# The Johns Hopkins University
# Claude D. Pepper Older Americans Independence Center
# 2016 OAIC Annual Directory

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**Table of Contents**



## ***Section I.*** ***DESCRIPTION OF CENTER***

The **Johns Hopkins Older Americans Independence Center (OAIC)** was established in June 2003 in order to support and develop the next generation of research and researchers necessary to determine causes and treatments for frailty in older adults. The central theme of the JHU OAIC is frailty, a syndrome of wasting and vulnerability characterized by the aggregate, age-related decline of a number of physiologic systems and presenting, clinically, as an identifiable syndrome. This syndrome is predictive of the onset and progression of disability, falls and mortality in older adults. A major recent focus of research in frailty at the Johns Hopkins Medical Institutions (JHMI) has been the characterization of potential causes of frailty and initial translation into testing of both pharmacological and behavioral interventions. Our fundamental research has laid the groundwork for such investigation into the proximate mechanisms, including molecular genetic mechanisms leading to frailty.

The JHU OAIC has six cores that work synergistically to accomplish these goals. The Leadership and Administrative Core provide scientific leadership, organization and infrastructure to lead and oversee the frailty-focused activities of the JHU OAIC. The Research Career Development Core (RCDC) provides research training, infrastructure, salary support and protected time to junior faculty who will become leaders and mentors in scholarship on frailty. The Pilot and Exploratory Studies Cores (PESC) supports cutting-edge pilot and exploratory studies that advance the development of effective prevention and /or therapies for frailty. Resource Core 1: Biostatistics Core provides data analytic and management expertise, and the development of new methodologies, for research on frailty. Resource Core 2: Biological Mechanisms Core provides state of the art expertise, infrastructure, and technology necessary to move forward biological and etiological research related to frailty. Resource Core 3: Clinical Translation and Recruitment Core provides clinical research training, oversight, and support in developing and implementing clinical research studies among frail older adults.

With the renewal of the center in July 2013, the JHU OAIC builds upon its driving frailty hypotheses, its high quality, committed, frailty-focused biological and biostatistical core expertise and training, and institutional commitment that have been cornerstones of this OAIC since its inception. It further builds on key frailty-related biological studies from the last cycle of this OAIC, which have provided focus on inflammation, mitochondrial biology, and the angiotensin system as intervention development targets. It now includes the addition of a transformative clinical translational and recruitment resource core to accelerate the translation of JHU OAIC frailty-related discoveries into clinical interventions. This evolution has greatly facilitated the mission of OAIC: To provide a

hypothesis driven, frailty-focused, highly interdisciplinary center where supported investigators are supplied with the expertise, resources, and training necessary to make fundamental etiological discoveries related to frailty and then move these discoveries towards frailty-focused interventions. We propose to accomplish this through the following specific aims.

The specific aims for this OAIC are selected to propel and translate research on frailty across the Johns Hopkins Medical Institutions, and in collaborations between OAICs. We aim to:

1) To stimulate, lead and develop effective frailty-focused interdisciplinary research programs that promote the maintenance of independence. Frailty will be the framework from which biological discovery and intervention development will be built.
2) To translate the frailty-focused new knowledge generated in this OAIC into targeted prevention and treatment strategies that help older adults maintain independence. A new clinical translational and recruitment resource core and a continuing frailty registry will facilitate this effort.
3) To provide the highest quality interdisciplinary expertise, support, infrastructure and technology in biological, data analytic and clinical research methodologies relevant to frailty research to OAIC supported trainees and investigators. These are offered to accelerate progress in frailty research.
4) To support the development of new and innovative methodologies, research strategies and technologies essential to the study of frailty. Special focus will be placed to leverage areas in which this OAIC has made substantial progress in the previous funding cycle.
5) To provide tailored frailty-related training and mentorship to junior investigators interested in developing careers focused on maintaining independence in older adults. We continue with a leadership team that is highly expert and committed to training the next generation of frailty-focused investigators.
6) To attract outstanding investigators and trainees to frailty research from across the Johns Hopkins University and beyond. We will do this in part by providing highly visible educational and training activities on a local and national level.

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## ***Section II.*** *RESEARCH, RESOURCES AND ACTIVITIES*

### II.A. RESOURCE CORE-1 (RC-1): BIOSTATISTICS CORE

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The Johns Hopkins Older Americans Independence Center (OAIC) has empowered by many-fold the creation of significant research, training and practice paradigms for addressing frailty in older adults. The functions supplied by the **Resource Core 1 (RC-1) Biostatistics Core** have been central in this. They include: our central role in the mentorship and training of junior colleagues in the statistics of frailty and aging; our development and dissemination of emerging resources and technologies for data

management and analysis; our provision of database and statistical expertise and support to scholarship on frailty and aging, needed methodological innovation, and collaborative intellectual leadership for the creation and translation of research on frailty. Outcomes of this Core, in collaboration in this OAIC and beyond, include advancement of knowledge on the ascertainment, biological and etiological underpinnings, health consequences, and treatment of frailty, research surmounting significant methodological challenges to the study of frailty, and the creation of intellectual capital and infrastructure for further advances. These have laid crucial groundwork for intervening on frailty. For close to 14 years our Biostatistics Core has dedicated a critical mass of leadership from gerontologically informed biostatisticians toward the amelioration of frailty in older adults through our OAIC, and its leadership has dedicated the same to research on aging for more than 20 years. Our leadership and our external advisory committee consider it crucial that this Core continue to contribute to the OAIC's overarching aims through the intellectual innovation, collaboration and support it provides. We propose to supply these contributions through specific aims to:

1. Mentor junior scholars supported by our Research Career Development Core (RCDC) and broader OAIC, with the goals of optimizing their: access to data analytic expertise and support; usage of modern database and analytic resources; training in quantitative methods needed to effect high quality research and effectiveness of collaboration with statistical colleagues. In all, we aim for mentored faculty to gain: recognition of the analytic challenges posed by the complexity of data on frailty, resources to accomplish valid and insightful research, and the ability to translate research into clinical practice.
2. Provide resources in data infrastructure and emerging computing technologies essential to discovery on frailty, and not possible absent an OAIC or its equivalent. We would continue to create modern, integrated, user-focused databases for the collection, documentation, and dissemination of high-quality clinical and biological data; and assist access to data onsite and that are publicly available, and to powerful analytic and computing hardware and software residing within this Core, OAIC, and our institution.
3. Stimulate and advance research on frailty at our institution, by:
    a. Providing analytic and data management support for research on frailty sponsored as high-priority by this OAIC, including RCDC and Pilot and Exploratory Studies Core (PESC) projects, external projects (EPs) and development projects (DPs) of other Cores. Specifically we would create sound study designs; assist the secure collection and housing of data; and design and implement valid statistical analyses to address studies' scientific aims. We would further collaborate with RC-2 to ensure the development of valid, reproducible findings from the many molecular markers that Core makes available and with RC-3 to avail expertise and resources on the design, analysis and implementation of translational studies to OAIC-affiliated researchers.
    b. Developing new methodologies for data analysis needed to translate basic research into clinical practice. Methods created through this Core's DPs have significantly advanced capability for validating frailty phenotypes and endophenotypes, laid groundwork for the study of frailty through genome and next-generation sequencing, and developed a framework for evaluating the dynamical properties of physiological systems and their implications for frailty. Building on these, we now propose work to further elucidate a potential multisystem etiology underlying frailty, design mechanistic studies to evaluate the dynamics of such an etiology, and translate resulting findings into intervention designs.
4. Partner with our fellow OAIC Cores, the scholarly community on aging at Johns Hopkins, and fellow OAICs to promote scholarship on frailty and aging, its translation into effective prevention and intervention strategies, and heighten its visibility. We would continue to provide

active leadership in our Leadership Council (LC) within our Leadership and Advisory Core (LAC) in identifying cutting-edge directions for the science of frailty; collaborate with all OAIC Cores and colleagues within and outside our institution, to advance knowledge on frailty and subsequent directions for translation between basic and clinical research; maintain a website optimizing public access to the advances of this OAIC, and attract new scientists to research on frailty.

The Biostatistics Core is dedicated to empowering our institution's scientists with the quantitative support and expertise needed to create, and translate into clinical practice, the next generations of research on frailty. It works to achieve this goal through (A) the provision of first-rate statistical reasoning and database resources to OAIC-affiliated research projects; (B) the development and support of new methodologies that are essential to studying the complex syndrome of frailty; (C) and the mentoring in quantitative methods of junior investigators with promise to develop into leaders in research on frailty.

To accomplish (A), we provide analytic and data management support for high priority research on frailty by assisting researchers in the design, development, and implementation of data systems; data acquisition and cleaning; refinement of study hypotheses; study design; design and implementation of data analyses; and preparation of manuscripts, presentations, and applications for research funding. To accomplish (B), we develop and test new methodologies for data analysis needed to translate basic research into clinical practice.

To accomplish (C), we provide individualized explication of statistical techniques as well as more general mentoring. Support spans study design, analytic design and implementation, and data management. In the current year our core continues to play a central role in the Pepper Scholars program, which aims to feedback for research in a formative stage, connect junior faculty to resources and collaborators that can broaden their reach and strengthen their research quality, and strengthen the network for research on frailty at our institution. The Scholars sessions have become a fixture of our program, occurring faithfully on a monthly basis.

A major contribution of our work is to provide analytic and data management support to OAIC-supported scholars and investigators. The work of OAIC scholars is detailed in the RCDC and Pilot Project sections of this report and our contributions outlined under key outcomes and publications below.

In this reporting period, we additionally have provided scientific leadership in four emerging topics that are key to the advancement of frailty research:

1) The first is our continuing RC1 Development Project work on the refinement of the physical frailty phenotype (development project). Multiple studies have proposed adaptations of the PFP. Many find that simplifications of the PFP perform essentially as well as the original PFP for predicting risk of adverse outcomes. However, no previous study has systematically compared the possible subsets of the five PFP criteria for their accuracy in discriminating the risk of frail and non-frail persons for adverse outcomes of aging. More importantly, no simplification of the PFP has been evaluated for its accuracy in identifying frailty syndrome relative to the original PFP. To address this, we have compared all 15 combinations of 3 or 4 PFP criteria to the 5-criterion PFP for their construct validity regarding frailty syndrome identification, and predictive validity for adverse outcomes of aging. All abbreviated PFPs exhibit high specificity and negative predictive value for identifying frailty syndrome, but

differ in their sensitivity and positive predicted value (PPV). Three-item PFPs proved insensitive but were best performers for PPV, well exceeding the original PFP on this metric. Regarding predictive validity, it was not merely the number of manifestations constituting the abbreviated PFPs but the specific manifestation combinations that distinguished the risk of adverse outcomes. Our findings support the need to tailor the choice of frailty tool to the intended use and purpose. These findings were published in the American Journal of Epidemiology. Efforts are underway to validate the results in the Cardiovascular Health Study.

2) The second project we initiated develops new, nationally representative estimates of frailty prevalence among older adults in the U.S., using data from the National Health and Aging Trends Study (NHATS). It also characterized by frailty status the risk of multiple adverse events affecting health care costs and quality of life for older adults. We found 15% of the older U.S. non-nursing home population to be frail, and 45% to be pre-frail. Age-related increases in frailty prevalence were from 9% in persons 65 to 69 to 38% of those 90 or older. Sizable race, income and regional disparities in frailty prevalence were observed. Adverse health outcomes were 2 to several times more common among frail vs. robust individuals. Frail individuals frequently exhibited disability, but considerably often did not, whereas robust individuals only rarely were disabled. Pursuit of findings regarding frailty disparities and progression among the pre-frail has potential to reduce disparities and extend the robust health span in older adults. These findings were published in the Journals of Gerontology: Medical Sciences in November 2015.
3) A third project is the development of a statistical methodology program in causal inference related to frailty. This project emerged from engagement with JHU School of Public Health faculty who participated in a pair of Committee for National Statistics / NIA sponsored conferences on innovative study designs for causal inference. To develop this topic, Dr. Bandeen-Roche formed a working group that also includes Dr. Xue (RC1 director), Dr. Gross (RCDC awardee) and faculty in Biostatistics, Mental Health, and Geriatric Medicine. The goal is the development novel statistical methods built around an important scientific question in aging, namely elucidating the etiology of frailty and role of multisystem dysregulation. This project is well under development and we envision the submission of a grant application in the coming months.
4) A fourth project is led by Dr. Reyhan Westbrook and uses Interleukin 10tm1Cgn (IL10tm) mice as a model of chronic inflammation and declining health span to test the hypothesis that older IL10tm frail mice would have alterations similar to frail, older humans in measured parameters of glucose metabolism, oxygen consumption (VO2), respiratory quotient (RQ), spontaneous locomotor activity, body composition and plasma adipokine levels. In order to test this hypothesis, Dr. Westbrook and his team performed insulin tolerance tests, glucose tolerance tests, body composition analysis, indirect calorimetry with activity monitoring, and plasma adiponectin and leptin measurements in cohorts of 3, 10, and 20 month old IL10tm female mice and compared them to age and gender matched C57Bl/6 mice. Dr. Xue and student analyst Parichoy Pal Choudhury assisted Dr. Westbrook with the analysis of data on oxygen consumption and body composition measures. Interestingly, old IL10tm mice had significantly decreased VO2 when normalized by lean mass, but not when normalized by fat mass or the lean/fat mass ratio. In addition, NMR based body composition analysis and dissection weights show that fat mass is decreased with age in IL10tm mice compared to controls. Dr. Westbrook won 1st prize in the Post-Doctoral Fellow & Junior Faculty category for his poster at the 7th Annual Research on Aging Showcase at the Johns Hopkins Bloomberg School of Public Health in April 2014, and presented a poster at the 2015 Annual Pepper Center meeting in April 2015. The results of this project are reported in a manuscript which is under final review by collaborators and will be ready for submission shortly. In the meantime,

Parichoy is leading a paper on the methods that were developed to test local and global differences in oxygen consumption trajectories between the experimental groups.

The RC1 continues to play important national and international scientific leadership roles. Dr. Bandeen-Roche led a symposium on "Disparities in Physical Functioning and Frailty among Older Americans: Findings from the NHATS," at the 2015 Annual Meeting of the Gerontological Society of American in Orlando, FL on November 21, 2015. At the National Pepper Centers Annual Meeting held in April 2016, Dr. Bandeen-Roche led the session on "ICTR workgroup on aging – research and educational CTSA/OAIC collaborations to move translation forward."

