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

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

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

CENTER DESCRIPTION

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

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

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

The goals of the Duke Pepper Center are:

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

CORES

Leadership and Administrative Core (LAC)

Leader 1:	Kenneth Schmader, MD	kenneth.schmader@dm.duke.edu
Leader 2:	Cathleen Colón-Emeric, MD, MHS	cathleen.colonemeric@duke.edu

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

Research Education Component (REC)

Leader 1:	Cathleen Colón-Emeric, MD, MHS	colon001@mc.duke.edu
Leader 2:	Kimberly Johnson, M.D.	kimberly.s.johnson@duke.edu
Leader 3:	Barrett Bowling, M.D.	barrett.bowling@duke.edu

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

Pilot and Exploratory Studies Core (PESC)

Leader 1:	Heather E. Whitson, MD	heather.whitson@duke.edu
Leader 2:	Susan N. Hastings, MD	susan.hastings@duke.edu

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

Analysis (AC)

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

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

Health and Mobility Measures Core (HMC)

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

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

Molecular Measures Core (MMC)

Leader 1: Virginia B. Kraus, MD, PhD vbk@duke.edu
Leader 2: James Bain, PhD james.bain@duke.edu

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

CAREER DEVELOPMENT

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

Sonali Advani, MBBS, MPH 2022-2024 /
Assistant Professor of Medicine / Department of Medicine 5 (total)
Deprescribing intervention to reduce inappropriate antibiotic exposure and improve resilience in older adults 4 (1st/Sr)

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

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

Leah Acker, MD, PhD 2022-2024 /
Medical Instructor / Department of Anesthesiology 3 (total)
Pilot testing of a non-invasive neuroimmune modulation tool— transcutaneous auricular vagus nerve stimulation (taVNS)—to enhance perioperative cognitive resilience in older adults 0 (1st/Sr)

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

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

Kimberly Hreha, EdD, OTR/L 2022-2024 /
Assistant Professor / Department of Orthopaedic Surgery 1 (total)
Evaluating Physical Resilience and Best Practices in Vision Rehabilitation of Stroke Patients: A Mixed Methods Approach 0 (1st/Sr)

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

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

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Past Scholars

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

(2018-2020)
Brian James Andonian, MD MHSc, Department of Medicine, Division of Rheumatology and Immunology (2020-2022)
Ming-Feng Hsueh, PhD, Department of Orthopaedic Surgery (2020-2022)
Daniel Parker, MD, Department of Medicine (2020-2022)

PILOT/EXPLORATORY PROJECTS (8 Pilot Projects Listed)

1. **Project Title:** **ApoE: A new target to improve aged bone healing**
   Leader: **Gurpreet Baht, PhD**

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

2. **Project Title:** **Resilience after heart transplant or LVAD in patients with advanced heart failure**
   Leader: **Adam DeVore, MD MHS**

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

3. **Project Title:** **Mechanisms underlying variation in primate physiological reserve**
   Leader: **Elaine Gomez Guevara, PhD**

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

4. **Project Title:** **Understanding the role of IL-15 signaling in podocyte resilience and survival**
   Leader: **Gentzon Hall, MD PhD**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DEVELOPMENT PROJECTS (3 Development Projects Listed)

1. **Project Title:** **Cellular senescence burden as a molecular indicator of resilience**
   Leader: **Virginia Kraus, MD PHD**
   Core(s):

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

2. **Project Title:** **Testing the resilience of the latent class trajectory model when the conditions of the model are not met**
   Leader: **Carl Pieper, DrPH and Jane Pendergast, PhD**
   Core(s): Analysis (AC)

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

3. Project Title: **Developing Resiliency Related Health Data Science Capacity**

Leader: **Juliessa Pavon, Katherine Hall**

Core(s):

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

RESEARCH (0 Projects Listed)

