRD) is one of the most common, intensive, and challenging forms of informal caregiving (Basu et al., 2021; Connors et al., 2020). Caregivers for this population, often middle-aged adult children (Kasper et al., 2015), are vicariously exposed to negative consequences of aging (e.g., memory and autonomy loss, deterioration of sense of self, frailty; Dubljevic, 2020), influencing their expectations for their own transition to older adulthood and potential for developing health issues. Informal caregivers of persons living with ADRD consistently report a strong motivation to make meaning of their caregiving experiences, including identifying lessons learned (e.g., Cherry et al., 2019). The proposed study will establish themes of relations between recalled experiences from informal caregiving for a parent with ADRD, a) personal health preferences and behaviors, and b) perceived caregiving efficacy.

10. Project Title: Improving Hospital-Level Mortality Performance for Major Surgery in Older Adults: A Mixed Methods Study: small REC (2021-2022)

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 exceptional-performing 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 high-mortality 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.

DEVELOPMENT PROJECTS (4 Development Projects Listed)**1. Project Title: Yale Study Support Suite (YES3): Exporter (2021-2022)****Leader: Katy Araujo****Core(s):**

The YES3 Exporter provides substantial enhancements over the standard REDCap export which allows downloading in either vertical or horizontal format, faster download times, customized data dictionary, and a crosswalk file for external reporting. This latter feature will be incorporated as a beta feature (pending additional funding to expand and refine) and was inspired by our involvement with NIA-CROMS reporting requirements using Advanced Programming Interfaces (APIs) to report enrollment data to NIH.

2. Project Title: Yale Study Support Suite (YES3): Data Visualization (2021-2022)**Leader: Brent Vander Wyk****Core(s):**

Dr. Vander Wyk is collaborating on a joint development project between the BC and the Operations Core (OC) called the Yale Study Support Suite (YES3): Data Visualization. The goal is to partially automate the time-consuming process of generating consort diagrams and descriptive tables for submission of original reports to scientific journals.

3. Project Title: COVID-19 in Older Adults: A Longitudinal Assessment (VALIANT): (2020-2022)**Leader: Andrew Cohen, Lauren Ferrante, Alexandra Hajduk****Core(s):**

The objective of this longitudinal study is to learn about the long-term effects of COVID-19 on the health outcomes that matter most to older adults, including physical function, cognition, and freedom from burdensome symptoms.

4. 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).

RESEARCH (22 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: CIRCADIAN RHYTHM AS A NOVEL THERAPEUTIC TARGET IN THE INTENSIVE CARE UNIT

Leader(s): KNAUERT, MELISSA P

YALE UNIVERSITY

NIH K23HL138229 / (2018 - 2022)

Core(s):

PROJECT SUMMARY Candidate: My long-term career goal is to be an independent patient-oriented researcher who will improve outcomes in the intensive care unit (ICU) by investigating questions and developing interventions at the intersection of sleep physiology, circadian biology, and critical illness. I have proposed career development activities that will prepare me to successfully conduct a series of investigations focused on understanding ICU circadian rhythm abnormalities and the associated effects on ICU sleep disruption, delirium, and broader critical illness outcomes. I have relevant clinical training in critical care and sleep medicine. I have gained initial patient-oriented research experience by conducting several studies related to sleep disruption in the ICU. In this K23 application, I am proposing specific training in circadian biology with a focus on (1) circadian rhythm measurement, (2) circadian entrainment interventions, and (3) longitudinal data analysis. Completion of these training activities will bridge current knowledge gaps and set up future success as an independent investigator. **Mentors and Environment:** I will be mentored by Drs. Henry Klar Yaggi, Margaret Pisani, and Nancy Redeker, a team of experienced, committed experts in the fields of sleep medicine, critical care medicine, circadian measurement, ICU delirium, and patient-oriented research. This team has demonstrated collaborative success, and each member brings unique expertise. I will also work with advisors Dr. Kenneth Wright (circadian biology expert) and Dr. Terrence Murphy (analytics expert). My department Chairperson (Dr. Gary Desir) and Section Chief (Dr. Naftali Kaminski) have provided assurance that I will dedicate at least 75% of my time to career development activities. We will recruit study subjects from the Yale-New Haven Hospital Medical ICU which is a high volume ICU with sufficient patients to make this project feasible. Our section's Translational Research Core and Medical ICU Biorepository will support this project. **Mentored Research Project:** Delirium affects 50-80% of medical ICU patients. Prevention and treatment strategies are limited, and delirium is associated with poor outcomes including increased mortality. Because ICU sleep disruption is likely to be a contributor to the development of ICU delirium, sleep promotion is recommended for delirium treatment and prevention. Currently, there is a lack of investigation regarding the potentially significant contribution of circadian abnormalities to the problem of ICU sleep disruption and consequent delirium. Circadian abnormalities are potentially modifiable, and thus constitute a novel therapeutic target for ICU delirium. This project will prospectively study ICU patients (N=100) with detailed circadian measures. We will examine the impact of ICU light levels on circadian abnormalities and examine the association between circadian abnormalities and days of delirium. In addition, we will conduct a pilot randomized controlled trial (N=50) to assess the feasibility of providing daytime bright light to ICU patients to promote circadian entrainment.