During this reporting period (May 2015 to present), the RC1 Biostatistics Core assisted 21 researchers in 15 projects and 9 grants on frailty and other aging phenotypes, including the design, development, and implementation of data systems; data acquisition and cleaning; refinement of study hypotheses; study design; design and implementation of data analyses; and preparation of manuscripts, presentations, and applications for research funding. This support has resulted in 9 publications to date in this reporting period. In addition, we've provided statistical consultation to two other U01s led by other Pepper center PIs. The RC1 has most recently provided mentorship to Drs. Brown (RCDC), Gross (RCDC), Mathur (Pilot), McAdams Demarco (RCDC, Pilot) and Piggott (external project) regarding K-award development. Additionally, RC1 has played an essential role in the development, implementation and management of the online frailty assessment calculator that launched in January 2016. We currently have over 40 registered users from the United States, Europe, Asia, Australia, and the Caribbean.

Dr. Bandeen-Roche was recognized with the 2016 Marvin Zelen Leadership Award in Statistical Science by the Harvard T.H. Chan School of Public Health.

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## II.B. RESOURCE CORE-2 (RC-2): BIOLOGICAL MECHANISMS CORE

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In Year 13 of our award, the **Resource Core 2 (RC-2) OAIC Biological Mechanisms Core** continues to expand its scope of support into a comprehensive molecular core that builds on the evolving science, infrastructure, and expertise across the Johns Hopkins Medical Institution. In the past decade, advances in molecular biology, in "omics" and in computational technologies have provided a logical basis for searching and identifying specific biomarkers associated with human phenotypes and diseases. These approaches can not only provide markers for human disease that are useful for nosology in heterogeneous clinical phenotypes but, more importantly, provide deep insight into pathophysiology and disease mechanisms that will form the bases for therapy. Consequently, the rationale for RC-2 is to provide the expertise, technology access and infrastructure, mentoring, and training necessary to facilitate the highest quality etiologic research in frailty.

Specific Aims:

1) **To provide state-of-the-art scientific expertise, technology and infrastructure necessary to facilitate cost-effective and efficient use of omics, other molecular approaches, and downstream computational technologies relevant to frailty research**. This aim brings the relevant technologies to the investigator either by core-supported analysis (genetic, genomic, epigenetic), access to a specialized JHU laboratory (telomere length, mitochondrial function, proteomic) or through an outside vendor (genetic, epigenetic, metabolomic) for biological measurements. However, choice of technology, access to expertise, study design, bioinformatics and integrative omics data analyses are supported within this core.
2) **To provide access to relevant biological samples from human subjects and animal models using either fresh or stored samples, and whole animals as needed to study frailty**. The core will assist in identifying the relevant samples and provide access, along with assistance and training in sample procurement and processing, as needed by each supported investigator.
3) **To facilitate the translation of RC-2 frailty research findings into intervention- or prevention-focused clinical studies in collaboration with the leadership of all other cores**. This aim focuses on molecular and computational methods for translational projects that are similar to aim 1 (discovery) but will usually differ in matters of scale and access to biological materials.
4) **To provide training, mentorship and guidance to the most promising junior investigators who can contribute to frailty research using molecular studies**. RC-2 faculty will provide them with guidance on available technologies/assays, study design, technical training (by technology transfer to their lab after laboratory rotation in an expert's lab), access to the resources in aims 1-3, and mentoring on study objectives, data analyses and interpretation.
5) **To continue to provide institutional, national, and international access and visibility for RC-2-related science and activities**. This aim seeks to identify at Johns Hopkins both biologically motivated junior faculty who value omics technology and technologically motivated junior faculty who value frailty research to contribute to this area.

During this reporting period (Year 13), RC-2 continues to evolve into a comprehensive molecular core that builds on the evolving science, infrastructure, and expertise across the Johns Hopkins Medical Institutions. Multiple senior leaders from across the JHMI have been engaged to supply the necessary expertise and infrastructure and to a) facilitate analytical strategies needed to analyze genetics and epigenetics data being generated, b) incorporate measurements of oxidative stress, mitochondrial function, inflammatory cytokines, senescent TCell markers, DNA methylation, and gene expression as needed into RC-2 sponsored frailty research, and c) develop improved access to human and/or animal biological samples and phenotypic data for needed for additional frailty research. This expansion has allowed RC-2 to support and develop integration of key biological and technological advances into frailty related studies. We continue to provide assay development support, access to samples and rodent models, sample processing, and biological expertise to all of our RCDC supported and PESC supported scholars and continue to provide a wide range of external support and expertise to individual investigators from across JHU regarding frailty endo-phenotype development, frailty measurement, human genetics, mouse model development, renin-angiotensin system measurement, DNA methylation measurement, biomarkers related to frailty, and in the use of frailty and the biomarkers of frailty as a risk factor for organ transplantation failure, surgery, and anesthesia. Important new findings help to differentiate between the impact of aging and chronic inflammation on renin-angiotensin system activity, novel insights into the frail mouse metabolism and metabolomics measures. Dr. Arking and colleagues found a crucial link between mitochondrial copy number and mortality and frailty.

Important new findings include the following:

- Ko F, Abadir P, Marx R, Westbrook R, Cooke C, Yang H, Walston J. Impaired mitochondrial degradation by autophagy in the skeletal muscle of the aged female interleukin 10 null mouse. Exp Gerontol. 2016 Jan;73:23-7. doi: 10.1016/j.exger.2015.11.010. Epub 2015 Nov 18.PMID: 26596403. PMCID: PMC4725733.
- Burks TN, Marx R, Powell L, Rucker J, Bedja D, Heacock E, Smith BJ, Foster DB, Kass D, O'Rourke B, Walston JD, Abadir PM. Combined effects of aging and inflammation on renin-angiotensin system mediate mitochondrial dysfunction and phenotypic changes in cardiomyopathies. Oncotarget. 2015 May 20;6(14):11979-93. PMCID: PMC4494917.
- Faghih M, Hosseini SM, Smith B, Ansari AM, Lay F, Ahmed AK, Inagami T, Marti GP, Harmon JW, Walston JD, Abadir PM. Knockout of Angiotensin AT2 receptors accelerates healing but impairs quality. Aging (Albany NY). 2015 Dec;7(12):1185-97. PMCID: PMC4712341.
- Tin A, Grams ME, Ashar FN, Lane JA, Rosenberg AZ, Grove ML, Boerwinkle E, Selvin E, Pankratz N, Arking DE. Association between Mitochondrial DNA Copy Number in Peripheral Blood and Incident Chronic Kidney Disease: Results from the Atherosclerosis Risk in Communities (ARIC) Study. J Am Soc Nephrol. 2016 Jan 21. PMID: 26794963

Key outcomes or other progress by specific aim:

1) To provide state-of-the-art scientific expertise, technology and infrastructure necessary to facilitate cost-effective and efficient use of omics, other molecular approaches, and downstream computational technologies relevant to frailty research. Genetic Studies: We continue to supply internal and external support in this area, with ongoing external support to the Long Life Family Study (LLFS; U01AG023744) through phenotype development and through the development of novel mitochondrial copy number analyses. A grip strength manuscript is in press with Aging Cell that represents a collaborative effort between investigators in 20 large aging cohort studies. Important new findings related to mitochondrial copy number, frailty, and mortality were published in the past year. Epigenetic studies: For the further development and adaptation of DNA methylation technologies we continue to provide recruitment and phenotypic development to external support to Dr. Andrew Feinberg and postdoctoral fellow Dr. Amy Vandiver, who published a manuscript and is submitting a second this year as she completes her PhD (R01 AG042187). Altered gene and protein expression: This support is provided through our leverage of state-of-the-art technology and genomic analysis, senior expertise, mentorship, and leadership available at JHMI towards frailty research via the laboratory of Drs. Arking and Chakravarti. Mitochondrial and oxidative stress: We have developed a panel of mitochondrial measurements that facilitated the funding of R-01 applications for Drs. Abadir and provide the basis of methodology development for another R01. Ongoing work in this areas has led to the publication of two papers in the frail mouse model in 2015, including one on mitophagy abnormalities and one on the interface between angiotensin system, aging, and inflammation. Bioinformatics necessary to integrate and interpret biological data: Additional measurement expertise for biomechanical measurement related to aging and inflammation has also been added in the past year with new collaborations developed with the Department of Bioengineering under the leadership of Denis Wirtz, PhD. This has resulted in the publication of one manuscript and the development of a second one related to a novel way to measure cellular aging. This may have broad clinical implications and will continue to be an ongoing developmental effort.

2) To provide access to relevant biological samples from human subjects and animal models using either fresh or stored samples, or whole animals as needed to study frailty. We continue to

provide and facilitate access to human and animal tissue samples on an as needed basis to trainees and supported investigators from established studies previously supported by the NIA including the Cardiovascular Health Study (CHS), the Women's Health and Aging Study (WHAS), and the Baltimore Longitudinal Study on Aging (BLSA). We also providing ready access to mouse models of frailty and biological samples derived from frail mouse models, including the IL-10-/- frail mouse and ATR1 and ATR2 KO mice developed in part by RC-2 support. We continue support ongoing work by, EP investigator Abadir, AFAR supported investigators Burks, Westbrook, and multiple other external investigators. We continue to provide access to an institutionally supported mouse phenotyping data base related to frailty in order to facilitate the identification and utilization of other mouse models with frailty or related phenotypes. This includes mouse tissues to Enid Neptune from Pulmonary medicine, Linda Resar from Hematology, Denis Wirtz from Bioengineering, and to a newly funded stem cell investigator, Aleksandra Leszczynska with a recent Pilot award.

3) To facilitate the translation of RC-2 frailty research findings into intervention- or prevention-focused clinical studies in collaboration with the leadership of all other cores. This aim focuses on molecular and computational methods for translational projects that are similar to aim 1 (discovery) but will usually differ in matters of scale and access to biological materials. We continue to focus on the development of clinical trials, on measurements important to the outcomes and biological discovery within those clinical trials. These include the Vitamin D study U01 led by Dr. Appel, "Vitamin D Supplements to Prevent Falls in Older Adults: A Dose-Response Trial," and the losartan study detailed in the PESC section, where we provide inflammatory measurement expertise, and a U01 led by Dr. Walston focused on inflammatory phenotype and intervention development in collaboration with Dr. Bandeen-Roche and others in RC1. Finally, the RC2 has helped to facilitate the development of a novel wound care technology that targets diabetic and chronic non-healing wounds in older adults. Building on an ARB based approach, investigator Abadir and Walston have leveraged and NIA R21 and Maryland technology development grant to 4 separate patents and to the development of a commercialization strategy that has resulted in the licensing of the technologies to a startup Biotech company in Baltimore. The first publication is in revision to Science Translational Medicine.

4) To provide training, mentorship and guidance to the most promising junior investigators who can contribute to frailty research using molecular studies. RC-2 faculty will provide them with guidance on available technologies/assays, study design, technical training (by technology transfer to their lab after laboratory rotation in an expert's lab), access to the resources in aims 1-3, and mentoring on study objectives, data analyses and interpretation. We have continued to work with all RCDC and Pilot supported investigators, and with postdoctoral fellows Dr. Tyesha Burks and Dr. Reyhan Westbrook on their biologically focused projects. We have provided technology, laboratory supplies, measurement expertise, critical reviews, and career guidance to these individuals as they develop K awards. We also provide ongoing support to External Project (EP) investigators Feinberg, Leng, Abadir, Wirtz, Resar, Franco, Gross, Piggott, Brown, Hogue, Chung, Neptune, and Fedarko as they develop manuscripts related to frailty, aging, inflammation, mitochondrial biology, and the renin angiotensin system.

5) To continue to provide institutional, national, and international access and visibility for RC-2-related science and activities. This aim seeks to identify at Johns Hopkins both biologically motivated junior faculty who value omics technology and technologically motivated junior faculty who value frailty research to contribute to this area. We have established this core as the

'go to' place for collaboration and expertise development across surgical, medical, and now engineering disciplines over the past year through provisions of services and expertise listed above. We continue to provide broad exposure to our work through outreach efforts at the Gerontological Society of America Annual Meetings, the annual International Frailty and Sarcopenia Meetings, including a key note address on the biology of frailty in 2015 and a frail mouse symposium in 2016.

RC2 Development projects, 2014-2016:

- Year 11-12 RC-2 Development Project: "Integrative omics analyses of the IL10Tm/Tm frail mouse" PI: Dan Arking, PhD; co-investigator: Dr. Reyhan Westbrook, OAIC Diversity Supplement Awardee. The IL10Tm/Tm mouse, like frail humans, develops age-related skeletal muscle weakness, endocrine abnormalities, inflammatory pathway activation, mitochondrial abnormalities, and early mortality. These findings support the further use of this mouse to dissect molecular pathways that may impact frailty. During the first year of this award, Dr. Westbrook collaborated extensively with Dr. Rafael De Cabo of the NIA in order to more extensively characterize the metabolic phenotype of this mouse model. Findings include marked decrease in metabolic rate later in life, as well as marked decrease in fat pads and adipokines. Manuscript is developed and nearly ready for submission.
- From this same project, metabolomic profiling has been completed and analysis is underway. Significant differences in tryptophan metabolism, in TCA cycle components, and in lipid metabolites between chronically inflamed and control mice have been identified. Working with Dr. Walston and members of the Biology of Healthy Aging Research team, Dr. Westbrook has established collaborative efforts for improved targeted detection methodology with Dr. Ruin Moaddel at the NIA and with Dr. Anne Le of Johns Hopkins Department of Pathology. Each of these investigators is working closely with him and with the OAIC RC2 to optimize a targeted detection approach for crucial pathways related to energy expenditure, mitochondrial energy production, and tryptophan metabolism. This work is crucial to the developmental efforts of the OAIC in that it provides an important new tool in detecting frailty and chronic inflammation related metabolic alterations that highlight underlying organismal vulnerabilities related to frailty and inflammation. This work has resulted in the awarding of the 2016 AFAR Translational Research Post-Doctoral Fellowship Award to Dr. Westbrook. This award enables him to continue on this line of investigation, and will allow him to translate his mouse related findings into human subjects with an eye towards improving diagnostics for frailty and chronic inflammation consequences in older adults.

