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

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CENTER DESCRIPTION

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

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

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

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

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

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

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

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

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

CORES

Leadership and Administrative Core (LAC)

Leader 1: Karen Bandeen-Roche, PhD kbandee1@jhu.edu
Leader 2: Jeremy Walston, MD jwalston@jhmi.edu

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

Research Education Component (REC)

Leader 1: Gary Gerstenblith, MD gblith@jhmi.edu
Leader 2: Esther Oh, MD, PhD eoh9@jh.edu

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

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

Pilot / Exploratory Studies Core (PESC)

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

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

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

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

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

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

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

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

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

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

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

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

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

Information Dissemination Core (IDC)

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

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

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

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

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

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

CAREER DEVELOPMENT

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

Thomas Laskow, MD
Assistant Professor / School of Medicine, Division of Geriatric Medicine and Gerontology

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

Physical Frailty, Inflammation, and Response to Clinical Stressors

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

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

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

CaMKII oxidation links oxidative stress to inflammation, frailty, and premature death

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

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

Past Scholars

Alden Gross, PhD, Epidemiology (2014-2016)
Charles H. Brown IV, MD , Anesthesiology and Critical Care Medicine (2014-2016)
Charles H. Brown IV, MD , Anesthesiology and Critical Care Medicine (2014-2016)
Rani Hasan, MD, MHS, Cardiology (2015-2018)
Tae Chung, MD, Physical Medicine and Rehabilitation (2016-2018)

Abdulla Damluji, MD, PhD, Cardiology (2017-2019)
Orla Sheehan, MD, PhD, Geriatric Medicine (2018-2020)
Pei-Hsun Wu, PhD, Institute for NanoBioTechnology (2018-2020)
Bharath Ambale-Venkatesh, PhD, Radiology and Radiological Science (2018-2020)
Reyhan Westbrook, PhD, Geriatric Medicine (2018-2020)
Keenan Walker, PhD, Neorology (2019-2019)
Sabra Lewsey, MD, Division of Cardiology (2020-2021)
Jude Phillip, PhD, Department of Biomedical Engineering (2020-2021)
Melissa deCardi Hladek PhD, CRNP, FNP-BC , Johns Hopkins School of Nursing (2021-2023)
Gizem Keceli, PhD, Johns Hopkins School of Medicine, Division of Cardiology (2021-2023)
Lolita Nidadavolu, M.D., Ph.D., Johns Hopkins University School of Medicine (2021-2023)
Nicholas R. Rowan, MD, Johns Hopkins Department of Otolaryngology-Head and Neck Surgery (2021-2023)
Jenny Pena Dias, Endocrinology/Medicine (2022-2022)

PILOT/EXPLORATORY PROJECTS (14 Pilot Projects Listed)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6. Project Title: **Effects of Neurotoxic Kynurenines on Peripheral Nerve Regeneration**

Leader: **Tae Chung, MD**

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

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

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

Leader: Reyhan Westbrook, PhD

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

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

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

Leader: **Kathy Wilson, PhD**

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

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

Leader: **Alden Gross, PhD**

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

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

Leader: **Lee Goeddel MD, MPH**

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

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

Leader: Jude M. Phillip, PhD

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

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

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

Leader: Amal Wanigatunga, PhD

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

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

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

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

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

14. Project Title: **Artificial intelligence-based phenotypic biosignals of frailty**

Leader: **Najim Dehak, PhD, and Laureano Moro-Velazquez, PhD**

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

DEVELOPMENT PROJECTS (7 Development Projects Listed)

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

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

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

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

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

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

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

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

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

   Leader: **Frederick Sieber, MD**

   Core(s):

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

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

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

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

Core(s):

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

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

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

Core(s):

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

6. Project Title: **High-throughput screening of mitochondrial function**

Leader: **Dan Arking, PhD**

Core(s):

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

7. Project Title: **Development of a novel technology for the sustained delivery of valsartan and senolytics to frail older adults with chronic wounds**

Leader: **Efrosini Kokkoli**

Core(s):

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

RESEARCH (0 Projects Listed)