3. Project Title: THE PREDICT STUDY (PRE-ICU DETERMINANTS OF POST-ICU FUNCTIONAL OUTCOMES AMONG OLDER ADULTS)

**Leader(s): FERRANTE, LAUREN
YALE UNIVERSITY
NIH K76AG057023 / (2017 - 2022)**

Core(s):

PROJECT SUMMARY/ABSTRACTCandidate: My career goal is to become an independent physician-scientist and national leader in geriatriccritical care outcomes research whose body of work improves the long-term functional outcomes of critically illolder adults. My clinical training as a Pulmonary & Critical Care Medicine (PCCM) physician and researchtraining in Geriatric Clinical Epidemiology have prepared me to pursue this career path. My track record ofearly success is evidenced by the publication of high-impact original reports and the receipt of 3 grants,including a GEMSSTAR award. I have already distinguished myself as a national leader in my specialty as wellas in geriatrics: I founded and am co-chair of the American Thoracic Society Critical Care Assembly's Agingand Geriatrics Working Group, and was recently selected as an incoming co-chair of the American GeriatricsSociety (AGS) Medical Subspecialties Section. My research efforts have been recognized nationally, with theAGS New Investigator Award, and at Yale, with the prestigious Iva Dostanic Physician-Scientist Award.Mentors and Environment: I have an exceptional team of mentors and advisors, including my primary mentorDr. Thomas Gill (Geriatrics), a leading expert on the epidemiology and prevention of disability, co-mentor Dr.Margaret Pisani (PCCM), an expert in critical care outcomes research, and advisor Dr. Terrence Murphy, abiostatistician with expertise in longitudinal studies of aging and critical care outcomes research. My researchand career development plans draw on the wealth of resources available at Yale, including the Yale Programon Aging/Claude D. Pepper Older Americans Independence Center, the Yale School of Public Health, and oneof the largest intensive care units (ICUs) in the country at Yale-New Haven Hospital. These resources, and thesupport provided by the Section of Pulmonary, Critical Care, and Sleep Medicine at the Yale School ofMedicine, provide an ideal environment for my career development and execution of the proposed research.Mentored Research Project: Nearly 1.4 million older adults survive an ICU stay each year, and many of theseswill suffer from increased disability. Our prior work has demonstrated that premorbid factors are stronglyassociated with the course of disability after a critical illness yet no mechanism exists to identify which olderICU patients are at risk of increased disability. To address this knowledge gap, I have proposed an innovativeresearch project that leverages the wealth of resources available at Yale in addition to two high-qualitylongitudinal datasets: the National Health and Aging Trends Study (NHATS) and Precipitating Events Project(PEP). The overall objective is to develop, externally validate, and pilot test a predictive tool (that incorporatespremorbid risk factors) to identify older ICU patients at risk of worsening post-ICU disability and provide apersonal estimate of the increase in disability. The results will inform the design and conduct of a largerspective cohort study to test the accuracy of the tool in predicting post-ICU disability as well as asubsequent clinical trial testing interventions to improve post-ICU functional outcomes among older adults.