- Year 13 RC-2 Development Project: "Altered skeletal muscle metabolic pathways in the pathogenesis of sarcopenia." PI: Pingbo Zhang; Mentors: Richard Semba, Luigi Ferrucci. Sarcopenia plays a central role in frailty. Our ongoing studies demonstrate that muscle quality, defined as the amount of strength generated by a unit of muscle mass, is a better definition for sarcopenia than muscle mass or muscle strength alone. Muscle quality shows a linear decline with older age. The biological pathways that lead to the age-related decline in muscle quality are not well understood. Animal studies show that there are circulating factors, most of which are uncharacterized, that rejuvenate aging skeletal muscle. Using a targeted metabolomics approach, our preliminary studies have identified three novel metabolic pathways involving circulating polyamines, methionine, and tryptophan in association with muscle quality in older adults. It is not known whether these same metabolites are altered in skeletal muscle itself or whether the plasma and skeletal muscle tissues levels of metabolites are correlated. We hypothesize (1) low putrescine (a polyamine), high methionine, and high tryptophan in both

skeletal muscle and plasma are associated with low muscle quality, and (2) there is a significant correlation of polyamines, methionine, and tryptophan levels between skeletal muscle and plasma. The specific aims are to characterize the relationship of skeletal muscle and plasma (1) polyamines, (2) methionine, and (3) tryptophan with muscle quality in adults and to examine the correlation of polyamines, methionine, and tryptophan between plasma and skeletal muscle. To address these hypotheses, we will measure skeletal muscle and plasma metabolites in cross-sectional, pilot study of 80 adults who have quadriceps muscle biopsy, plasma, and concurrent muscle quality measurements in the Baltimore Longitudinal Study of Aging. Metabolites will be measured using liquid chromatography-tandem mass spectrometry. These metabolites are potentially modifiable risk factors. Further insight of their relationships with the age-related decline in muscle quality may drive new investigations that target specific metabolic pathways involved in sarcopenia. Pilot data from this study will be used to support a future NIH grant application on sarcopenia and frailty. Progress Updates: Plasma metabolites have been measured in 80 BLSA participants using LC-MS/MS. Metabolites were extracted and concentrations were measured. In the next few months, skeletal muscle samples from the same 80 BLSA participants will be homogenized using a bead-based homogenizer in combination with a simple extraction protocol. Skeletal muscle metabolites will be measured using the same methods as for plasma.

Externally Supported projects:

- Sean Leng, MD, PhD. NIH/NIAID R01 AI108907. Influenza Vaccine Failure in Adults over Age 75: Role of Chronic CMV Infection. Funded 2014. This project receives ongoing support.
- Dorry Segev, MD, PhD. NIH/NIA R01 AG042504. Frailty and Risk Prediction in Older Adults Considering Kidney Transplantation. Funded 2013. This project receives ongoing support.
- Sean Leng, MD, PhD. NIH/NIA R21 AG043874. Chronic CMV Infection in the Elderly: Diagnosis and Link to Chronic Inflammation. Funded 2013. This project receives ongoing support.
- Jeremy Walston, MD, and Peter Abadir, MD. NIH/NIA R21 AG043284. Novel Formulation of ARB based for Treatment of Wounds in Aging. This project receives ongoing laboratory and animal model support.
- Peter Abadir, MD. NIH/NIA K23 AG0305005 and new related R01AG046441: Age Related Changes in Angiotensin Receptors and its Role in Chronic Inflammation. This project receives ongoing support.
- Andy Feinberg, MD. NIH/NIA R01AG042187: The Role and Genetic Mechanism of Epigenetic Plasticity in Age-Related Disease. This project receives ongoing support.

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## II.C. RESOURCE CORE-3 (RC-3): CLINICAL TRANSLATION AND RECRUITMENT CORE

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In order to more effectively meet JHU OAIC's goal of translating frailty-related etiological discoveries into clinical studies that help maintain independence in older adults, and to overcome the substantial barriers to success in clinical investigation for junior investigators, the leadership of this OAIC made a

strategic decision to develop this resource core. The **Resource Core 3 (RC-3) Clinical Translation and Recruitment Core** provides to supported OAIC investigators: 1) comprehensive training and mentorship in clinical research that spans from study design through implementation through outcome interpretation, 2) clinical research space and assistance with all aspects of forms and protocol development, data collection, and recruitment of human subjects, 3) an active registry of more than 1000 older adults who have consented to be contacted for aging and frailty related studies, and 4) synergy with other cores in order to optimize all aspects of frailty-related study design, data collection, and biological measurement and junior faculty training. This synergy is greatly augmented core leader, Dr. Robert Wise, who has considerable expertise in the development, implementation, and conduct of clinical physiological studies and clinical trials. In addition, the daily operations are led by a highly skilled and experienced research program manager with expertise in the measurement of frailty, mobility, and cognition, as well as expertise in protocol development and implementation and in minority subject recruitment and retention. This initiative, which is closely aligned with the JHU Division of Geriatric Medicine and Gerontology goals of better integrating clinical practice with clinical research, is in large part funded by philanthropic resources from the Division. RC3 supports the study design, implementation, training, mentorship, and recruitment needs of the Losartan pilot study (Dr. Lee), the recruitment and coordinating needs of ATP skeletal muscle kinetics pilot (Dr. Weiss), and the coordinating and measurement needs of our RCDC and Pilot scholars, as needed. The core also supports external projects that require frailty-related recruitment and clinical research study support, including: support to the R01 award and the K-23 award of former Pilot / RCDC supported investigators, Dr. Leng and Dr. Abadir, respectively; support for recruitment into an NIH supported clinical trial for anemia of unexplained etiology in older adults; and recruitment, minority outreach, and frailty measurement expertise to an R-01 focused on reducing disability in community dwelling older adults.

The goals of RC-3 are outlined in the following <u>specific aims</u>:

1) To provide mentorship and training in all aspects of human subjects research to OAIC supported investigators, including study conceptualization, study design and outcomes, definition of interventions, measurement, protocol development and implementation, regulatory approval, quality assessment procedures, and standard operating procedures for all RC-3 supported investigators
2) To provide the oversight necessary to ensure optimal and safe performance of clinical studies supported by this OAIC, including oversight of human subject protection, IRB applications, FDA applications, and data safety and monitoring board (DSMB) development.
3) To provide the clinical research infrastructure and services necessary to facilitate the successful conduct of frailty-related clinical studies, including
    a) Provision of space to perform clinical research
    b) Direct assistance with protocol development, standard operating procedures, regulatory documentation preparation, data safety and monitoring board development by an experienced research program manager.
    c) Direct assistance with data collection in human subjects, including advertising for studies, recruitment of human subjects from a registry and the community, clinical measurement assistance (frailty, function, mobility, cognition), and phlebotomy assistance to all OAIC supported investigators. This will include training of clinical research staff in these areas as well.

To further develop and maintain a research registry of older adults categorized by frailty status and consented to be contacted for future clinical research projects related to aging and frailty. The utilization of this registry will be prioritized to OAIC supported investigators.

**Healthy Aging Studies Unit:** The central hub of RC-3 is the Healthy Aging Studies Unit (HASU; formerly called the Clinical Translational Unit). In preparation for the conduct of frailty-related clinical and clinical intervention studies, we recognized the value of creating a unit broadly aimed at aiding investigators in the design, recruitment, and implementation of clinical studies involving human subjects. The HASU was founded on the Bayview Medical Campus, adjacent to the Division of Geriatric Medicine and Gerontology clinical sites and adjacent to the Biology of Healthy Aging laboratories. It supports recruitment and clinical translation for RCDC and PESC supported investigators Abadir, Weiss, and Schoenborn, and external projects led by Feinberg, Leng, Chung, and Walston. It includes the frailty registry (described below) and also supports Dr. Walston's study of the "Physiologic and Molecular Basis of the Syndrome of Frailty" (IRB# NA_00052046; also known as MAPPS). Dr. Leng's influenza focused R01 receives support to recruit and study over 150 individuals, and Dr. Walston is recruiting over 600 older adults in a surveillance study of pneumococcal colonization in response to vaccination sponsored by the CDC (PI: Harrison).

**Frailty Registry:** In view of the challenges of enrolling older study subjects in clinical studies, particularly those who are frail and pre-frail, the OAIC established a registry of patients to assist in recruitment and enrollment efforts. To that end, we obtained IRB approval for the project, entitled "A Registry of Older Adults Who May Be Willing to Participate in Research (IRB# NA_00013162)." This registry is composed of volunteer outpatients recruited from the Beacham Geriatric Medicine Clinic, the Bayview General Internal Medicine Outpatient clinic, and volunteers who call in from throughout the Baltimore metropolitan area in answer to newspaper advertisements. If they agree to participate and sign the consent form, patients undergo frailty screening protocol by trained personnel and demographic information is collected. Further data, including past medical history and laboratory results, are systematically abstracted from their medical records. RC-1 staff created and maintains a data base to store data and enable data base inquiries. Most OAIC supported investigators have utilized this resource since its inception. There are currently over 1200 participants in registry database who have been characterized for frailty, many of whom have agreed to be re-contacted for additional research studies.

**Current projects supported by the RC-3:**

OAIC Pilot Study: Peter Abadir, MD, Jeremy Walston, MD: "A Study of Muscle Strength Maintenance in Older Adults." Please see full description provided in the Pilot Core report. RC-3 provides recruitment, scheduling and measurement support.

OAIC Pilot Study: Robert Weiss, MD: "Energy Production in Frailty: Skeletal Muscle ATP Kinetics in Frail, Older Adults." Please see full description provided in the Pilot Core report. RC-3 provides recruitment.

OAIC Pilot Study: Nancy Schoenborn, MD: "Understanding patient preferences for prognosis communication among older adults across the spectrum of frailty." Please see full description provided in the Pilot Core report. RC-3 provides recruitment assistance.

K23 Grant: Peter Abadir, MD, PhD: "Age Related Change in Angiotensin Receptors and its Role in Chronic Inflammation." With this NIA K23 award, Dr. Abadir aims to evaluate specific factors that may play a role in late life weakness, increased morbidity and mortality. Angiotensin receptors 1 and 2 (AT1R and AT2R) are found on the surface and on the inside of virtually all human cells. This study evaluates the relationships among these receptors in immune system cells as people age, and

determines how these changes might influence chronic inflammation, frailty and late life vulnerability. RC-3 has provided recruitment support.

R01 Grant: Andrew Feinberg, MD: MAPPS Sub-Study for "The Role and Genetic Mechanism of Epigenetic Plasticity in Age-Related Disease." Dr. Feinberg's R01 grant explores the relationship between genes, epigenetic modifications of DNA, and age-related phenotypes that increase susceptibility to disease, focusing on two hypotheses: (1) that genes control the mean values of DNA methylation and the mean values of phenotypes and (2) that genes control the variability, or spread, of DNA methylation and phenotypes in a population. To study frailty as one of these phenotypes, Dr. Feinberg utilizes Dr. Walston's MAPPS study and the OAIC RC-3 has provided recruitment and phlebotomy support from the registry.

R01: Sean Leng: "Influenza Vaccine Failure in Adults over Age 75: Role of Chronic CMV Infection." Dr. Leng's recently funded R01 grant investigates the role of chronic CMV infection as defined by cellular CMV DNA and its underlying humoral and T-cell mechanisms contributing to the influenza vaccine failure. RC-3 provides recruitment, scheduling and evaluation support.

CDC/MD Department of Mental Health and Hygiene / Johns Hopkins Bloomberg School of Public Health: L. Harrison (PI). "Surveillance study of pneumococcal colonization in response to vaccination." RC-3 provides recruitment, scheduling, and assessment/measurement.

U01: Lawrence Appel: The NIA funded U01 "Vitamin D Supplements to Prevent Falls in Older Adults: A Dose-Response Trial" is led by Dr. Lawrence Appel and Dr. Walston leads the ancillary studies committee. The study aims to conduct a dose response trial that will determine if supplemental vitamin D can prevent falls, and other poor outcomes, in older persons. The trial is designed to identify the best overall dose of vitamin D supplementation and confirm the level of efficacy of that dose for fall prevention. The OAIC RC3 plans to provide recruitment

U01: J Walston: "Variability of inflammatory markers in older adults." Funding is pending for this study. If funding is forthcoming, recruitment for this study would commence in the summer/fall at JHU. RC3 personal would be responsible for the implementation and recruitment of this study.

R23: J Walston: "Lactoferrin Pilot." Funding is pending for this study. If funding is forthcoming, recruitment for this study would commence in the summer/fall at JHU. RC3 personal would be responsible for the implementation and recruitment of this study.

**Data and Safety Monitory Board (DSMB):** An OAIC DSMB was established to provide independent safety review for all OAIC interventional human subjects studies. All five members of the DSMB are external to the OAIC, with two members from the University of Maryland, and all have been approved by the NIA Program Officer. The DSMB meets semi-annually, or more frequently as needed, to review progress, findings and all potential safety issues related to OAIC human subjects research projects. The DSMB first convened in February 2014 to carefully review and discuss its operating charter. The DSMB then met in May 2014 and has since met every 6 months, with the most recent meeting taking place in January 2016. The DSMB meets semi-annually, or more frequently as needed, to review progress, findings and all potential safety issues related to OAIC human subjects research projects. Reports and minutes from each meeting have been submitted to the NIA Program Officer. The next meeting will take place in July 2016.

## II.D. RESEARCH CAREER DEVELOPMENT CORE (RCDC)

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The purpose and function of the **Research Career Development Core (RCDC)** of the Johns Hopkins OAIC are to identify, attract, select, and to provide training, mentoring and translational research skills for junior faculty who will become leaders in the development and implementation of research in the field of frailty and interventions that preserve independence for older adults. Led by Gary Gerstenblith, MD, Professor of Medicine and Director of Clinical Research for the Cardiology Division, it emphasizes the development of skills required to apply basic research findings to clinical investigation and interventions, translate clinical findings into mechanistic studies, and disseminate the results of clinical investigation to the health provider and broader community, with the aim of decreasing the likelihood for the development of frailty and improving clinical outcomes for frail older adults. Per NIA director, this RCDC will be restructured as a **Research Education Component** for the coming year.

Consonant with this purpose, the specific aims of the RCDC to accomplish these goals are:

1) To identify, attract, and select for career development support a diverse and interdisciplinary group of junior investigators from across JHU with the greatest potential to become outstanding research leaders focused on frailty and how to ameliorate it, and on maintaining independence with increasing age.
2) To provide the research infrastructure and salary support to these junior investigators so as to enable them to successfully bridge the critical transition to independent research leadership and grant funding. The resources provided will ensure protected research time and access to core resources necessary to advance their productivity and interdisciplinary training.
3) To provide each supported individual with mentorship individualized to his or her needs and to monitor the progress of the research project and career development.
4) To develop for each supported individual a program of subject-area, methodological and leadership training needed to equip them to excel in their career goals, and promote its successful completion.
5) To provide an academic home and an intellectual 'stimulus zone' for supported faculty as well as postdoctoral fellows, pre-doctoral students, and junior faculty working on frailty-related projects. Its cornerstones will include an energetic and welcoming senior faculty; a monthly research-in-progress forum fostering interactions among the senior faculty, RCDC supported investigators, all other OAIC supported investigators, and the larger community on aging at JHU; the sponsorship of a seminar series on frailty in collaboration with the LAC and the Johns Hopkins Center on Aging and Health (COAH); and the provision of an informational network facilitating access to the many other intellectual enrichment opportunities at JHU. In all we aim to create the critical mass of investigators needed to spark clinical multidisciplinary research interaction and collaboration among supported faculty.