PUBLICATIONS

2024

2023

1. **Hearing Loss and Frailty among Older Adults: The Atherosclerosis Risk in Communities Study.**
   Assi S, Garcia Morales EE, Windham BG, Lin FR, Bandeen-Roche K, Shukla A, Palta P, Deal JA, Reed NS, Martinez-Amezcua P
   J Am Med Dir Assoc, 2023 Sep 23
   pii: S1525-8610(23)00747-8. https://doi.org/10.1016/j.jamda.2023.08.023 | PMID: 37748754
   Citations: NA | AltScore: NA
2. **Substitution of self-reported measures for objectively assessed grip strength and slow walk in the Physical Frailty Phenotype: ramifications for validity.**
   Bandeen-Roche K, Tian J, Buta B, Walston J, Xue QL
   BMC Geriatr, 2023 Jul 22, 23(1): 451
   https://doi.org/10.1186/s12877-023-04105-8 | PMID: 37481528 | PMCID: PMC10362666
   Citations: NA | AltScore: NA
3. **?3AR-Dependent Brain-Derived Neurotrophic Factor (BDNF) Generation Limits Chronic Postischemic Heart Failure.**
   Cannavo A, Jun S, Rengo G, Marzano F, Agrimi J, Liccardo D, Elia A, Keceli G, Altobelli GG, Marcucci L, Megighian A, Gao E, Feng N, Kammers K, Ferrara N, Finos L, Koch WJ, Paolocci N
   Circ Res, 2023 Mar 31, 132(7): 867-881
   https://doi.org/10.1161/CIRCRESAHA.122.321583 | PMID: 36884028 | PMCID: PMC10281793
   Citations: 1 | AltScore: 61.55
4. **Development and Validation of an Abridged Physical Frailty Phenotype for Clinical Use: A Cohort Study Among Kidney Transplant Candidates.**
   Chen X, Chu NM, Thompson V, Quint EE, Alasfar S, Xue QL, Brennan DC, Norman SP, Lonze BE, Walston JD, Segev DL, McAdams-DeMarco MA
   J Gerontol A Biol Sci Med Sci, 2023 Jul 19
   pii: glad173. https://doi.org/10.1093/gerona/glad173 | PMID: 37466327
   Citations: NA | AltScore: 4.6
5. **Deletion of quinolinate phosphoribosyltransferase gene accelerates frailty phenotypes and neuromuscular decline with aging in a sex-specific pattern.**
   Chung T, Bopp T, Ward C, Notarangelo FM, Schwarcz R, Westbrook R, Xue QL, Walston J, Hoke A
   Aging Cell, 2023 Apr 20, 22(7): e13849
   https://doi.org/10.1111/acel.13849 | PMID: 37078472 | PMCID: PMC10352574
   Citations: 1 | AltScore: 4.25
6. **Decoding Angiotensin Receptors: TOMAHAQ-Based Detection and Quantification of Angiotensin Type-1 and Type-2 Receptors.**
   Cosardereliogl C, Kreimer S, Plaza-Rodriguez AI, Iglesias PA, Talbot CC Jr, Siragy HM, Carey RM, Ubaida-Mohien C, O'Rourke B, Ferrucci L, Bennett DA, Walston J, Abadir P
   J Am Heart Assoc, 2023 Sep 19, 12(18): e030791
   https://doi.org/10.1161/JAHA.123.030791 | PMID: 37681524 | PMCID: PMC10547273