4. 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 makedeisions. 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 iskown 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 shape treatment decisions when an ideal surrogate is exercising substituted judgment. Aim 3 involves the development 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 an exceptional mentorship team. His primary mentor, Dr. Terri Fried, is an internationally-recognized authority on decision-making for older adults with serious illness. He has recruited three co-mentors and an advisor whose diverse academic backgrounds will contribute a remarkable richness of perspectives and expertise both to the proposed research and to the career development plan. Dr. Cohen has outlined a rigorous program of training that draws upon resources from across Yale University as well as national training opportunities in mixed methods research and leadership development. The extraordinary resources available from the Yale Section of Geriatrics and Program on Aging provide an ideal environment for the execution of the proposed research and for Dr. Cohen's emergence as an independent investigator at the forefront of geriatrics, medical decision-making, and ethics.

5. 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-1 β 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.

6. 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.

7. Project Title: THE IMPACT OF AGING AND HIV INFECTION ON IMMUNOLOGIC AND TRANSCRIPTOMIC SIGNATURES OF INFLUENZA VACCINE RESPONSE

**Leader(s): SHAW, ALBERT C; KANG, INSOO ;
YALE UNIVERSITY
NIH R01AG055362 / (2017 - 2022)**

Core(s):

It is estimated that approximately half of HIV-infected individuals in the United States are over 50 years of age. Aging of the HIV-infected population has linked alterations in immune responses associated with age and their immunologic consequences of chronic HIV infection. This intersection of HIV and aging will influence host defense against infection and response to vaccines. As a result, understanding the nexus of HIV-associated immune activation and immunosenescence takes on particular urgency. We will leverage insights from our published and ongoing studies on the effects of aging on dysregulated innate immune pattern recognition receptor (PRR) function, a novel population of pro-inflammatory IL-7 receptor alpha effector memory (EM) CD8 T cells that are expanded in HIV-negative older adults, and on expansion of EM CD8 T cells in older HIV-positive adults. We have also elucidated gene expression and immunologic signatures of influenza vaccine response in young and older HIV-negative adults. These findings position us to illuminate the effects of aging and HIV infection on innate and adaptive immune function, particularly following influenza vaccination. To address these questions, we have assembled an interdisciplinary group of investigators with expertise in the study of aging of the innate and adaptive human immune systems, and in HIV immunology, biology and clinical care. Our overarching hypothesis is that the pro-inflammatory environment associated with age and with suppressed HIV infection potentiates immunosenescence in older adults with HIV disease. To test this hypothesis, we will enroll young (age 21-35) and older (age over 65) adults with HIV infection receiving high-dose influenza vaccine. We will employ state of the art methods including multichannel mass cytometry on whole blood to assess development and activation of major populations (e.g. monocytes, dendritic cells, NK cells, lymphocytes, neutrophils), including novel studies of platelets pre- and post-vaccine. We will evaluate innate immune PRR function (including Toll-like and NOD-like receptor family members), where we previously found age-associated alterations in cytokine production and costimulatory protein expression that were related to influenza vaccine response. We will also study T cell responses to in vitro vaccine antigen stimulation, including the IL-7 receptor alpha EM CD8 T cell subset. Statistical modeling will include clinical and functional covariates (e.g. CD4+ T cell count, estimated duration of HIV disease and of ART, medical co-morbidities, medication use, functional status). Finally, we will derive gene expression

signatures of influenza vaccineresponse in young and older adults with HIV disease, and compare these to those we previously identified inHIV-negative adults. We will employ state of the art analytic methods to integrate gene expression andimmunologic data to obtain a comprehensive view of the human immune response in the context of age andimmune suppression. These studies ultimately are aimed at identifying pathways amenable to pharmacologictargeting to improve immune and vaccine responses in older (and young) adults with HIV disease.

8. 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 between spouses 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 earlstage 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.

9. Project Title: FEASIBILITY OF VIRTUAL COACHING IN MAKING INFORMED CHOICES ON ELDER MISTREATMENT SELF-DISCLOSURE (VOICES)

**Leader(s): ABUJARAD, FUAD
YALE UNIVERSITY
NIH R01AG060084 / (2018 - 2022)**

Core(s):