The RCDC serves as a center of training, mentorship and networking for talented junior investigators spanning 3 levels of development: 1) K-Eligible Investigators: We dedicate our highest level of support for junior faculty members deemed to have promise for K or other career development awards. We have designed our Core to provide salary support to 3 individuals in any given year. These individuals also are provided with material support from all 3 RCs. 2) R-Eligible Investigators: Junior investigators supported by K or other career development awards, and who are actively engaged in

research relevant to the goals of this OAIC, are prioritized for external project support from the RCs and encouraged to apply for PESC resources as needed. They also receive ongoing mentorship and education to facilitate the awarding of an independent investigator (e.g. R-01) award. 3) Other Trainees: Interested junior faculty, post-doctoral fellows and pre-doctoral students are encouraged to participate in OAIC-sponsored activities, provided with mentorship, and encouraged to develop research and career goals that will enable them to be eligible for formal OAIC support. In recent years, such trainees have made substantial contributions to the scientific life of this OAIC. Many have become RCDC, PESC, EP, and diversity supplement supported scholars.

RCDC awardees, 2015-2016:

1) Charles Brown, MD. "The association between baseline frailty and postoperative delirium or functional decline after cardiac surgery, and a potential intervention to improve outcomes." Mentors: Charles Hogue, Jeremy Walston. This study aims to determine the association between frailty and postoperative delirium or functional decline, using rigorous assessments of delirium and functional status. Also, optimizing depth of anesthesia represents a potential intervention, since frail adults may be vulnerable to a relative anesthetic overdose. However, randomized trials of anesthetic depth in cardiac surgery patients have not been reported, nor has the range of anesthetic depth been examined in frail cardiac surgery patients. This gap in understanding motivates this study to measure depth of anesthesia in frail cardiac surgery patients to determine if reducing depth of anesthesia is a modifiable target to improve postoperative outcome. Progress Updates: Dr. Brown has successfully enrolled 80 patients (goal was n=72). Further enrollment is also ongoing. He is evaluating data for data cleaning, missing-ness, and will next begin analyzing the data for manuscripts.
    - Awarded an Johns Hopkins inHealth grant to evaluate mobility after cardiac surgery
    - Awarded an International Anesthesia Research Society Grant
    - Awarded a Johns Hopkins Clinician Scientist Award.
    - Robinson TN, Walston JD, Brummel NE, Deiner S, Brown CH 4th, Kennedy M, Hurria A. Frailty for Surgeons: Review of a National Institute on Aging Conference on Frailty for Specialists. J Am Coll Surg. 2015 Dec;221(6):1083-92. doi: 10.1016/j.jamcollsurg.2015.08.428. Epub 2015 Sep 11. Review. PMID: 26422746. PMC4673051.
    - Brown CH 4th, Max L, LaFlam A, Kirk L, Gross A, Arora R, Neufeld K, Hogue CW, Walston J, Pustavoitau A. The Association Between Preoperative Frailty and Postoperative Delirium After Cardiac Surgery. Anesth Analg. 2016 Apr 19. [Epub ahead of print] PMID: 27096563. NIHMS ID: NIHMS761046. In process at NIHMS.

2) Alden Gross, PhD, MHS. Research Career Development Core (RCDC). "Intersection of Domain-specific Cognitive Performance and Frailty: An Integrative Data Analysis." Mentors: Qian-Li Xue, Ravi Varadhan, Michelle Carlson. The overall goal of this proposed research is to determine the role of global and domain-specific cognitive performance in the development of frailty using a pooled analysis of three large longitudinal observational studies with prospectively measured data on cognitive performance and frailty among more than 6,500 adults over age 70. Dr. Gross hypothesizes that although frailty and cognitive impairment are both age-related phenomena, common but distinct processes underlie them and thus the conditions overlap more with age. Progress Updates: A manuscript was recently published in Journals of Gerontology: Medical Science. Dr. Gross was awarded an NIA K01 award, starting in April 2016.

- Gross AL (PI). NIH/NA K01 AG050699. Intersection of Physiologic Frailty and Cognitive Performance in Older Adults: An Integrative Data Analysis
- Gross AL, Xue QL, Bandeen-Roche K, Fried LP, Varadhan R, McAdams-DeMarco MA, Walston J, Carlson MC. Declines and Impairment in Executive Function Predict Onset of Physical Frailty. J Gerontol A Biol Sci. 2016 Apr 15. pii: glw067. [Epub ahead of print] PMID: 27084314. PMC Journal – In Process

3) Rani Hasan, MD, MHS. Research Career Development Core (RCDC). "Frailty in Elderly Patients Undergoing Transcatheter Aortic Valve Replacement (TAVR) for Symptomatic Severe Aortic Valve Stenosis: Impact on Outcomes, Effect of TAVR on the Frailty Phenotype, and Association with Inflammation." Mentors: Drs. Jon Resar, Gary Gerstenblith, and Bruce Leff. This study proposes to: 1) evaluate the prognostic impact of frailty on outcomes following TAVR, through a retrospective analysis of this patient group to evaluate whether pre-procedure frailty is independently associated with adverse outcomes among elderly patients undergoing TAVR for AS; 2) evaluate the impact of TAVR on frailty through a prospective observational study of elderly patients with AS undergoing TAVR at JHMI with serial assessment of frailty before and at one month and six months after TAVR; and 3) investigate inflammation as a pathophysiologic link between aortic stenosis and frailty by evaluating pre- and post-TAVR levels of inflammatory markers that are implicated as a possible link between the pathophysiology of AS and frailty. Progress Updates: Dr. Hasan has an approved IRB protocol for his proposed studies: IRB00054646. There have been no adverse events to date. Dr. Hasan met and reviewed statistical plans with Biostatistics Core Leader, Dr. Bandeen-Roche. Preliminary statistical analysis for retrospective study is underway. Recruitment for prospective study has begun and is ongoing. As part of the prospective study, Dr. Hasan has begun a collaborative efforts with Drs. Karin Neufeld and Atsushi Kamiya of the Department of Psychiatry to study delirium and its impact in the same patient population. Dr. Hasan is also planning a substudy to evaluate provider and patient perceptions of frailty within the prospective study; this should begin in June. Dr. Hasan presented at the JHU OAIC Pepper Scholars Meeting on "Frailty in Elderly Patients Undergoing Transcatheter Aortic Valve Replacement (TAVR) for Symptomatic Severe Aortic Valve Stenosis" on February 3, 2016.

Significant results:

Investigators supported by the JHU OAIC Research Career Development Core have published a number of articles important to advancements in the field of frailty research. These include:

- **Brown CH 4th (current RCDC awardee)**, Max L, LaFlam A, Kirk L, **Gross A (current RCDC awardee)**, Arora R, Neufeld K, Hogue CW, Walston J, Pustavoitau A. The Association between Preoperative Frailty and Postoperative Delirium after Cardiac Surgery. Anesth Analg. 2016 Apr 19. [Epub ahead of print] PMID: 27096563. NIHMS ID: NIHMS761046. In process at NIHMS.
- **Gross AL (current RCDC awardee)**, Xue QL, Bandeen-Roche K, Fried LP, Varadhan R, McAdams-DeMarco MA, Walston J, Carlson MC. Declines and Impairment in Executive Function Predict Onset of Physical Frailty. J Gerontol A Biol Sc i. 2016 Apr 15. pii: glw067. [Epub ahead of print] PMID: 27084314. PMC Journal – In Process
- **McAdams-DeMarco MA (former RCDC awardee)**, Tan J, Salter ML, Gross A (current RCDC awardee), Meoni LA, Jaar BG, Kao WL, Parekh RS, Segev DL, Sozio SM. Frailty and Cognitive Function in Incident Hemodialysis Patients. Clin J Am Soc Nephrol. 2015 Nov 16. pii: CJN.01960215. [Epub ahead of print] PMID: 26573615. PMCID: PMC4670760.

- **Wang GC (former RCDC awardee)**, Han C, Detrick B, Casolaro V, Levine DM, Fried LP, Walston JD. Herpesvirus Infections and Risk of Frailty and Mortality in Older Women: Women's Health and Aging Studies. J Am Geriatr Soc. 2016 Apr 30. doi: 10.1111/jgs.14090. [Epub ahead of print] PMID: 27131018. NIHMS ID: NIHMS756218. In process at NIHMS.

Dr. Jeremy Walston was recognized with a 2015 David M Levine Excellence in Mentoring Award by the Johns Hopkins Department of Medicine.

Key outcomes or other progress:

The JHU OAIC RCDC has helped to establish the careers of many of its RCDC-supported faculty through the **successful support of K01/K23 funding**. Drs. Peter Abadir, George Wang, Frank Lin, Rita Kalyani, Mara McAdams-DeMarco, and Yuri Agrawal have each been award NIH career development awards in the past several years. Most recently, RCDC awardee Dr. Alden Gross received a **K01 award** (after receiving a merit score of 10), for his project "Intersection of Physiologic Frailty and Cognitive Performance in Older Adults: An Integrative Data Analysis" that began in April 2016. Additionally, Drs. Abadir and Leng, both former RCDC supported scholars, received their **first R01 awards** with OAIC support in the past years. We continue to support many other present and former scholars for R award development. We have effectively utilized our Pepper Scholars Program, a monthly research in progress series, and the Frailty Working Group (both described above) as mechanisms to help stimulate and develop a 'farm team' of investigators who are committed to developing research in this area, and ensuring that they are able to generate the data necessary to move their science and careers forward with assistance from the OAIC.

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## II.E. PILOT / EXPLORATORY STUDIES CORE

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The overall goal of the OAIC **Pilot and 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 provides funding, access to biostatistical, biological, and clinical research core resources, and mentoring and oversight to completion of pilot and exploratory studies. Because of the importance of these studies to the development of new scientific priorities, institutional resources have been added to this core to help maximize productivity and development around frailty science. The PESC Core leaders, in close collaboration with the OAIC Leadership Council, set scientific goals for the next stages of frailty research, and then work to identify investigators whose expertise and career goals would be applicable to furthering knowledge in these target areas. The leadership and resources of these cores are then focused on the development, conduct and eventual translation of high impact pilot studies. The proposed studies must be novel, hypothesis-driven research that establishes potential mechanisms, etiologies, screening approaches or evaluates potential therapies to prevent or ameliorate the syndrome of frailty and related endophenotypes and hence maintain independence. It is expected that PESC supported studies will establish preliminary data that will lead to substantive, long term external funding that can bring this research to completion. Given the recent progress of OAIC supported investigators findings related to mitochondria, inflammation, and angiotensin dysregulation in frailty and aging, special focus was given to these areas for the choices of pilot and exploratory studies

articulated in Year 11 and continuing into Year 12, the current reporting period. The specific aims of this Pilot core are:

1) To solicit, select, and support pilot and exploratory studies (PES) that advance the biological understanding of frailty, or studies that move OAIC biological discoveries related to frailty towards intervention development. This process enables the PESC and other core leaders to identify areas of focus that are crucial to accelerating the progress of frailty-related research.
2) To support development of well-designed and informative PES, by providing intellectual leadership that articulates the scientific vision, goals and priorities of the center, and ensures optimal study design and utilization of the extensive intellectual and research resources offered by other OAIC cores.
3) To provide and conduct longitudinal mentorship and oversight, from conception to translation, for investigators whose pilot proposals are supported by the OAIC. This includes content and career mentorship, assistance in helping the awardee understand how the project fits into the overall theme of frailty-related research, facilitating successful, timely completion of projects, and guiding the awardee in developing further independent funding of PESC supported research.
4) Guide the translation of pilot and exploratory study results developed within this core into a deeper understanding of the basic biology of frailty, or into interventions that will prevent or treat frailty and improve independence in older adults through fostering interdisciplinary communication and collaboration between supported investigators and participants in other OAIC cores.
5) To expand the research environment and network of investigators focused on frailty research by bringing the scientific progress of pilot and other OAIC supported studies to the attention of individuals with the potential to contribute to the study of frailty, by helping awardees present their research at local and national forums, by placing awardees in contact with other individuals at Johns Hopkins and nationally whose interests intersect with the topic they are researching, and by encouraging discussion of frailty and the potential application of the pilot studies being supported in clinical, epidemiological and basic science forums throughout the medical institutions and nationally.

The PESC studies in Year 13 have been both methodologically and substantively innovative. The PES-1 concerns a potential novel treatment for frailty and frailty related conditions. PES-2 has utilized state of- the art technology (magnetic resonance spectroscopy), applied it to frailty research, specifically to core areas of frailty-related biological focus of this OAIC. Newly funded PES 3-6 explore a range of important frailty studies, including stem cell reparability in mice, clinical utility among thyroidectomy patients and ESRD patients, and a qualitative study on patient perspectives on frailty.

Pilot Studies, 2014-2016:

1) Peter Abadir, MD; Jeremy Walston, MD: "A Study of Muscle Strength Maintenance in Older Adults" (Funded July 2013). JHU OAIC investigators Burks and Cohn found that blocking the angiotensin type 1 receptors (AT1R) with losartan in older mice markedly accelerated injured skeletal muscle healing and decreased vulnerability to disuse atrophy and strength decline. These findings provide a potent rationale for testing the hypothesis that losartan attenuates strength decline and other frailty-related measures in older adults. To test this hypothesis, a randomized, placebo-controlled pilot clinical trial of losartan in prefrail adults over age 70 is proposed that aims to assess whether losartan can maintain muscle strength in older adults. The specific aims of this study are: 1) To assess the safety, tolerability and dosing range of losartan

treatment in 24 pre-frail adults age 70 and older using a blinded, placebo-controlled study design; 2) To determine if there are differences in lower extremity peak force measurements (primary outcome) and 6 minute walk time, frailty phenotype, serum markers of inflammation, and TGF-beta activity (secondary outcomes) between treatment and control groups. Progress Updates: As of February 2016, 20 participants have compliantly completed the study; 4 participants are currently active in the study and active recruitment is ongoing, with a target of 24 per-protocol completers. This study was reviewed and approved for continuation by the DSMB of the JHU OAIC in January 2016. The DSMB will review the study again in July 2016.