PUBLICATIONS

2024

2023

1. **Beyond implementation: Uncovering the parallels between de-implementation and antimicrobial stewardship.**
   Advani SD, McKay V
   Antimicrob Steward Healthc Epidemiol, 2023, 3(1): e73
   https://doi.org/10.1017/ash.2023.150 | PMID: 37113202 | PMCID: PMC10127237
   Citations: 2 | AltScore: NA
2. **Remotely Supervised Weight Loss and Exercise Training to Improve Rheumatoid Arthritis Cardiovascular Risk: Rationale and Design of the Supervised Weight Loss Plus Exercise Training-Rheumatoid Arthritis Trial.**
   Andonian B, Ross LM, Zidek AM, Fos LB, Piner LW, Johnson JL, Belski KB, Counts JD, Pieper CF, Siegler IC, Bales CW, Porter Starr KN, Kraus WE, Huffman KM
   ACR Open Rheumatol, 2023 May, 5(5): 252-263
   https://doi.org/10.1002/acr2.11536 | PMID: 36992545 | PMCID: PMC10184018
   Citations: NA | AltScore: NA
3. **Editorial: The immune system and inflammation in musculoskeletal health, aging, and disease.**
   Baht GS, Grol MW
   Front Immunol, 2023, 14: 1218118
   https://doi.org/10.3389/fimmu.2023.1218118 | PMID: 37275852 | PMCID: PMC10233133
   Citations: NA | AltScore: NA
4. **Which types of stress are associated with accelerated biological aging? Comparing perceived stress, stressful life events, childhood adversity, and posttraumatic stress disorder.**
   Bourassa KJ, Caspi A, Brennan GM, Hall KS, Harrington H, Houts R, Kimbrel NA, Poulton R, Ramrakha S, Taylor GA, Moffitt TE
   Psychosom Med, 2023 Apr 6, 85(5): 389-396
   https://doi.org/10.1097/PSY.0000000000001197 | PMID: 37053097 | PMCID: PMC10239326
   Citations: NA | AltScore: 18.35
5. **Physical Function Assessment of Older Veterans With Serious Mental Illness.**
   Browne J, Elbogen EB, Mueser KT, Rudolph JL, Wu WC, Philip NS, Mills WL, Sloane R, Hall KS
   Am J Geriatr Psychiatry, 2023 Sep, 31(9): 657-666
   https://doi.org/10.1016/j.jagp.2023.02.048 | PMID: 36941144 | PMCID: PMC10474249
   Citations: 2 | AltScore: NA
6. **Elevated C-Reactive Protein and Subsequent Patient-Reported Cognitive Problems in Older Breast Cancer Survivors: The Thinking and Living With Cancer Study.**
   Carroll JE, Nakamura ZM, Small BJ, Zhou X, Cohen HJ, Ahles TA, Ahn J, Bethea TN, Extermann M, Graham D, Isaacs C, Jim HSL, Jacobsen PB, McDonald BC, Patel SK, Rentscher K, Root J, Saykin AJ, Tometich DB, Van Dyk K, Zhai W, Breen EC, Mandelblatt JS
   J Clin Oncol, 2023 Jan 10, 41(2): 295-306
   https://doi.org/10.1200/JCO.22.00406 | PMID: 36179271 | PMCID: PMC9839283