7. PROJECT SUMMARY Elder mistreatment (EM) is a major public health problem with prevalence estimate ranges from 7.6% to 12.7% among older adults. EM causes serious adverse outcomes for its victims including injury, increased service utilization, mental distress and increased mortality. A major barrier in EM is the inability to accurately identify EM victims. It is estimated that only 1 in 24 cases become known to authorities. This is problematic as older adults are not likely to report that they are being mistreated. To improve the screening for EM and promote self-disclosure we will study the Feasibility of Virtual Coaching in making Informed Choices overcoming Elder Mistreatment Self-Disclosure (VOICES). The overarching aim of this project is to VOICES that run on tablets and used by older adults screen for EM. VOICES will be utilizing virtual coaching, interactive multimedia libraries (e.g. graphics, video clips, animations, etc.), techniques from electronic screening for intimate partner violence, and brief motivational interviewing designed to enhance identifying EM among older adults. This project includes developing new screening framework, as well as a study to examine the feasibility of this complex interventions in real-world settings. Our aims are: 1) to develop and refine the interactive VOICES tool, which will promote self-identification and self-disclosure to increase reporting of EM at point-of-care in the ED setting. 2) to conduct a feasibility study (N= 800) examining the use of VOICES in a busy ED, and 3) to perform a preliminary evaluation of the accuracy of VOICES as a screening tool in correctly classifying EM cases that were referred to Adult Protective Services (APS).

10. 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 SUMMARY In the United States, an estimated 5.5 million persons are affected by Alzheimer's disease, the most common type 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 the patient 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 needs of patients and their caregivers, including those based within health care systems and those based in the community. These programs have been implemented at either single sites or on a relatively small scale; none has 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 pragmatic clinical trial to compare the effectiveness of health-systems-based care (based on the UCLA Alzheimer's and Dementia Care program) with community-based care (based on the Benjamin Rose Institute Care Consultation program) on patient- and caregiver-reported outcome measures, including behavioral symptoms and caregiver distress (co-primary outcomes), and secondary outcomes of caregiver strain, unmet needs, and depression over 18-months. Because of PCORI's mandate, neither intervention will be compared to usual care (thus, only relative 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 active treatment arms. It will also allow evaluation of whether paying for such care will offset the costs and determination of which intervention is more cost effective. The study will also conduct exploratory analyses of tertiary outcomes of both interventions versus usual care including mortality, time spent at home, long-term nursing home placement, physician and patient/caregiver satisfaction and comparing all three groups on several types of utilization and out-of-pocket expenses. The study's questions are fundamental to planning for the clinical care of persons with dementia. They address both clinical effectiveness and cost-effectiveness. By answering these questions, clinicians, health systems, and insurers can make decisions about which programs to promote, scale and disseminate.

11. 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 Summary Participation in ambulatory cardiac rehabilitation (CR) by patients with ischemic heart disease (IHD) remains low. By recent estimates, fewer than two thirds of eligible patients are referred, and fewer than half of those referred 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 particularly high in older adults (age =70), due to factors such as physical impairments or transportation barriers, although these 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 increase engagement by reducing participation barriers, but it remains largely untested outside of small studies in relatively healthy young persons. It is therefore unclear what proportion of older adults with IHD and barriers to traditional CR are able to engage with mHealth-CR, and whether mHealth-CR leads to better outcomes than usual care. Therefore, we propose RESILIENT: Rehabilitation at home using mobile health in older adults after hospitalization for ischemic heart disease. This is a prospective, multicenter, non-blinded randomized clinical trial (with blinded assessment of primary endpoint) to evaluate engagement and outcomes with mHealth-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 conducted at two academic medical centers: NYU School of Medicine and Yale School of Medicine, which collectively serve a diverse patient population and have a track record of successfully recruiting older adults in clinical research 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, with baseline counseling and weekly phone calls by an exercise therapist over 3 months. Intervention and usual care groups will also receive a standard referral to ambulatory CR in accordance with guidelines, as well as dynamic assessment of activities of daily living (ADLs). The primary efficacy endpoint is change in functional capacity, assessed by 6 minute walk distance. Secondary efficacy endpoints are goal attainment, health status, ADLs, hospital readmission, and death. The engagement endpoint is defined by weekly completion of mHealth-CR tasks. We hypothesize that mHealth-CR will improve a range of outcomes, and that distinct patterns of engagement will be discerned. The PI for this project (Dr. Dodson) is an Early Stage Investigator with a focus on cardiovascular outcomes research among older adults; additional investigators have a wide range 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 with IHD, and lay the groundwork for a subsequent large multi-center clinical trial.

**12. 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 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.

13. 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.

14. 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.