2) Robert G. Weiss, MD: "Energy Production in Frailty: Skeletal Muscle ATP Kinetics in Frail, Older Adults" (Funded July 2013). Declines in energy production have long been hypothesized to be an underlying etiology of frailty. The PI of this PES utilized a small pilot award to identify significant reductions in high-energy phosphate content and ATP synthesis rates that were identified in at rest muscle of frail compared to non-frail background strain mice. Based on these findings, the investigators hypothesize that older, frail adults have lower skeletal muscle phosphocreatine (PCr) levels and reduced rates of ATP synthesis through creatine kinase (CK) at rest and during plantar flexion exercise as compared to those in non-frail, age-matched subjects. To test this hypothesis, they propose to 1) compare first resting gastrocnemius PCr/Pi and the rate of ATP synthesis through CK and then after exercise using 31P MRS between frail and 20 age- and gender-matched non-frail older adults, and 2) determine the relationship, if any, between serum based inflammatory mediators, and energy related measurements. Progress updates: Enrollment and assessment is underway with support from OAIC RC-3 staff. As of February 2016, Dr. Weiss and staff have enrolled and performed the plantar flexion 31P MRS/MRI stress test in approximately 19 older subjects. We continue to enroll elderly subjects from the OAIC database who are either 1) non-frail or 2) frail by JHU frailty phenotype criteria. To date, 12 non-frail and 7 frail have been studied.

3) Aleksandra Leszczynska, PhD: "Effect of Age and Frailty on the Reparative Capacity of the Stem Cell Secretome" (Funded November 2015 - May 2016). Frailty and advanced age are associated with a diminished capacity to respond to a superimposed stress of disease or injury. One reason for this vulnerability may be an associated decline in the performance of stem cells. In addition to differentiating to vascular and muscle cells, bone marrow mesenchymal stem cells (MSCs) also - and more importantly - release paracrine factors which have anti-inflammatory and anti-apoptotic properties and which "turn on" or "turn up" intrinsic repair mechanisms. Dr. Leszczynska and colleagues seek to understand how frailty and age affect the paracrine function of MSCs at baseline and under stress. They will investigate how frailty- and age- related changes in MSCs affect their paracrine secretome, and how frailty- and age-related changes in MSC paracrine function influence their cardio-protective effects. They will also examine whether and if so how age- and frailty- related differences in MSC paracrine function are amplified by stress. Finally, they will study whether frailty- and age-related changes in MSC paracrine function can be modified by exposure to factors from young, non-frail MSCs, or from stressed cardiomyoblasts. Progress Updates: Data has been gathered to submit a manuscript, possibly to the journal, Aging Cell, in the coming months. A poster on this work, entitled "Changes in the Exosomal Component of Young vs. Old MSC Secretome may Underlie Differences in their Regenerative Potential," was presented at the 2016 Pepper Centers Annual meeting on April 18, 2016.

4) Aarti Mathur, MD: "Frailty status as a predictor of alterations in speech, swallowing, and quality of life after thyroidectomy in the elderly population" (Funded November 2015). In the United States there are between 118,000 to 166,000 thyroidectomies performed annually, of which 25% are performed in people over the age of 65. There is a paucity of data regarding the impact of thyroidectomy on voice, swallowing, and quality of life in the elderly population, although this population may be at greater risk than younger patients. Additionally, voice and swallowing function also change with age due to atrophy of the cartilaginous and muscular support of the larynx. Our central hypothesis is that there is a high incidence of voice and swallowing dysfunction after thyroidectomy in the elderly population and that frailty status may help predict which patients are more prone to these changes. Identifying patients at risk to develop these problems is critical for the development of therapeutic interventions. The main goal of this proposal is to perform a pilot study to explore the association of frailty status as a predictor of post-thyroidectomy alterations in voice and swallowing function in elderly patients. This will serve as critical preliminary data for an NIH mentored career development award. Additionally, this pilot can support the collection of other thyroid specific markers that may augment the predictive power of frailty and can be studied more fully in the final study. Progress Updates: the study has received IRB approval, and recruitment is underway.

5) Mara McAdams DeMarco, PhD: "Prehabilitation for Older Adults with End Stage Renal Disease on the Kidney Transplant Waitlist" (Funded November 2015). "Prehabilitation" is a novel approach to increase functional capacity and physiologic reserve. We will enroll 60 older adults with ESRD (including 50% frail and 50% nonfrail patients) who are likely to receive KT within 3-6 months (both live and deceased donor recipients). A prehabilitation program of moderate aerobic exercise and resistance exercises will occur at Johns Hopkins Hospital in conjunction with the Department of Physical Medicine and Rehabilitation and will be ongoing for 3 months at a minimum (duration of prehabilitation will be the time between enrollment and KT). The main goal of aim 1 will be to identify an optimal prehabilitation regime that can be systematically administered to all older adults who will receive a KT. We will assess feasibility through: recruitment, enrollment, retention, and adherence rates. We will also look at outcomes of the prehabilitation including changes in walk speed and quality of life at the time of KT. Additionally, we will test whether prehabilitation has a positive impact on short- and long-term outcomes in frail and non-frail older KT recipients. Participants in the pilot study will be compared to recent matched controls from our ongoing cohort study of frailty in KT recipients. We will leverage this ongoing R01 funded study as a practical mechanism to identify appropriate controls to represent outcomes under the standard of care. We will test for a change in frailty status after KT for those enrolled in the pilot study and our controls. We will test whether participants in a prehabilitation program have improvements in frailty status after KT as well as better short-term (length of stay, early hospital readmission, and DGF) and long-term (acute rejection, graft loss and mortality) outcomes than controls. We will also test for differences in important and clinically meaningful subgroups: by frailty status at evaluation for KT. Progress Updates: The study has received IRB approval (JHSPH IRB 00006786) as of March 23, 2016, and recruitment is underway. We are calling participants to start scheduling the prehabilitation next week. Also, we have completed the physician Delphi study on frailty and prehabilitation. The study contained 2 rounds of 47 and 43 clinicians, respectively (both response rates >90%). We developed a consensus about frailty in the second round and prehabilitation in the first round. We will be presenting our findings on the consensus on frailty at the COAH Showcase on Aging on 4/22 and have submitted an abstract on this topic to the Gerontological Society of America Annual meeting.

6) Nancy Schoenborn, MD: "Understanding patient preferences for prognosis communication among older adults across the spectrum of frailty" (Funded to start March 2016). There is growing literature supporting the clinical application of frailty. How frailty and its prognostic implications should be communicated with patients in the clinical setting has not been explored. This is a critical knowledge gap that needs to be addressed in order to more widely apply frailty in clinical practice to improve the care of older adults. Older adults who are frail or pre-frail may not have a specific terminal illness and their increased risk for mortality and functional decline may be over the time frame of a few years. Therefore, frail older adults may have different expectations and preferences around prognosis communication than previously studied populations. This proposal aims to better understand the perspectives and preferences of older adults across the frailty spectrum, regarding whether and how they would like to receive communication about frailty-informed prognosis information in clinical settings. Because little is known about this area, we propose focus groups with 30-40 adults to understand the range of patient perspectives. We plan to recruit the participants from an existing registry of older adults maintained by the Older Americans Independent Center (OAIC) where the participants' frailty status has already been assessed. If we find that the participants have more to say and the focus group was not providing enough individual attention to allow each participant to fully express their opinions, we will replace one focus group with individual interviews to ensure that we fully capture the patients' perspectives. We will investigate the range of older adult perspectives regarding 1) whether patients want to know the associated mortality risk and functional dependency risk as predicted by frailty status; 2) for those patients who want to know the above information, how they would prefer to receive the prognosis communication. We will also explore the factors that modify and influence these perspectives and preferences. Progress updates: The study has IRB approval and recruitment efforts began in March 2016.

Significant results:

Investigators supported by the JHU OAIC Pilot and Exploratory Studies Core have published articles important to advancements in the field of frailty research during the last year. These include:

- **Xue QL**, Yang H, Li HF, Abadir PM, Burks TN, Koch LG, Britton SL, Carlson J, Chen L, Walston JD, Leng SX. Rapamycin increases grip strength and attenuates age-related decline in maximal running distance in old low capacity runner rats. Aging (Albany NY). 2016 Mar 19. [Epub ahead of print] PMID: 26997106.

- **Pustavoitau A**, Barodka V, Sharpless NE, Torrice C, Nyhan D, Berkowitz DE, Shah AS, Bandeen Roche KJ, Walston JD. Role of senescence marker p16(INK4a) measured in peripheral blood T-lymphocytes in predicting length of hospital stay after coronary artery bypass surgery in older adults. Exp Gerontol. 2016 Feb;74:29-36. doi: 10.1016/j.exger.2015.12.003. Epub 2015 Dec 9. PMCID: PMC4718794.

Key outcomes or other progress:

**Previously funded PESC Studies:**

Honggang Cui, PhD: "The Specific Delivery of Pharmaceuticals into Mitochondria" (Funded July 2013-June 2015). Age-related dysfunction in mitochondria is associated with the development of

frailty, disability and chronic disease states. JHU OAIC supported investigators have recently found declines in ATP production and mitophagy in the frail mouse, a functional angiotensin system in the mitochondria that is down-regulated with age and up-regulated with losartan, and mitochondrial DNA variation that associates with frailty. Dr. Honggang Cui was recruited to develop this exploratory study that aims to develop a delivery system that specifically targets mitochondria with pharmaceutical agents. Dr. Cui is a Johns Hopkins School of Engineering faculty with considerable expertise in fabrication of peptide-based supramolecular nanostructures for drug development. The hypothesis states that pharmaceutically active substances linked to a mitochondrial targeting sequence (MTS) used for sorting proteins into mitochondria can be delivered into mitochondria, and that the pharmaceutically active substance can then be cleaved and function as an active substance. The following specific aims are proposed to test this hypothesis: 1) To determine an effective protein sorting sequence at delivering pharmaceutical agents into mitochondria; 2) To determine if those sequences that effectively deliver pharmaceutical agents can be separated from targeting sequences within mitochondrial and become active pharmaceutical agents. Progress Updates: A poster, "A Dual Peptide Conjugation Strategy for Improved Cellular Uptake and Mitochondria Targeting," was presented at the 2015 Annual Pepper Centers Meeting. This work has been published in the journal, Bioconjugate Chemistry.

- Lin R, Zhang P, Cheetham AG, Walston J, Abadir P, Cui H. Dual peptide conjugation strategy for improved cellular uptake and mitochondria targeting. Bioconjug Chem. 2015 Jan 21;26(1):71-7. doi: 10.1021/bc500408p. Epub 2014 Dec 30. PMID: 25547808. PMCID: PMC4306504.

Sevil Yasar, MD, PhD: "Impact of vitamin D supplementation on functional outcomes in pre-frail older adults with vitamin D." The OAIC had funded a vitamin D pilot to intervene on trajectory for frailty and pro-inflammatory state. The study aimed to enroll 60 pre-frail patients but no participants were enrolled due to eligibility criteria. Participants had to be in the insufficient range for vitamin D status. The study team screened close to 40 individuals for vitamin D status and none were eligible; vitamin D levels were largely too high, though some were low. Also, since the project funding began, a large intervention trial has been funded, with Hopkins as a site, using vitamin D to impact likelihood of stability and fall risk. For the new study there is a higher cut-point for inclusion, which should allow for improved enrollment. There is blood draw in this larger study, and potential for ancillary studies.

Qian-Li Xue, PhD: "Effects of Inflammation, Hormonal Alteration and mTOR Signaling in Modulating Age-related Declines in Muscle Strength." Dr. Xue and colleagues are conducted a pilot trial with 24 female low capacity runner (LCR) rats. LCR rats were selected because they develop an age-related phenotype that closely resembles the frailty syndrome including weakened muscle strength. They also exhibit compromised mitochondrial function and β-adrenergic activation and lipolysis in skeletal muscle, as well as increased levels of inflammation and oxidative stress compared to high capacity runners (HCR). The investigators included a rapamycin+metformin arm to test the hypothesis that metformin may counteract the "diabetogenic" effects of rapamycin. In addition Dr. Xue and colleagues measured serum levels of inflammatory biomarkers and anabolic hormones and fasting glucose repeatedly over time, and collected muscle biopsies to measure histologic parameters of Soleus and EDL muscles including fiber type count and protein content.
Dr. Xue presented this work at the April 2014 Annual Pepper Centers Meeting in Bethesda and *won the Poster Award in the Basic Science category*. This study was published in the Aging:

- Xue QL, Yang H, Li HF, Abadir PM, Burks TN, Koch LG, Britton SL, Carlson J, Chen L, Walston JD, Leng SX. Rapamycin increases grip strength and attenuates age-related decline in

maximal running distance in old low capacity runner rats. Aging (Albany NY). 2016 Mar 19. [Epub ahead of print] PMID: 26997106.

Mary Armanios: "Telomere length and Clinical Outcomes in the Women's Health Aging Study." This study aimed to examine the role of telomere length as a biomarker of clinical outcomes. Dr. Armanios and colleagues are currently in the process of analyzing the telomere length data. There has previously been no trial of this size using the laborious assay used in this project, and Dr. Armanios expects that she will finish generating the data soon She has completed the telomere length measurement with high data quality. She is currently completing an interim analysis with support from the OAIC Biostatistics Core.

Aliaksei Pustavoitau, MD, "A Prospective Cohort Study Evaluating the Use of p16INK4a Transcriptional Factor Level as a Marker of Molecular Age and Predictor of Perioperative Outcomes." Dr. Pustavoitau is an anesthesiologist with a long standing interest in determining risk factors for adverse outcomes in older adults undergoing surgery. This study investigated associations between p16 levels in CD3+ LDPB of elderly patients undergoing coronary artery bypass surgery and frailty and chronological age, as well as the association between p16 levels and length of ICU and hospital stay, morbidity and mortality. This study was published in Experimental Gerontology:

- Pustavoitau A, Barodka V, Sharpless NE, Torrice C, Nyhan D, Berkowitz DE, Shah AS, Bandeen Roche KJ, Walston JD. Role of senescence marker p16(INK4a) measured in peripheral blood T-lymphocytes in predicting length of hospital stay after coronary artery bypass surgery in older adults. Exp Gerontol. 2016 Feb;74:29-36. doi: 10.1016/j.exger.2015.12.003. Epub 2015 Dec 9. PMCID: PMC4718794.