Citations: 10 | AltScore: 248.012

7. **Synergistic roles of CBX4 chromo and SIM domains in regulating senescence of primary human osteoarthritic chondrocytes.**
Chen YH, Zhang X, Attarian D, Kraus VB
Arthritis Res Ther, 2023 Oct 12, 25(1): 197
https://doi.org/10.1186/s13075-023-03183-8 | PMID: 37828576 | PMCID: PMC10568837
Citations: NA | AltScore: NA
8. **Association of Dipeptidylpeptidase 4 (CD26) With Chondrocyte Senescence and Radiographic Progression in Knee Osteoarthritis.**
Chen YH, Zhang X, Chou CH, Hsueh MF, Attarian D, Li YJ, Kraus VB
Arthritis Rheumatol, 2023 Jan 27, 75(7): 1120-1131
https://doi.org/10.1002/art.42455 | PMID: 36704903 | PMCID: PMC10313751
Citations: 1 | AltScore: NA
9. **Reply.**
Chen YH, Zhang X, Kraus VB
Arthritis Rheumatol, 2023 Mar 12, 75(9): 1679-1680
https://doi.org/10.1002/art.42500 | PMID: 36908027
Citations: NA | AltScore: NA
10. **RELATIONSHIP BETWEEN REPRODUCTIVE AND BONE BIOMARKERS AND OSTEOARTHRITIS IN ZOO ASIAN (ELEPHAS MAXIMUS) AND AFRICAN (LOXODONTA AFRICANA) ELEPHANTS.**
Chusyd DE, Brown JL, Golzarri-Arroyo L, Dickinson SL, Kraus VB, Siegal-Willott J, Griffin TM, Huebner JL, Edwards KL, Allison DB, Austad SN
J Zoo Wildl Med, 2023 Jan, 53(4): 801-810
https://doi.org/10.1638/2021-0080 | PMID: 36640083 | PMCID: PMC10150656
Citations: NA | AltScore: NA
11. **Ageing and physical resilience after health stressors.**
Colon-Emeric C, Schmader K, Cohen HJ, Morey M, Whitson H
Stress Health, 2023 Mar 6, 39(S1): 48-54
https://doi.org/10.1002/smi.3241 | PMID: 36879359 | PMCID: PMC10480330
Citations: 2 | AltScore: 1.85
12. **Calorie restriction modulates the transcription of genes related to stress response and longevity in human muscle: The?CALERIE study.**
Das JK, Banskota N, Candia J, Griswold ME, Orenduff M, de Cabo R, Corcoran DL, Das SK, De S, Huffman KM, Kraus VB, Kraus WE, Martin CK, Racette SB, Redman LM, Schilling B, Belsky DW, Ferrucci L
Aging Cell, 2023 Oct 12 e13963
https://doi.org/10.1111/acel.13963 | PMID: 37823711
Citations: NA | AltScore: 281.588
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RECOGNITION AND AWARDS (2023-2024)

Heather Whitson, MD, MHS (2023)

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

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

Virginia Byers Kraus, MD, PhD (2023)

- Elected to The American Clinical and Climatological Association

MINORITY RESEARCH

General Brief Description of Minority Activities:

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

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

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

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

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

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

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

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

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

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

Kimberly S. Johnson, MD, MHS, PI

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

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

Minority Trainee(s):