Citations: NA | AltScore: 5.1

7. **Sarcopenia and Cardiovascular Diseases.**
Damluji AA, Alfaraidhy M, AlHajri N, Rohant NN, Kumar M, Al Malouf C, Bahrainy S, Ji Kwak M, Batchelor WB, Forman DE, Rich MW, Kirkpatrick J, Krishnaswami A, Alexander KP, Gerstenblith G, Cawthon P, deFilippi CR, Goyal P
Circulation, 2023 May 16, 147(20): 1534-1553
https://doi.org/10.1161/CIRCULATIONAHA.123.064071 | PMID: 37186680 | PMCID: PMC10180053
Citations: 7 | AltScore: 585.38
8. **Hierarchical Development of Physical Frailty and Cognitive Impairment and Their Association With Incident Cardiovascular Disease.**
Damluji AA, Ijaz N, Chung SE, Xue QL, Hasan RK, Batchelor WB, Orkaby AR, Kochar A, Nanna MG, Roth DL, Walston JD, Resar JR, Gerstenblith G
JACC Adv, 2023 May, 2(3):
pii: 100318. https://doi.org/10.1016/j.jacadv.2023.100318 | PMID: 37538136 | PMCID: PMC10399211
Citations: NA | AltScore: NA
9. **Physical Frailty and Brain White Matter Abnormalities: The Atherosclerosis Risk in Communities Study.**
Ducca EL, Gomez GT, Palta P, Sullivan KJ, Jack CR, Knopman DS, Gottesman RF, Walston J, Windham BG, Walker KA
J Gerontol A Biol Sci Med Sci, 2023 Feb 24, 78(2): 357-364
https://doi.org/10.1093/gerona/glac111 | PMID: 35596270 | PMCID: PMC9951053
Citations: 3 | AltScore: 2.75
10. **Associations of perceived stress, depressive symptoms, and caregiving with inflammation: a longitudinal study.**
Elayoubi J, Haley WE, Roth DL, Cushman M, Sheehan OC, Howard VJ, Hladek MD, Hueluer G
Int Psychogeriatr, 2023 Feb, 35(2): 95-105
https://doi.org/10.1017/S1041610222000370 | PMID: 35543307
Citations: NA | AltScore: 0.25
11. **Particulate matter composition drives differential molecular and morphological responses in lung epithelial cells.**
Engels SM, Kamat P, Pafilis GS, Li Y, Agrawal A, Haller DJ, Phillip JM, Contreras LM
bioRxiv, 2023 May 20
pii: 2023.05.17.541204. https://doi.org/10.1101/2023.05.17.541204 | PMID: 37292596 | PMCID: PMC10245696
Citations: 1 | AltScore: NA
12. **Order of Onset of Physical Frailty and Cognitive Impairment and Risk of Repeated Falls in Community-Dwelling Older Adults.**
Ge ML, Chu NM, Simonsick EM, Kasper JD, Xue QL
J Am Med Dir Assoc, 2023 Apr, 24(4): 482-488.e4
https://doi.org/10.1016/j.jamda.2023.01.020 | PMID: 36852758 | PMCID: PMC10167733
Citations: 1 | AltScore: 13.35
13. **Serum and plasma protein biomarkers associated with frailty in patients with cirrhosis.**
Ha NB, Seetharaman S, Kent DS, Yao F, Shui AM, Huang CY, Walston J, Lai JC
Liver Transpl, 2023 Oct 1, 29(10): 1089-1099
https://doi.org/10.1097/LVT.0000000000000128 | PMID: 36932707 | PMCID:

PMC10509322
Citations: NA | AltScore: NA

14. **Complex Percutaneous Coronary Intervention Outcomes in Older Adults.**
Hanna JM, Wang SY, Kochar A, Park DY, Damluji AA, Henry GA, Ahmad Y, Curtis JP, Nanna MG
J Am Heart Assoc, 2023 Oct 3, 12(19): e029057
https://doi.org/10.1161/JAHA.122.029057 | PMID: 37776222
Citations: NA | AltScore: NA
15. **The Association of Intensive Blood Pressure Treatment and Non-Fatal Cardiovascular or Serious Adverse Events in Older Adults with Mortality: Mediation Analysis in SPRINT.**
Krishnaswami A, Rich MW, Kwak MJ, Goyal P, Forman DE, Damluji AA, Solomon M, Rana JS, Kado DM, Odden MC
Eur J Prev Cardiol, 2023 Apr 25, 30(10): 996-1004
pii: zwad132. https://doi.org/10.1093/eurjpc/zwad132 | PMID: 37185634 | PMCID: PMC10390235
Citations: NA | AltScore: 2.35
16. **Plasma inflammation-related biomarkers are associated with intrinsic capacity in community-dwelling older adults.**
Lu WH, Gonzalez-Bautista E, Guyonnet S, Lucas A, Parini A, Walston JD, Vellas B, de Souto Barreto P, MAPT/DSA Group
J Cachexia Sarcopenia Muscle, 2023 Apr, 14(2): 930-939
https://doi.org/10.1002/jcsm.13163 | PMID: 36660894 | PMCID: PMC10067471
Citations: 6 | AltScore: 1.5
17. **Exploring Olfactory Dysfunction as a Marker of Frailty and Postoperative Outcomes in Head and Neck Cancer.**
Mady LJ, De Ravin E, Vohra V, Lu J, Newman JG, Hall DE, Dalton PH, Rowan NR
JAMA Otolaryngol Head Neck Surg, 2023 Sep 1, 149(9): 828-836
https://doi.org/10.1001/jamaoto.2023.1935 | PMID: 37498617 | PMCID: PMC10375382
Citations: NA | AltScore: 10.1
18. **The Association of Peripheral and Central Olfaction With Frailty in Older Adults.**
Nagururu NV, Bernstein IA, Voegtline K, Olson S, Agrawal Y, Rowan NR
J Gerontol A Biol Sci Med Sci, 2023 Jul 8, 78(7): 1276-1283
https://doi.org/10.1093/gerona/glac237 | PMID: 36502375 | PMCID: PMC10329228
Citations: 3 | AltScore: 460.4
19. **Management of Stable Angina in the Older Adult Population.**
Nanna MG, Wang SY, Damluji AA
Circ Cardiovasc Interv, 2023 Apr, 16(4): e012438
https://doi.org/10.1161/CIRCINTERVENTIONS.122.012438 | PMID: 36916288 | PMCID: PMC10121835
Citations: 1 | AltScore: NA
20. **Interleukin-6 Drives Mitochondrial Dysregulation and Accelerates Physical Decline: Insights from an Inducible Humanized IL-6 Knock-In Mouse Model.**
Nidadavolu LS, Cosardereliogl C, Merino Gomez A, Wu Y, Bopp T, Zhang C, Nguyen T, Marx-Rattner R, Yang H, Antonescu C, Florea L, Talbot CC, Smith B, Foster DB, Fairman JE, Yenokyan G, Chung T, Le A, Walston JD, Abadir PM
J Gerontol A Biol Sci Med Sci, 2023 Jun 13, 78(10): 1740-1752
pii: glad147. https://doi.org/10.1093/gerona/glad147 | PMID: 37310873 | PMCID:

PMC10562892
Citations: NA | AltScore: 24.1

21. **Associations between circulating cell-free mitochondrial DNA, inflammatory markers, and cognitive and physical outcomes in community dwelling older adults.**
Nidadavolu LS, Feger D, Chen D, Wu Y, Grodstein F, Gross AL, Bennett DA, Walston JD, Oh ES, Abadir PM
Immun Ageing, 2023 May 23, 20(1): 24
https://doi.org/10.1186/s12979-023-00342-y | PMID: 37221566 | PMCID: PMC10204157
Citations: 2 | AltScore: NA
22. **Hydropersulfides (RSSH) attenuate doxorubicin-induced cardiotoxicity while boosting its anticancer action.**
Pharoah BM, Zhang C, Khodade VS, Keceli G, McGinity C, Paolocci N, Toscano JP
Redox Biol, 2023 Apr, 60: 102625
https://doi.org/10.1016/j.redox.2023.102625 | PMID: 36773545 | PMCID: PMC9929489
Citations: 5 | AltScore: NA
23. **Interaction Between Frailty and Dementia.**
Rubin DS, Xue QL
JAMA Surg, 2023 Aug 1, 158(8): 888-889
https://doi.org/10.1001/jamasurg.2023.0378 | PMID: 37017961
Citations: NA | AltScore: NA
24. **Reimbursement for Olfactory Testing: A Growing Need at a Unique Time in History.**
Saraswathula A, Schlosser RJ, Rowan NR
JAMA Otolaryngol Head Neck Surg, 2023 Jul 1, 149(7): 567-568
https://doi.org/10.1001/jamaoto.2023.0837 | PMID: 37166819
Citations: NA | AltScore: NA
25. **A protocol for a wait list control trial of an intervention to improve pain and depressive symptoms among middle-aged and older African American women.**
Taylor JL, Clair CA, Lee JW, Atkins S, Riser TJ, Szanton SL, McCoy MC, Thorpe RJ Jr, Wang C, Gitlin LN
Contemp Clin Trials, 2023 Sep, 132: 107299
https://doi.org/10.1016/j.cct.2023.107299 | PMID: 37478967 | PMCID: PMC10527967
Citations: NA | AltScore: NA
26. **Context Matters: A Qualitative Synthesis of Adherence Literature for People on Hemodialysis.**
Taylor KS, Umeukeje EM, Santos SR, McNabb KC, Crews DC, Hladek MD
Kidney360, 2023 Jan 1, 4(1): 41-53
https://doi.org/10.34067/KID.0005582022 | PMID: 36700903 | PMCID: PMC10101575
Citations: NA | AltScore: 15.85
27. **Potential Role for Diet in Mediating the Association of Olfactory Dysfunction and Cognitive Decline: A Nationally Representative Study.**
Vohra V, Assi S, Kamath V, Soler ZM, Rowan NR
Nutrients, 2023 Sep 7, 15(18):
https://doi.org/10.3390/nu15183890 | PMID: 37764674 | PMCID: PMC10538071
Citations: NA | AltScore: NA
28. **The Association of Multiple Sensory Impairment and Telomere Length: The Health ABC Study.**
Vohra V, Cheng MZ, Xue QL, Simonsick EM, Lane AP, Agrawal Y, Rowan NR
Laryngoscope, 2023 Jun 23, 133(11): 3132-3138