15. 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 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 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 robust 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 explanatory variables that include modifiable patient-centered variables, and assesses the use of post-surgical palliative 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 basis 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 longitudinal study that includes 7,600+ community-living persons aged 65+ years with oversampling of Blacks, comprehensive annual assessments with patient-centered phenotypic data that are not available in administrative datasets, 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 systems-based research on the quality of surgical care. We will rigorously test three distinct but related hypotheses: (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 outcomes 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 mechanisms of potential disparities in outcomes after major surgery. These actionable results will inform novel interventions, collaborations, and policies designed to improve these outcomes in disadvantaged older persons.

16. 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.

17. 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.

18. 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.

19. 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 of benefit 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 the context 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 trial with 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 understand their 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 will inform 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 its effectiveness and safety for deprescribing for PlwD and their caregivers.

20. Project Title: **UNINTENDED PROLONGED OPIOID USE**
Leader(s): **HOOTEN, W. MICHAEL**
MAYO CLINIC
NIH U01TR002743 / (2019 - 2023)

Core(s):

PROJECT SUMMARY Misuse of prescription opioids remains a public health crisis. Appropriate short-term use of these medications in opioid-naïve patients is indicated in select health care settings, but intentional short-term use is emerging as a previously under-recognized segue to unintended prolonged opioid use (UPOU). Clinical strategies aimed at preventing UPOU in health care settings are lacking due, in part, to absence of information about how this poorly-understood clinical phenomenon develops. Investigators at Mayo Clinic recently organized a group of thought leaders to develop a conceptual framework to explain UPOU. Such a framework is essential both to guide the study of this problem and to identify potential targets for interventions to reduce UPOU. The framework is comprised of three domains, including (1) patient characteristics; (2) practice environment characteristics; and (3) opioid prescriber characteristics that interact to either 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 this framework does not currently exist. The widespread adoption of electronic health records (EHR) provides unique potential opportunities for translational research, including identifying subjects eligible for study participation and serving as a data source for retrospective or prospective studies. However, interoperability between 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 healthcare information sources, including commercial pharmacy records. The Hugo platform has tremendous potential to facilitate clinical research, especially research conducted across multiple centers as information from diverse source 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) will explore the Hugo platform's potential to facilitate clinical research, with the UPOU study as a use case. We will use the Hugo platform to identify incident cases of UPOU and prospectively recruit patients and opioid prescribers for assessments, as well as to evaluate the proposed conceptual framework using structural equation models. At this study's conclusion, we will have successfully deployed a highly innovative mHealth platform across multiple centers and this platform will be immediately available for widespread dissemination across the entire CTSA consortium and other clinical research sites. The information gained about UPOU will significantly advance core knowledge about this poorly understood clinical phenomenon. This newly

acquired information will be used design, test, and deploy prevention strategies aimed at mitigating the risks of UPOU.

21. 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 and technical expertise in all aspects of research supporting the design and execution of high impact Demonstration 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 available to facilitate research partnerships in VA and DoD health systems. The PMC3 will leverage the expertise of the Pain Research, Informatics, Multimorbidities and Education (PRIME) Center of Innovation based at the VA Connecticut Healthcare System (VACHS) and its partners at VACHS and Yale, including the VA Cooperative Studies Program Coordinating Center/Clinical Epidemiology Research Center and the Yale Center for Analytical Sciences and Yale Center for Medical Informatics, enhanced by a strong partnership with colleagues at the Uniformed Services University for the Health Sciences Center for Rehabilitation Sciences Research and a novel Military Treatment Facility Engagement Committee comprised of collaborating DoD and university-affiliated investigators, clinicians and educators devoted to facilitating successful pragmatic trials in DoD settings. We will use our expertise in pain management, electronic health records (EHR), data systems and the design and coordination of multi-site pragmatic trials to accomplish these objectives in collaboration with our VA, DoD and Yale partners. To achieve these objectives, three specific aims will be addressed: Aim 1: To develop, adapt and adopt technical policy guidelines and best practices for the effective design and conduct of pragmatic trials; Aim 2: To work collaboratively with and provide operational, technical, design and other support to Demonstration Project teams to develop, initiate and implement a research protocol; and Aim 3: To widely disseminate NIH-DoD-VA Pain Management Collaboratory endorsed policies and best practices and lessons learned within military and veteran health care systems. Achievement of these objectives and Specific Aims promise to significantly accelerate the integration of evidence-based non-pharmacological approaches for the management of pain into routine clinical care in military and veteran health care systems consistent with key recommendations from the National Pain Strategy.