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## II.F. LEADERSHIP AND ADMINISTRATIVE CORE

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The **Leadership/Administrative Core (LAC)** spearheads the vision for the Johns Hopkins Older Americans Independence Center (JHU OAIC), sets goals through which to implement it, and assures energy and quality in accomplishing goals. It leads in identifying the next generation of research on frailty that should be created, supports research planning and recruitment of investigators, and sets and monitors progress benchmarks. It is the OAIC base for recruiting and nurturing a critical mass of investigators dedicated to the creation of innovative, high impact research essential to the prevention and treatment of frailty in older adults. It administrates the OAIC and its Cores for soundness of operations and accomplishes required reporting. It promotes a stimulating intellectual environment around scholarship on frailty so as to attract outstanding researchers and knit them into an interdisciplinary community. It creates visibility for the accomplishments of the OAIC locally and globally. It is led by OAIC Principal and Co-Principal Investigators with diverse disciplinary expertise

and institutional reach, closely engages the leaders of all other OAIC Cores, and is robustly advised by a Leadership Council which it engages monthly, an Internal Advisory Committee engaged quarterly, and an External Advisory Board which reviews it annually. The LAC provides essential leadership in planning, integrating, sustaining, implementing and monitoring OAIC operations. Its goals are to ensure the conduct of these OAIC functions within the broader goals of the support of research aiming to develop new strategies to enhance independence in older Americans and the creation of a new generation of research leaders in the field. To these ends, the **specific aims** of the LAC are to:

1) Provide the interdisciplinary intellectual leadership needed to stimulate and sustain the development of innovative frailty focused research, facilitate translation between basic and clinical research on frailty, develop innovative intervention and prevention strategies, and ensure effective, high impact utilization of each of the cores of the OAIC.
2) Identify and attract the next generation of frailty-focused research leaders at Johns Hopkins University (JHU) and facilitate training, career development and access to resources to promote their emergence as independent, interdisciplinary investigators in this field.
3) 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.
4) Prepare reports for non-competing renewal applications, annually, and administrative documents as needed, including data safety monitoring documentation. 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.
5) Maximize JHU OAIC scholarly visibility locally and nationally via local programming and participation in the annual OAIC scientific meeting and the annual meetings of the aging-related societies (e.g. Gerontological Society of America) and other relevant societies.
6) Organize independent panels for review of:
    a. Resource Core Developmental Projects; Pilot/Exploratory Studies; and for the selection of specific junior faculty to receive salary support from the Research Career Development Core.
    b. Progress towards OAIC goals, conducted annually by an External Advisory Board external to JHU.

In summary, the JHU OAIC LAC provides vision, leadership and management in the development and maintenance of a tightly focused and interdisciplinary program of scholarship on frailty in older adults. It works to assure that this OAIC contributes significantly to frailty-related advances, shifts paradigms for concepts and methods to enhance independence for older persons, and achieves high and broad-reaching impact by:

- Ensuring a coherent research agenda for the OAIC and the highest quality of resultant science;
- Propelling discoveries into prevention / intervention strategies to prolong independence for older adults;
- Soundly administering OAIC resources and implementing processes to promote productivity, quality, and synergistic interactions between the cores;
- Recruiting outstanding junior and senior scholars to a focus on frailty;
- Organizing the Cores in the provision of infrastructure, expertise, mentorship, and training needed to produce the next generation of scholars interested in ameliorating frailty-related adverse outcomes and optimize their career development;
- Promoting the visibility of frailty-related scholarship and investigators across JHU, the country, and world.

Please see the following results and outcomes:

Scientific Leadership: Our OAIC has worked closely with investigators from across the Johns Hopkins Medical Institutions to foster the highest quality science related to aging and frailty as evidenced by numerous publications, including recent **high visibility, high impact symposia and publications**. The Leadership Council of our OAIC has helped to develop key areas of focus for potential intervention development in the renin-angiotensin system, in inflammation and the immune system, mitochondrial biology, sarcopenia, hearing and vestibular function, and in overall risk assessment using the frailty phenotype. As described in our RCDC, PESC, and RC3 sections, intervention studies are underway that focus on muscle maintenance and the use of Losartan among pre-frail older adults, as well as vitamin D and inflammation interventions among frail and non-frail older adults. We continue to foster other areas of investigation with long term promise for further development in mitochondrial biology, epigenetics, systems biology and human genetics.

The OAIC has continued to foster programs that enable important scientific developments around frailty research. The JHU OAIC collaboration-building project, known as the **Pepper Scholars Program**, has continued to hold ongoing monthly research-in-progress sessions that allow for OAIC-supported investigator interaction and discourse, along with progress updates and access to mentors and methodological experts.
**These monthly investigator forums** have convened supported faculty together with the OAIC leadership and members of the broader community on aging to discuss research in progress together. These been incredibly helpful in optimizing the quality of investigators' findings, creating a network and community among those involved with our OAIC, and helping to focus and propel the science of frailty.

The OAIC PI and co-PI also have continued to convene the **Frailty and Multisystem Dysregulation Working Group**, one of the core research working groups based in the JHU Center on Aging and Health. This group meets twice monthly to engage in scientific discussion, project and grant planning, manuscript development, and funding strategies. This group convenes both supported and affiliated faculty who form the most dedicated core of researchers on frailty at our institution to envision, advance, and develop research on important questions on the amelioration of frailty and its consequences and the translation of effective strategies into clinical practice. It has served a significant engine for propelling frailty related projects, including our participation in the International Conference on Frailty and Sarcopenia Research, new grant proposals, and as potentially high profile manuscripts currently in development.

The JHU OAIC has continued its efforts on **Roadmap Development for the Field of Frailty Research**. In February 2015, JHU OAIC leaders and investigators held a retreat where an initial roadmap was developed with four main priority areas: clinical practice; multisystem dysregulation; basic biology; and measurement. Over the past year, we have used the ongoing frailty working group meetings to further develop and define the roadmap. We have also created sub-working groups in each of these priority areas, which meet regularly to discuss and move forward specific objectives. For example, the measurement priority group held a series of meetings during the fall and winter of 2015-2016 to comprehensively review theories of frailty, clinical perspectives on frailty, and distinctions between primary and secondary frailty. The group is currently preparing a manuscript on a measurement paradigm for frailty assessment.

In an attempt to standardize the practice of frailty assessment and the computing algorithm, the JHU OAIC recently launched an updated online Frailty Assessment Calculator. Using the standardized measures of the frailty phenotype, the instrument was designed to maintain syndrome construct validity while maximizing feasibility and usability in both research and clinical settings. It can be accessed here: http://www.johnshopkinssolutions.com/solution/frailty/.

Programmatic Leadership: We have continued to be responsive to junior investigators and their mentors from across the institution when they express an interest in developing aging or frailty research. This includes **careful assessment of our Resource Cores'** funded faculty, staff, and supplies for statistical, biological and clinical translation support. The broad leadership structure that represents many disciplines has enabled us to maintain connections to trainees as they matriculate from a wide variety of training programs and facilitated the development of frailty research efforts early in their careers. This has resulted in outstanding multidisciplinary collaborations and very successful career development efforts. The JHU OAIC is actively infusing many medical and surgical disciplines with a geriatrics and frailty-focused research agenda.

During this reporting period, the Leadership / Administrative Core (LAC) convened the **OAIC Leadership Council** on a monthly basis to establish, propel, and review overall scientific goals and benchmarks of all cores, and the training and faculty development goals from the RCDC and Pilot Cores, as well as ongoing Core progress and accomplishments, and of the supported faculty (who submit progress reports quarterly).

The OAIC established an **External Advisory Board** for this grant cycle, and as approved by our NIA Program Official, the members of the current EAB are: Dr. Joan Bailey-Wilson; Dr. Gerald Beck; Dr. Howard Bergman; Dr. Harvey Cohen; and Dr. Luigi Ferrucci. The EAB convened on February 24, 2016 to review the second year of the renewal and provide big-picture guidance going forward. The meeting included an overview of the center's aims and accomplishments since the last EAB meeting in August 2014, with discussion of the prior feedback provided by the EAB and an overview of the OAIC core structure and supported scholarship. The group also discussed strategic planning efforts in the preceding year, including a review of the Frailty Research Retreat, and held a strategic discussion on the OAIC's opportunities, challenges, and renewal planning, including: international leadership in the field of frailty; 10-year vision for the center, and the integration of frailty into clinical decision-making. The thoughtful and motivating feedback and discussion from this meeting has helped to propel our scientific efforts during the remainder of the reporting period. The next EAB meeting will take place in the fall of 2016.

The OAIC established its **Data and Safety Monitory Board** to provide independent safety review for all OAIC interventional human subjects studies. All five members of the DSMB are external to the OAIC, with two members from the University of Maryland, and all have been approved by the NIA Program Officer. The DSMB meets semi-annually, or more frequently as needed, to review progress, findings and all potential safety issues related to OAIC human subjects research projects. Reports and minutes from each meeting have been submitted to the NIA Program Officer. The next meeting will take place in July 2016.

In partnership with the Division of Geriatric Medicine and the Center on Aging and Health, the OAIC sponsors a monthly **Scientific Seminars Series** of invited scientific presentations, including presentations by: Dr. Neal Fedarko, OAIC Pilot Core Leader in November 2015; Dr. Karen Bandeen-Roche, OAIC Co-PI, in December 2015; and Dr. Leocadio Rodriguez Manas, MD, PhD, Head of the

Department of Geriatrics at Hospital Universitario de Getafe (Madrid) and Professor of Geriatric Medicine (School of Medicine, Universidad Europea de Madrid) in May 2016.

The OAIC continues to interact with the leadership of the University of Maryland OAIC. This has allowed additional regional visibility. During the past couple years, our leadership and that of the University of Maryland OAIC have continued to work together on initiatives by which we might leverage our complementary strengths and foci to enrich the research environment for scholars associated with our OAICs, particularly our junior colleagues. These efforts have led to individual networking connections, joint participation in the annual
JHU Research on Aging Showcase poster competition for graduate students, postdoctoral fellows and junior faculty, and four Jointly-Sponsored Symposia presented collaboratively by our centers. In December 2015, our faculty participated in a joint speed-networking event for the aging trainees from UMB, Johns Hopkins, and NIA. Most recently, faculty, fellows and students from JHU, UMaryland, and NIA jointly participated in the annual Research on Aging Showcase on April 22, 2016. Trainees presented posters and our faculty from these institutions served as judges.

Significant results:

Our group continues to play important national and international scientific leadership roles. The OAIC has held several **high profile symposia** during this reporting period. Dr. Bandeen-Roche led a symposium on "Disparities in Physical Functioning and Frailty among Older Americans: Findings from the NHATS," at the 2015 Annual Meeting of the Gerontological Society of American in Orlando, FL on November 21, 2015. Dr. Walston led a symposium entitled "A Mouse Model of Chronic Inflammation, Sarcopenia and Phenotypic Frailty," at the 2016 International Conference on Frailty and Sarcopenia Research in Philadelphia PA on April 28, 2016.

We organized strong participation from our OAIC at the **National Pepper Centers Annual Meeting** held in April 2016. Our PI, Dr. Jeremy Walston, co-PI, Dr. Karen Bandeen-Roche, and Biostatistics Core Director, Dr. Qian-Li Xue, attended, along with supported investigators Drs. Abadir (former RCDC), Brown (RCDC), Gross (RCDC), Leszczynska (Pilot), and Mathur (Pilot). Drs. Walston and Bandeen-Roche participated as Senior Faculty personnel, Drs. Brown, Gross, and Leszczynska presented at the poster session, and Dr. Bandeen-Roche led the session on "ICTR workgroup on aging – research and educational CTSA/OAIC collaborations to move translation forward." Additionally, Dr. Walston moderated the panel discussion on "Early Human Trials in Translation" and Dr. Abadir served as one of the facilitators for the junior faculty clinical round table discussion.

Key outcomes or other progress:

These efforts have been highly successful in recent years with improved integration with other disciplines around important questions in frailty research. We have helped to establish the careers of the RCDC and Pilot supported faculty through the **successful support of K01/K23 funding** to Drs. Abadir, Wang, Lin, Kalyani, McAdams-DeMarco, and Agrawal in the past several years. Most recently, RCDC awardee Dr. Alden Gross received a **K01 award** (after receiving a merit score of 10), "Intersection of Physiologic Frailty and Cognitive Performance in Older Adults: An Integrative Data Analysis," that began in April 2016. Drs. Abadir and Leng, both former RCDC supported scholars, received their **first R01 awards** with OAIC support in the past years. We continue to support many other present and former scholars for R award development. We have effectively utilized our Pepper Scholars Program, a monthly research in progress series, and the Frailty Working Group (both described above) as mechanisms to help stimulate and develop a 'farm team' of investigators who are

committed to developing research in this area, and ensuring that they are able to generate the data necessary to move their science and careers forward with assistance from the OAIC. For example, Damani Piggott, MD, Assistant Professor of Medicine, received a **K23 award**, "Determinants and Consequences of Frailty Among Aging HIV-Infected Persons," from NIAID. The development of Dr. Piggott's K award was supported by the OAIC through the provision of advice to the award application's writing by our LAC and Biostatistics Core. RC-2 supported his work through measurements of inflammatory cytokines. Dr. Walston is a member of Dr. Piggott's mentorship team, and Dr. Bandeen-Roche is a member of his Mentorship Advisory Committee. Dr. Xue, Biostatistics Core Director, has received **two R03 grants** relevant to the mission of our OAIC. His recent NIA R03, "Frailty Assessment: Matching Simplification Efforts to Clinical Aims" was funded in August 2014. He previously received an NIA R03 focusing on "Clinical Significance of Short-Term Change and Variability of Grip Strength."

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**II.G. Diversity Supplement Award to Dr. Reyhan Westbrook (P30AG021334-11S1)**
***Mentor: Jeremy Walston, MD***
***Funded July 2013-2015.***

Dr. Westbrook received his Ph.D. in Molecular Biology, Microbiology and Biochemistry, August 2012 from the Southern Illinois University (SIU). He has an extensive background in metabolic research using the aging mouse as his model system. He has applied his skill set towards questions related to frailty and furthers his molecular training with investigators at John Hopkins University in the Older American Independence Center (OAIC). A major goal of this OAIC is to identify qualified junior investigators and trainees from the Johns Hopkins Medical Institutions and provide them with training and research resources and infrastructure that enable the development and performance of the highest quality aging and frailty-related research. The OAIC resources most relevant to Dr. Westbrook are RC1 and RC2. Dr. Westbrook has taken part in the ongoing statistical training opportunities and receives direct faculty and staff oversight and mentorship as he develops and analyses data gathered in his projects. Regular meetings between Dr. Westbrook and RC1 staff and faculty facilitated the highest quality study designs, the augmentation of data collection and management, access to statistical computing resources developed within this OAIC. The Biological Mechanism Core (RC-2) offers a broad array of molecular biological expertise and services highly relevant to Dr. Westbrook's projects, including frail mouse phenotype development and modeling, access to outstanding metabolomics proteomic, genomic methodology, mitochondrial measurement expertise, and direct access to highly expert and committed faculty members in the Institute of Genetic Medicine with expertise in the generation and analysis of complex biological data sets as proposed by Dr. Westbrook. He has also benefitted from the close integration of the cores and from the milieu of trainees in both biostatistics and basic scientists, and from the junior faculty trainees who meet on a monthly basis to review progress and present new data. He has gained important translational insights in this process as well, and learned how to move his own results towards meaningful interventions. Importantly, this OAIC is also dedicated to the development of a diverse scientific work force, and aims to develop a critical mass of under-represented minority investigators within this OAIC

**Research Plan Overview:** Dr. Westbrook focused on two major projects during his post-doctoral fellowship at Johns Hopkins as described below. The first project built on his considerable metabolic expertise and aimed to further develop his skill set in this area and apply it to the frail mouse model developed in our OAIC. For the second project, Dr. Westbrook helped to lead the RC-2 development

project on the integration of 'omic' analyses in the frail mouse. This enabled Dr. Westbrook to learn important new skills in molecular biology and in complex analytical modeling as described below.