https://doi.org/10.1002/lary.30842 | PMID: 37350340
Citations: NA | AltScore: NA

29. **Reduction in olfactory dysfunction prevalence among patients with diabetes taking metformin.**
Vohra V, Saraswathula A, Kamath V, Lane AP, Rowan NR
Int Forum Allergy Rhinol, 2023 Jul 7
https://doi.org/10.1002/alr.23236 | PMID: 37415545
Citations: NA | AltScore: 0.25
30. **A Study of Physical Resilience and Aging (SPRING): Conceptual framework, rationale, and study design.**
Walston J, Varadhan R, Xue QL, Buta B, Sieber F, Oni J, Imus P, Crews DC, Artz A, Schrack J, Kalyani RR, Abadir P, Carlson M, Hladek M, McAdams-DeMarco M, Jones R, Johnson A, Shafi T, Newman AB, Bandeen-Roche K
J Am Geriatr Soc, 2023 Jun 30, 71(8): 2393-2405
https://doi.org/10.1111/jgs.18483 | PMID: 37386913
Citations: NA | AltScore: NA
31. **Patterns of Daily Physical Movement, Chronic Inflammation, and Frailty Incidence.**
Wanigatunga AA, Chiu V, Cai Y, Urbanek JK, Mitchell CM, Miller ER 3rd, Christenson RH, Rebuck H, Michos ED, Juraschek SP, Walston J, Xue QL, Bandeen-Roche K, Appel LJ, Schrack JA
Med Sci Sports Exerc, 2023 Feb 1, 55(2): 281-288
https://doi.org/10.1249/MSS.0000000000003048 | PMID: 36170549 | PMCID: PMC9840658
Citations: 1 | AltScore: 3.25
32. **Wrist-Worn Accelerometry, Aging, and Gait Speed in the Baltimore Longitudinal Study of Aging.**
Wanigatunga AA, Liu F, Urbanek JK, Wang H, Di J, Zipunnikov V, Cai Y, Dougherty RJ, Simonsick EM, Ferrucci L, Schrack JA
J Aging Phys Act, 2023 Jun 1, 31(3): 408-416
https://doi.org/10.1123/japa.2022-0156 | PMID: 36241170
Citations: NA | AltScore: NA
33. **Interseason waning of vaccine-induced hemagglutination inhibition antibody titers and contributing factors to pre-existing humoral immunity against influenza in community-dwelling older adults 75?years and older.**
Wunderlich B, Laskow T, Li H, Zhang L, Abrams E, Tian J, Yu J, Chen Y, Tavenier J, Huang Y, Talaat K, Bream JH, Xue QL, Pawelec G, Leng SX
Immun Ageing, 2023 Jul 31, 20(1): 38
https://doi.org/10.1186/s12979-023-00362-8 | PMID: 37525151 | PMCID: PMC10388475
Citations: NA | AltScore: 1.75
34. **Olfactory Dysfunction and Balance Dysfunction are Associated with Increased Falls in Older Adults.**
Yesantharao LV, Vohra V, Cheng M, Simonsick EM, Agrawal Y, du Lac S, Rowan NR
Laryngoscope, 2023 May 9, 133(8): 1964-1969
https://doi.org/10.1002/lary.30733 | PMID: 37159236
Citations: NA | AltScore: 7.25

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RECOGNITION AND AWARDS (2023-2024)

Nicholas Rowan (2023)

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

Qinchuan Wang (2023)

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

MINORITY RESEARCH

General Brief Description of Minority Activities:

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

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

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

Minority Trainee(s):

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

No minority grant information specified.