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 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 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.

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Ann Surg, 2021 May 1, 273(5): 834-841

<https://doi.org/10.1097/SLA.0000000000004438> | PMID: 33074902 | PMCID: PMC8370041

Citations: 1 | AltScore: 3.95

32. Functional Effects of Intervening Illnesses and Injuries After Critical Illness in Older Persons.

Gill TM, Han L, Gahbauer EA, Leo-Summers L, Murphy TE, Ferrante LE

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Citations: | AltScore: 8.05

33. Falls in older adults after hospitalization for acute myocardial infarction.

Goldstein DW, Hajduk AM, Song X, Tsang S, Geda M, McClurken JB, Tinetti ME, Krumholz HM, Chaudhry SI

J Am Geriatr Soc, 2021 Dec, 69(12): 3476-3485

<https://doi.org/10.1111/jgs.17398> | PMID: 34383963 | PMCID: PMC8882265

Citations: 1 | AltScore: 14.55

34. Defining the Neuropathological Aggresome across *in Silico*, *in Vitro*, and *ex Vivo* Experiments.

Gomes GN, Levine ZA

J Phys Chem B, 2021 Mar 4, 125(8): 1974-1996

<https://doi.org/10.1021/acs.jpcc.0c09193> | PMID: 33464098 | PMCID: PMC8362740

Citations: | AltScore: 7

35. **Presentation, Treatment, and Outcomes of the Oldest-Old Patients with Acute Myocardial Infarction: The SILVER-AMI Study.**

Gupta A, Tsang S, Hajduk A, Krumholz HM, Nanna MG, Green P, Dodson JA, Chaudhry SI
Am J Med, 2021 Jan, 134(1): 95-103

<https://doi.org/10.1016/j.amjmed.2020.07.020> | PMID: 32805225 | PMCID: PMC7752813

Citations: 3 | AltScore: 5.7

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Haider SP, Qureshi AI, Jain A, Tharmaseelan H, Berson ER, Majidi S, Filippi CG, Mak A, Werring DJ, Acosta JN, Malhotra A, Kim JA, Sansing LH, Falcone GJ, Sheth KN, Payabvash S

Int J Stroke, 2021 Oct 13 17474930211050749

<https://doi.org/10.1177/17474930211050749> | PMID: 34569877 | PMCID: PMC9005571

Citations: | AltScore: 17.35

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Haider SP, Qureshi AI, Jain A, Tharmaseelan H, Berson ER, Zeevi T, Majidi S, Filippi CG, Iseke S, Gross M, Acosta JN, Malhotra A, Kim JA, Sansing LH, Falcone GJ, Sheth KN, Payabvash S

Eur J Neurol, 2021 Sep, 28(9): 2989-3000

<https://doi.org/10.1111/ene.15000> | PMID: 34189814 | PMCID: PMC8818333

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38. **Presentation, Treatment, and Outcomes of Older Adults Hospitalized for Acute Myocardial Infarction According to Cognitive Status: The SILVER-AMI Study.**

Hajduk AM, Saczynski JS, Tsang S, Geda ME, Dodson JA, Ouellet GM, Goldberg RJ, Chaudhry SI

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<https://doi.org/10.1016/j.amjmed.2021.03.003> | PMID: 33737057 | PMCID: PMC8243828

Citations: 1 | AltScore: NA

39. **Pain, Complex Chronic Conditions and Potential Inappropriate Medication in People with Dementia. Lessons Learnt for Pain Treatment Plans Utilizing Data from the Veteran Health Administration.**

Husebo BS, Kerns RD, Han L, Skanderson M, Gnjjidic D, Allore HG

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Citations: | AltScore: 15.58

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Leasure AC, Kuohn LR, Vanent KN, Bevers MB, Kimberly WT, Steiner T, Mayer SA, Matouk CC, Sansing LH, Falcone GJ, Sheth KN

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Lin Z, Chen X

SSM Popul Health, 2021 Jun, 14: 100767

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Lyttelton T, Zang E, Musick K