The IL10Tm/Tm mouse, like frail humans, develops age-related skeletal muscle weakness, endocrine abnormalities, inflammatory pathway activation, mitochondrial abnormalities, and early mortality. These findings support the further use of this mouse to dissect molecular pathways that may impact frailty. During the first year of this award, Dr. Westbrook collaborated extensively with Dr. Rafael De Cabo of the NIA in order to more extensively characterize the metabolic phenotype of this mouse model. Findings include marked decrease in metabolic rate later in life, as well as marked decrease in fat pads and adipokines. Manuscript is developed and nearly ready for submission.

From this same project, metabolomic profiling has been completed and analysis is underway. Significant differences in tryptophan metabolism, in TCA cycle components, and in lipid metabolites between chronically inflamed and control mice have been identified. Working with Dr. Walston and members of the Biology of Healthy Aging Research team, Dr. Westbrook has established collaborative efforts for improved targeted detection methodology with Dr. Ruin Moaddel at the NIA and with Dr. Anne Le of Johns Hopkins Department of Pathology. Each of these investigators is working closely with him and with the OAIC RC2 to optimize a targeted detection approach for crucial pathways related to energy expenditure, mitochondrial energy production, and tryptophan metabolism. This work is crucial to the developmental efforts of the OAIC in that it provides an important new tool in detecting frailty and chronic inflammation related metabolic alterations that highlight underlying organismal vulnerabilities related to frailty and inflammation. This work has resulted in the awarding of the **2016 AFAR Translational Research Post-Doctoral Fellowship Award to Dr. Westbrook**. This award enables him to continue on this line of investigation, and will allow him to take his mouse related findings into human subjects with an eye towards improving diagnostics for frailty and chronic inflammation consequences in older adults. Dr. Westbrook was recently selected for a **Provost's Postdoctoral Fellowship**, where he will continue his work characterizing the frailty phenotype using metabolomics methods.

Current list of presentations includes:

- Poster Presenter at The Bayview Research Symposium Baltimore, Maryland (November 2013) The Metabolic Characterization of the Interleukin-10tm1Cgn Mouse R. Westbrook, R. de Cabo, J.M. Langdon, C.N. Roy, J. Walston.
- 1st prize in the Post-Doctoral Fellow & Junior Faculty category at the 7th Annual Research on Aging Showcase at the Johns Hopkins Bloomberg School of Public Health. The Metabolic Characterization of Interleukin-10tm1Cgn Mouse Reyhan Westbrook, Rafa de Cabo, Jackie M. Langdon, Cindy N. Roy, Jeremy Walston
- Poster Presenter at the Claude D. Pepper Older Americans Independence Centers Annual Meeting Bethesda, Maryland (April 2014) The Metabolic Characterization of the Interleukin-10tm1Cgn Mouse R. Westbrook, R. de Cabo, J.M. Langdon, C.N. Roy, J. Walston
- Poster Presenter at The Bayview Research Symposium Baltimore, Maryland (October 2014) The Metabolic Characterization of the Interleukin-10tm1Cgn Mouse R. Westbrook, R. de Cabo, J.M. Langdon, C.N. Roy, J. Walston
- Presentation at the Pepper Scholars Program Research in Progress: Reyhan Westbrook, PhD, "The Metabolic Characterization of the Interleukin-$10^{tm1Cgn}$ Mouse." November 5, 2014.
- Poster Presenter at the Gerontological Society of America annual meeting Washington D.C. (November 2014) The Metabolic Characterization of the Interleukin-10tm1Cgn Mouse R. Westbrook, R. de Cabo, J.M. Langdon, C.N. Roy, J. Walston

- Poster presenter at Johns Hopkins Department of Medicine Research Retreat Baltimore Maryland (March 2015) Metabolic Alterations in the Frail Mouse Model R. Westbrook, R. de Cabo, J.M. Langdon, C.N. Roy, J. Walston
- Oral presenter at the Division of Geriatric Medicine and Gerontology Grand Rounds (March 26, 2015) "Metabolic Alterations in the Frail Mouse Model."
- Oral presenter: Reyhan Westbrook , PhD: The Metabolic Characterization of the Interleukin-10tm1Cgn Mouse, as part of the symposium "A Mouse Model of Chronic Inflammation, Sarcopenia and Phenotypic Frailty" (Chair: Dr. Walston) at the International Conference on Frailty and Sarcopenia Research, Philadelphia, PA, April 28, 2016.

***Section III.*** ***CAREER DEVELOPMENT (subsequent to Pepper Funding)***

**Subsequent funding by supported investigators:**

**Abadir, Peter (RCDC/Small Pilot)**

- Peter Abadir. K-23 award: Age Related Changes in Angiotensin Receptors and its Contribution to Chronic Inflammation. Funded 1/1/2011.
- Peter Abadir and Jeremy Walston. R21, NIA: Novel Formulation of Topical Losartan for Treatment of Wounds in Aging. Funded March 2013.
- Peter Abadir. R01: Age Related Change in Mitochondrial Angiotensin System and Mitochondrial Decline. NIA. 2014-2019.

**Agrawal, Yuri (RCDC/Pilot)**

- Yuri Agrawal. K23, NIDCD, Age-Related Changes in the Vestibular System and Functional Implications. Funded 3/14/2014 – 2/28/2019.

**Arking, Dan (Pilot)**

- Dan Arking. Association of KLOTHO with sub-clinical measures of cardiovascular disease in MESA. American Heart Association. Funded 7/1/2007-6/30/2009.
- Dan Arking. Integrative Genetic Analysis of Autism Brains. Simons Foundation Autism Research Initiative. Funded 07/01/09-06/30/2012.
- Dan Arking. Functional Dissection of the Sudden Cardiac Death Associated BAZ2B Locus, NHLBI, 12/15/2011-12/14/2016

**Boyd, Cynthia (RCDC)**

- Cynthia Boyd (Principal Investigator). Pfizer/AGS Foundation for Health in Aging Junior Faculty Scholars Program for Research on Health Outcomes in Geriatrics. 07/01/2002 to 12/31/04.
- Cynthia Boyd. R21: Improving Clinical Practice Guidelines for Complex Patients. AHRQ. 2009 -2011.
- Cynthia Boyd. Treatment Burden in Older Adults with Multimorbidity. Robert Wood Johnson Physician Faculty Scholars Program. 2008-2011.
- Cynthia Boyd. R21: Treatment Burden in Complex Older Patients as a Target for Intervention. AHRQ. 2008-2011.
- Cynthia Boyd. Methods for Balancing Harms and Benefits in Systematic Reviews. AHRQ EPC Methods Project. 2010-2012.
- Cynthia Boyd. Treatment Burden in Older Adults with Diabetes and Multimorbidity. NIA/AFAR/ Beeson. Funded. 9/15/2009-8/31/2014

**Brown, Charles (RCDC)**

- Charles Brown. IARS Mentored Research Award. International Anesthesia Research Society. Funded. 2015.
- Charles Brown. Awarded an Johns Hopkins inHealth grant to evaluate mobility after cardiac surgery, 2016
- Charles Brown. Awarded a Johns Hopkins Clinician Scientist Award, 2016

**Carlson, Michelle (RCDC)**

- Michelle C. Carlson, PhD (Principal Investigator). Cognitive pathways to disability. National Institute on Aging. Period: 9/30/2002-9/1/2007.
- Michelle C. Carlson, PhD (Principal Investigator). Diversity supplement to Cognitive pathways to disability. National Institute on Aging. Period: 3/1/06-9/1/2007.
- Michelle C. Carlson, PhD. Bechtel Foundation Gift: Toward a Cognitive Frailty Screen
- Period: 12/31/2004-12/31/2007.

**Chaves, Paulo (RCDC/CTU)**

- Paulo Chaves. Pathogenesis of Disability in Aging Women (R37). Funded 9/1/2008-8/31/2011.
- Paulo Chaves. Cardiovascular Health Study: Events. NHLBI (Subcontract to Dr. Bruce Psaty, University of Washington). Funded 12/16-06 – 5/31/14.
- Paulo Chaves. Anemia of Chronic Kidney Disease and Inflammation in Older Adults. Funded 7/1/2007-6/30/2009.

**Gross, Alden (RCDC)**

- Alden Gross. K01 award: Intersection of physiologic Frailty and Cognitive Performance in Older Adults: An Integrative Data Analysis (NIA). Funded: 4/1/2016 – 3/31/2021.

**Kalyani, Rita (RCDC/Pilot)**

- Rita Kalyani. K-23 award: Glucose, Insulin, and Muscle Loss (NIDDK). Funded 9/1/2012-7/31/2016.
- Rita Kalyani. R03 award: lean Body Mass and the Development of Diabetes (NIDDK). Funded 2/4/2016 – 1/31/2018.

**Leng, Sean (RCDC/Pilot)**

- Sean X. Leng. Paul Beeson Career Development Award in Aging Research (K23 AG028963): Vaccine-Induced Immunity against Influenza in frailty. National Institute on Aging (NIA) / American Federation for Aging Research (AFAR) and private foundations. 9/1/2006-8/31/2011.
- Sean X. Leng. The Peking Union Medical College Hospital Geriatric Medicine Program. China Medical Board of New York. Funded 7/1/2006-6/30/2010.
- Sean X. Leng (Principal Investigator). R21 AG024235: Inflammation-Gene Expression by Monocytes in Frailty. NIH/NIA. 9/1/2004-6/30/2006.
- Sean X Leng. R01, NIAID: Influence Vaccine Failure in Adults Over Age 75: Role of Chronic CMV Infection. Funded January 2014.

**Lin, Frank R. (RCDC)**

- Frank Lin. K-23 award: Impact of Hearing Loss on Health and Functioning in Older Adults. Funded 12/1/2010-11/30/2015.

**Makary, Martin (RCDC)**

- Martin Makary. Dennis W. Jahnigen Career Development Scholars Award. 2005.

**McAdams-Demarco, Mara (RCDC)**

- Mara McAdams-Demarco. K01, NIA: Frailty and Adverse Health Outcomes of Aging in Older Adults with Kidney Failure. Funded 12/1/2013 – 11/30/2018.

**Mielke, Michelle (Pilot)**

- Michelle Mielke. Blood-based lipid biomarkers reflective of Alzheimer-associated neurodegeneration (R21). Funded 7/1/2007-6/30/2010.
- Michelle Mielke. Development of blood lipid biomarkers for Alzheimer's disease progression. Funded 9/1/2007-8/31/2010.
- Michelle Mielke. Longitudinal Study of Lipids and APOE in the Development of AD and AD Pathology (U01). Funded 9/1/2011-7/31/2015.

**Neptune, Enid (Pilot)**

- Enid Neptune. The role of Hepatocyte Growth Factor Signaling in Airspace Homeostasis. Funded 8/1/2007-7/31/2012.
- Enid Neptune. Tissue-based validation of COPD Genetic Studies using Ling Health Study Cohort (R03). Funded 9/30/2008-9/29/2010.
- Enid Neptune. TGFB Modulation: Therapeutic Targeting for COPD-Emphysema (NHLBI, P50). Funded 6/1/2011-5/31/2013.
- Enid Neptune. R01: The Role of Hepatocyte Growth Factor Signaling Airspace Homeostasis. NHLBI. Funding period: 2011-2015.

**Piggott, Damani (External Project)**

- Damani Piggott. K23: Determinants and Consequences of Frailty among Aging HIV-Infected Persons. NIAID. 7/1/2013 – 6/30/2017.

**Polotsky, Vsevolod (RCDC / Small Pilot)**

- Vsevolod. Polotsky Sleep Apnea and Dysregulation of Lipid Metabolism (R01). NIH. Funded 4/1/10 – 3/30/15.

**Punjabi, Naresh (External Project)**

- Naresh Punjabi, R21: Effects of Aging of Sleep Architecture. NIA. Funded: 8/15/2005-7/31/2007.

**Roy, Cindy (RCDC)**

- Cindy Roy. Mechanisms of anemia of chronic inflammation, aging and frailty in mice. NIH. Funded. 9/15/2009- 8/31/2014.

**Segev, Dorry (External Project)**

- Dorry Segev. JHU Clinician Scientist Award. JHU. 2008.
- Dorry Segev. Doris Duke Clinical Scientist Development Award. Doris Duke. 2008.
- Dorry Segev. Atlantic Foundation's Health and Aging Policy Fellowship. Atlantic Foundation. 2008.
- Dorry Segev. R21: Exploring Factors Influencing Gender Disparities in Access to Transplantation. NIA. 10/2008.
- Dorry Segev. Beeson Award K23: Access to Kidney Transplantation in Elderly Patients. NIA. 2009-2012.
- Dorry Segev. R01: Frailty and Risk Prediction in Older Adults Considering Kidney Transplantation. NIA. 2013-2018.

**Semba, Richard (Pilot)**

- Richard Semba. Oxidative stress and pathogenesis of sarcopenia and disability in older women. (NIA, R01). Funded 9/1/2005-8/31/2015.
- Richard Semba. Hepcidin and the pathogenesis of anemia in older adults. (NIA, R01) Funded 3/1/2007-2/28/2011.

**Seplaki, Christopher (RCDC)**

- Christopher Seplaki. Aging-related biodemography of life course physiology and environmental modifiers (K01). Funded 3/15/2009-2/28/2014.

**Varadhan, Ravi (Pilot/RCDC)**

- Ravi Varadhan (PI). Methods to Study the Heterogeneity of Treatment Effects in Comparative Effectiveness Research. AHRQ. Funded 9/30/2009 to 01/29/2011.
- Ravi Varadhan. 2011 Brookdale Leadership in Aging Fellowship Award: research to better delineate the applicability of intervention trial findings to populations not well-represented in trials, such as older adults. Funded 3/1/2011.
- Ravi Varadhan. Structural and Nested Models for Assessing the Safety and Efficacy of Generic Drugs (FDA U01). Funded: 9/15/2015 – 8/3/2018.

**Walston, Jeremy (Pilot/Genetics)**

- Jeremy Walston. NFkB related genetic influences on inflammation and poor health in older adults (R01). Funded 9/1/2006-8/31/2010.
- Jeremy Walston. NIA Long Life Family Study (LLFS). Subcontract to University of Pittsburgh U01AG023744. Funded 5/1/05 – 5/31/10
- Jeremy Walston. Development of a Mouse Model for Frailty (R21). Funded 9/1/2007-5/31/2010.
- Jeremy Walston and Laura Dugan. Hartford/AFAR Collaborative Beeson Research Award: Systemic Inflammation and Central Nervous System Dysfunction: A Mechanistic and Translational Pilot. Funded 8/1/2007-7/31/2009.
- Jeremy Walston and Peter Abadir. Novel Formulation of Topical Losartan for Treatment of Wounds in Aging. (NIA, R21). Funded 4/1/2013-3/31/2015.