- Charity Oyedeji, MD, PESC Scholar, Assistant Professor of Medicine (Hematology)
  Dr. Charity Oyedeji's research focuses on implementing a geriatric assessment into clinical assessments of older adults with sickle cell disease. Due to advances in care and access, patients with sickle cell disease (SCD) are living longer than they have in previous generations. SCD is recognized as a condition that mimics accelerated aging, but little is known about aging with SCD. In particular, SCD patients face frequent health stressors including hypoxia, pain crises, and frequent hospitalizations, but little is known about how aging with SCD affects one's resilience to these stressors. The objective of this study is to test the feasibility and safety of focused geriatric assessment and provocative tests that measure physiological reserve in SCD patients over age 50 and to determine the feasibility of a protocol to assess resilience to the stressor of hospitalization in older SCD patients. In addition, biomarkers of inflammation, coagulation, and longevity will be compared in 20 older (age 50-70) people with SCD and 20 younger (age 18-49) people with SCD. Thus far, the study has demonstrated that focused geriatric assessment, including provocative performance measures was safe and well-tolerated by older SCD patients. 50% of the older participants experienced a hospitalization within 12 months of a baseline assessment, indicating the feasibility of a future study to prospectively measure resilience after hospitalization by following a cohort of well-characterized participants for 2 years. Measures of physiological reserve in older SCD patients, on average, were consistent with normative measures from healthy seniors 20-30 years older. In 2020, Dr. Oyedeji used these findings to support a successful application for funding from the American Society of Hematology. She was also the recipient of 3 outstanding abstract awards at national meetings, and the recipient of the 2019 Duke Maddox Award for Aging Research. In 2021, Dr. Oyedeji received a Duke REACH Equity Career Development Award, an invitation to present at the American Society of Hematology Annual Meeting in December, and submitted a manuscript to the ASH Education Program.
- Gentzon Hall, MD, PhD, Assistant Professor of Medicine (Nephrology)
  Dr. Hall is an Assistant Professor of Medicine (Nephrology) whose lab utilizes sophisticated genetic studies to better understand contributors to glomerulosclerosis (AAGS), a common cause of chronic kidney disease (CKD) in older adults. His ultimate goal is to identify targets for pharmacological intervention that will protect kidney function, especially in populations at highest risk for AAGS. Progressive loss of glomerular visceral epithelial cells (i.e. podocytes) with age is thought to be the principal driver of AAGS. Based on his own previous findings, Dr. Hall hypothesizes that impaired IL-15/IL-15R axis signaling reduces podocyte resiliency to proapototic stimuli, increasing risk of AAGS across the lifespan. In Aim 1 of his pilot study, he utilizes immortalized human podocyte lines to quantify podocyte apoptosis in gene knockdown and controls after exposure to two well-validated proapototic stimuli. In Aim 2, he will utilize targeted gene deletion in zebrafish embryos to understand the role of the IL-15 signaling in vivo. A validated surrogate model for albuminuria in humans will be used to detect and quantify proteinuria in knockdown IL-15 and IL-15R zebrafish compared to controls. If these experiments confirm the role ofIL-15 signaling in podocyte survival and function after nephrotoxic stressors, it will justify future research to develop IL-15 signaling agents to enhance kidney resilience and protect against AAGS.

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

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

Minority Grant(s):

1. **Project Title:** **FLUAD? vs. Fluzone? High-Dose Study**
   Leader(s): **SCHMADER, KENNETH**
   DUKE UNIVERSITY
   Centers for Disease Control and Prevention 200-2012-53663 / (2016-2021)

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

2. **Project Title:** **The Impact of Reactogenicity of the Recombinant Zoster Vaccine on the Physical Functioning and Quality of Life of Older Adults**
   Leader(s): **SCHMADER, KENNETH**
   DUKE UNIVERSITY
   Glaxo Smith Kline GSK Zoster 063 / (2017-2019)

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

3. **Project Title:** **EXPLORING THE EFFECTS OF EXERCISE TRAINING ON PTSD SYMPTOMS AND PHYSICAL HEALTH IN OLDER VETERANS WITH PTSD**
   Leader(s): **HALL, KATHERINE SHEPARD**
   DURHAM VA MEDICAL CENTER
   VA I01RX003120 / (2020-2024)

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

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

Leader(s): WHITE, JAMES P.

DUKE UNIVERSITY
NIH K01AG056664 / (2017-2022)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

16. Project Title: ADHERENCE TO VENOUS THROMBOEMBOLISM PROPHYLAXIS GUIDELINES IN HOSPITALIZED ELDERS

Leader(s): PAVON, JULIESSA M
DUKE UNIVERSITY
NIH R03AG048007 / (2014-2016)

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

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

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

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

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

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

18. Project Title: **EFFECTS OF AGING AND THE URINARY MICROBIOME ON RECURRENT URINARY TRACT INFECTIONS**

Leader(s): **SIDDIQUI, NAZEMA Y**
DUKE UNIVERSITY
NIH R03AG060082 / (2018-2020)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Leader(s): **KRAUS, WILLIAM E ; HOUMARD, JOSEPH A ; NICKLAS, BARBARA J ;**

DUKE UNIVERSITY

NIH U01AR071128 / (2016-2022)

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

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

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

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

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

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

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