J Marriage Fam, 2021 Nov 10, 84(1): 230-249

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Citations: 3 | AltScore: 89.85
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JCO Oncol Pract, 2021 Jun, 17(6): e848-e858
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Citations: 5 | AltScore: 11.75
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Qian Y, Chen X, Tang D, Kelley AS, Li J
J Gerontol A Biol Sci Med Sci, 2021 Sep 13, 76(10): 1846-1853
<https://doi.org/10.1093/gerona/glab043> | PMID: 33575783 | PMCID: PMC8436977
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Citations: 2 | AltScore: 42.9
- 62. A Multimodal Intervention to Improve the Quality and Safety of Interhospital Care Transitions for Nontraumatic Intracerebral and Subarachnoid Hemorrhage.**
Sather J, Littauer R, Finn E, Matouk C, Sheth K, Parwani V, Pham L, Ulrich A, Rothenberg C, Venkatesh AK
Jt Comm J Qual Patient Saf, 2021 Feb, 47(2): 99-106
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Szejko N, Kirsch E, Falcone GJ

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Thomas JM, Cooney LM Jr, Fried TR

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JAMA Netw Open, 2021 Mar 1, 4(3): e211271

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Travers JL, Naylor MD, Coe NB, Meng C, Li F, Cohen AB

Med Care, 2021 Jun 1, 59(6): 537-542

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Tu SS, O'Leary JR, Fried TR

J Pain Symptom Manage, 2021 Oct, 62(4): 805-812

<https://doi.org/10.1016/j.jpainsymman.2021.03.003> | PMID: 33716035 | PMCID:

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Citations: 3 | AltScore: 2.85

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van Dyck LI, Fried TR

J Am Geriatr Soc, 2021 Jul, 69(7): 2025-2028

<https://doi.org/10.1111/jgs.17080> | PMID: 33675032 | PMCID: PMC8273121

Citations: 1 | AltScore: 6.25

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van Dyck LI, Paiva A, Redding CA, Fried TR

J Pain Symptom Manage, 2021 Oct, 62(4): 778-784

<https://doi.org/10.1016/j.jpainsymman.2021.02.011> | PMID: 33587993 | PMCID:

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Citations: 2 | AltScore: 12.35

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Womack JA, Murphy TE, Ramsey C, Bathulapalli H, Leo-Summers L, Smith AC, Bates J, Jarad S, Gill TM, Hsieh E, Rodriguez-Barradas MC, Tien PC, Yin MT, Brandt C, Justice AC
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Wu H, Mach J, Gemikonakli G, Tran T, Allore H, Gnjudic D, Howlett SE, de Cabo R, Le Couteur DG, Hilmer SN

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Citations: 4 | AltScore: 8.2

74. Assessing elderly's functional balance and mobility via analyzing data from waist-mounted tri-axial wearable accelerometers in timed up and go tests.

Yu L, Zhao Y, Wang H, Sun TL, Murphy TE, Tsui KL

BMC Med Inform Decis Mak, 2021 Mar 25, 21(1): 108

<https://doi.org/10.1186/s12911-021-01463-4> | PMID: 33766011 | PMCID: PMC7995592

Citations: | AltScore: NA

75. Intergenerational upward mobility and racial differences in mortality among young adults: Evidence from county-level analyses.

Zang E, Kim N

Health Place, 2021 Jul, 70: 102628

<https://doi.org/10.1016/j.healthplace.2021.102628> | PMID: 34280713 | PMCID: PMC8328956

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Zang E, Lynch SM, West J

J Epidemiol Community Health, 2021 Jan, 75(1): 56-61

<https://doi.org/10.1136/jech-2020-214267> | PMID: 32855262 | PMCID: PMC8128513

Citations: 2 | AltScore: 28.998

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Zang E, West J, Kim N, Pao C

PLoS One, 2021, 16(11): e0259665

<https://doi.org/10.1371/journal.pone.0259665> | PMID: 34847174 | PMCID: PMC8631641

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<https://doi.org/10.1371/journal.pone.0260038> | PMID: 34813610 | PMCID: PMC8610237

Citations: 1 | AltScore: 0.75

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Zhang Y, Lu Q, Ye Y, Huang K, Liu W, Wu Y, Zhong X, Li B, Yu Z, Travers BG, Werling

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<https://doi.org/10.1186/s13059-021-02478-w> | PMID: 34493297 | PMCID: PMC8422619

Citations: 7 | AltScore: 15.88

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RECOGNITION AND AWARDS (2021-2022)

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Morgan Levine (2021)

- Vincent Cristofalo Rising Star Award in Aging Research

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.

Minority Grant(s):