**Wang, George (RCDC)**

- George Wang. Immunologic Dysregulations and Inflammation in the Pathogenesis of Frailty of Old Age: The Role of CMV Infection. T. Franklin Williams. Funded 7/1/2008-6/30/2010.
- George Wang. NIH K23: CMV-specific memory CD8+T cells and TCR diversity and frailty. Funded 9/30/2010.

**Xue, Qian-Li (Biostatistics / Pilot)**

- Qian-Li Xue. Clinical Significance of Short-Term Change and Variability of Grip Strength (R03). NIA. Funded 4/1/2012 – 3/31/2014.
- Qian-Li Xue. Frail Assessment: Matching Simplification Efforts to Clinical Aims. (R03). NIA. Funded: 8/15/14-6/30/2016.

**Yuh, David (RCDC)**

- David Yuh. Outcomes in Older Patients Undergoing Cardiac Surgery. (NCRR, M01). Funded 12/1/2006-9/16/2007.

***Section IV.*** ***PUBLICATIONS (directly resulting from Pepper Resources)***

**Publications, 2015-2016**


1. Abadir PM, Siragy HM. Angiotensin type 1 receptor mediates renal production and conversion of prostaglandins E2 to F2α in conscious diabetic rats. J Renin Angiotensin Aldosterone Syst. 2015 Dec;16(4):774-9. doi: 10.1177/1470320315592566. Epub 2015 Jul 20. PMCID: PMC4831567.

2. Bakulski KM, Feinberg JI, Andrews SV, Yang J, Brown S, L McKenney S, Witter F, Walston J, Feinberg AP, Fallin MD. DNA methylation of cord blood cell types: Applications for mixed cell birth studies. Epigenetics. 2016 May 3;11(5):354-62. doi: 10.1080/ 15592294.2016.1161875. Epub 2016 Mar 28. PMID: 27019159. PMCID: PMC4889293

3. Bandeen-Roche K, Seplaki CL, Huang J, Buta B, Kalyani RR, Varadhan R, Xue QL, Walston JD, Kasper JD. Frailty in Older Adults: A Nationally Representative Profile in the United States. J Gerontol A Biol Sci Med Sci. 2015 Nov;70(11):1427-34. doi: 10.1093/gerona/glv133. Epub 2015 Aug 21. PMCID: PMC4723664.

4. Bigelow RT, Semenov YR, Trevino C, Ferrucci L, Resnick SM, Simonsick EM, Xue QL, Agrawal Y. Association Between Visuospatial Ability and Vestibular Function in the Baltimore Longitudinal Study of Aging. J Am Geriatr Soc. 2015 Sep;63(9):1837-44. doi: 10.1111/jgs.13609. Epub 2015 Aug 27. PMID: 26311169. PMCID: PMC4883683.

5. Brown CH 4th, Max L, LaFlam A, Kirk L, Gross A, Arora R, Neufeld K, Hogue CW, Walston J, Pustavoitau A. The Association between Preoperative Frailty and Postoperative Delirium after Cardiac Surgery. Anesth Analg. 2016 Apr 19. [Epub ahead of print] PMID: 27096563. NIHMS ID: NIHMS761046. In process at NIHMS.

6. Burks TN, Marx R, Powell L, Rucker J, Bedja D, Heacock E, Smith BJ, Foster DB, Kass D, O'Rourke B, Walston JD, Abadir PM. Combined effects of aging and inflammation on renin-angiotensin system mediate mitochondrial dysfunction and phenotypic changes in cardiomyopathies. Oncotarget. 2015 May 20;6(14):11979-93. PMCID: PMC4494917

7. Buta B, Walston JD, Godino JG, Park M, Kalyani RR, Xue QL, Bandeen-Roche K, Varadhan R. Frailty Assessment Instruments: Systematic Characterization of the Uses and Contexts of Highly-Cited Instruments. Ageing Res Rev. 2016 Mar;26:53-61. doi: 10.1016/j.arr.2015.12.003. Epub 2015 Dec 7. PMCID: PMC4806795.

8. Cohen HJ, Walston JD, Rao SV, Schrier SL, Artz A; Partnership for Anemia: Clinical and Translational Trials in the Elderly Consortium. Renal Toxicity Associated with Salsalate in Elderly Adults with Anemia. J Am Geriatr Soc. 2016 Apr;64(4):898-9. doi: 10.1111/jgs.14065. PMID: 27100595. PMCID: PMC4863444.

9. Faghih M, Hosseini SM, Smith B, Ansari AM, Lay F, Ahmed AK, Inagami T, Marti GP, Harmon JW, Walston JD, Abadir PM. Knockout of Angiotensin AT2 receptors accelerates healing but impairs quality. Aging (Albany NY). 2015 Dec;7(12):1185-97. PMCID: PMC4712341.

10. Gross AL, Xue QL, Bandeen-Roche K, Fried LP, Varadhan R, McAdams-DeMarco MA, Walston J, Carlson MC. Declines and Impairment in Executive Function Predict Onset of Physical Frailty. J Gerontol A Biol Sci. 2016 Apr 15. pii: glw067. [Epub ahead of print] PMID: 27084314. PMC Journal – In Process

11. Huisingh-Scheetz M, Walston J. How should older adults with cancer be evaluated for frailty? J Geriatr Oncol. 2016 Jun 16. pii: S1879-4068(16)30060-1. doi: 10.1016/j.jgo.2016.06.003. [Epub ahead of print]

12. Ko F, Abadir P, Marx R, Westbrook R, Cooke C, Yang H, Walston J. Impaired mitochondrial degradation by autophagy in the skeletal muscle of the aged female interleukin 10 null mouse. Exp Gerontol. 2016 Jan;73:23-7. doi: 10.1016/j.exger.2015.11.010. Epub 2015 Nov 18.PMID: 26596403. PMCID: PMC4725733.

13. Lee KT, Abadir PM. Failure of Glucose Monitoring in an Individual with Pseudohypoglycemia. J Am Geriatr Soc. 2015 Aug;63(8):1706-8. doi: 10.1111/jgs.13572. PMID: 26289697. NIHMS ID: NIHMS785936. In process at NIHMS.

14. Matteini AM, Tanaka T, Karasik D, Atzmon G, Chou WC, Eicher JD, Johnson AD, Arnold AM, Callisaya ML, Davies G, Evans DS, Holtfreter B, Lohman K, Lunetta KL, Mangino M, Smith AV, Smith JA, Teumer A, Yu L, Arking DE, Buchman AS, Chibinik LB, De Jager PL, Evans DA, Faul JD, Garcia ME, Gillham-Nasenya I, Gudnason V, Hofman A, Hsu YH, Ittermann T, Lahousse L, Liewald DC, Liu Y, Lopez L, Rivadeneira F, Rotter JI, Siggeirsdottir K, Starr JM, Thomson R, Tranah GJ, Uitterlinden AG, Völker U, Völzke H, Weir DR, Yaffe K, Zhao W, Zhuang WV, Zmuda JM, Bennett DA, Cummings SR, Deary IJ, Ferrucci L, Harris TB, Kardia SL, Kocher T, Kritchevsky SB, Psaty BM, Seshadri S, Spector TD, Srikanth VK, Windham BG, Zillikens MC, Newman AB, Walston JD, Kiel DP, Murabito JM. GWAS analysis of handgrip and lower body strength in older adults in the CHARGE consortium. Aging Cell. 2016 Jun 21. doi: 10.1111/acel.12468. [Epub ahead of print]. PMID: 27325353

15. McAdams-DeMarco MA, Tan J, Salter ML, Gross A, Meoni LA, Jaar BG, Kao WL, Parekh RS, Segev DL, Sozio SM. Frailty and Cognitive Function in Incident Hemodialysis Patients. Clin J Am Soc Nephrol. 2015 Nov 16. pii: CJN.01960215. [Epub ahead of print] PMID: 26573615. PMCID: PMC4670760.

16. McAdams-DeMarco MA, Isaacs K, Darko L, Salter ML, Gupta N, King EA, Walston J, Segev DL. Changes in Frailty After Kidney Transplantation. J Am Geriatr Soc. 2015 Oct;63(10):2152-7. doi: 10.1111/jgs.13657. Epub 2015 Sep 29. PMID: 26416770. PMCID: PMC4618021.

17. Phillip JM, Aifuwa, Walston JD, Wirtz D. The Mechanobiology of Aging. Annu Rev Biomed Eng. 2015 Dec 7;17:113-41. doi: 10.1146/annurev-bioeng-071114-040829. PMID: 26643020. PMCID: PMC4886230.

18. Piggott DA, Varadhan R, Mehta SH, Brown TT, Li H, Walston JD, Leng SX, Kirk GD. Frailty, Inflammation, and Mortality Among Persons Aging With HIV Infection and Injection Drug Use. J Gerontol A Biol Sci Med Sci. 2015 Dec;70(12):1542-7. doi: 10.1093/gerona/glv107. Epub 2015 Sep 18. PMCID: PMC4643614.

19. Pustavoitau A, Barodka V, Sharpless NE, Torrice C, Nyhan D, Berkowitz DE, Shah AS, Bandeen Roche KJ, Walston JD. Role of senescence marker p16(INK4a) measured in peripheral blood T-lymphocytes in predicting length of hospital stay after coronary artery bypass surgery in older adults. Exp Gerontol. 2016 Feb;74:29-36. doi: 10.1016/j.exger.2015.12.003. Epub 2015 Dec 9. PMCID: PMC4718794.

20. Robinson TN, Walston JD, Brummel NE, Deiner S, Brown CH 4th, Kennedy M, Hurria A. Frailty for Surgeons: Review of a National Institute on Aging Conference on Frailty for Specialists. J Am Coll Surg. 2015 Dec;221(6):1083-92. doi: 10.1016/j.jamcollsurg.2015.08.428. Epub 2015 Sep 11. Review. PMID: 26422746. PMCID: PMC4673051.

21. Semenov YR, Bigelow RT, Xue QL, Lac SD, Agrawal Y. Association Between Vestibular and Cognitive Function in U.S. Adults: Data From the National Health and Nutrition Examination Survey. J Gerontol A Biol Sci Med Sci. 2016 Feb;71(2):243-50. doi: 10.1093/gerona/glv069. Epub 2015 Jul 28. PMID: 26219850. PMC Journal – In Process.

22. Sun DQ, Huang J, Varadhan R, Agrawal Y. Race and fall risk: data from the National Health and Aging Trends Study (NHATS). Age Ageing. 2016 Jan;45(1):120-7. doi: 10.1093/ageing/afv173. PMCID: PMC4711659. PMCID: PMC4711659.

23. Theou O, Walston J, Rockwood K. Operationalizing Frailty Using the Frailty Phenotype and Deficit Accumulation Approaches. Interdiscip Top Gerontol Geriatr. 2015;41:66-73. doi: 10.1159/000381164. Epub 2015 Jul 17. PMID: 26301980. PMCID: PMC4886227.

24. Vandiver AR, Irizarry RA, Hansen KD, Garza LA, Runarsson A, Li X, Chien AL, Wang TS, Leung SG, Kang S, Feinberg AP. Age and sun exposure-related widespread genomic blocks of hypomethylation in nonmalignant skin. Genome Biol. 2015 Apr 16;16:80. doi: 10.1186/s13059-015-0644-y. PMCID: PMC4423110

25. Walston JD. Connecting Age-Related Biological Decline to Frailty and Late-Life Vulnerability. Nestle Nutr Inst Workshop Ser. 2015 Oct;83:1-10. doi: 10.1159/000382052. Epub 2015 Oct 20. PMID: 26485518. PMCID: PMC4871248.

26. Walston JD, Bandeen-Roche K. Frailty: a tale of two concepts. BMC Med. 2015 Aug 11;13:185. doi: 10.1186/s12916-015-0420-6. PMID: 26265077. PMCID: PMC4531437

27. Wang GC, Han C, Detrick B, Casolaro V, Levine DM, Fried LP, Walston JD. Herpesvirus Infections and Risk of Frailty and Mortality in Older Women: Women's Health and Aging Studies. J Am Geriatr Soc. 2016 Apr 30. doi: 10.1111/jgs.14090. [Epub ahead of print] PMID: 27131018. NIHMS ID: NIHMS756218. In process at NIHMS.

28. Xue QL, Yang H, Li HF, Abadir PM, Burks TN, Koch LG, Britton SL, Carlson J, Chen L, Walston JD, Leng SX. Rapamycin increases grip strength and attenuates age-related decline in maximal running distance in old low capacity runner rats. Aging (Albany NY). 2016 Mar 19. [Epub ahead of print] PMID: 26997106. PMCID: PMC4887575.

29. Xue QL, Tian J, Fried LP, Varadhan R, Kalyani R, Walston JD, Bandeen-Roche K. Physical Frailty Assessment: Can Simplification Be Achieved without Loss of Syndrome Measurement Validity? Am J Epidemiol. 2016; doi: 10.1093/aje/kwv272. PMC Journal – In Process.

***<u>Section V</u>. External Advisory Board Members Names, Institutions and Years of service***

| EAB Member | Affiliation | Years of Service |
|---|---|---|
| Joan E. Bailey-Wilson, Ph.D. | Head, Statistical Genetics Section; Co-Branch Chief, Inherited Disease Research Branch; National Human Genome Research Institute; National Institutes of Health | 8 |
| Gerald Beck, Ph.D. | Section Head, Clinical Trials; Design and Analysis, Department of Quantitative Health Sciences, Cleveland Clinic Foundation | 3 |
| Howard Bergman, M.D. | Chair, Department of Family Medicine, Professor of Family Medicine, Medicine and Oncology, Dr. Joseph Kaufmann Professor of Geriatric Medicine, McGill University | 3 |
| Harvey J. Cohen, M.D. | Division Chief of Geriatrics, Director of the Center for the Study of Aging and Human Development, Duke University Medical Center | 13 |
| Luigi Ferrucci, M.D., Ph.D. | NIA Scientific Director, Senior Investigator and Chief, Longitudinal Studies Section | 13 |

**The Johns Hopkins University**
**Claude D. Pepper Older Americans Independence Center**
**2016 OAIC Annual Directory: Additional Information**

1. **Recognition and Awards (non-grant honors and awards)**:

   - Dr. Karen Bandeen-Roche received the 2016 Marvin Zelen Leadership Award in Statistical Science by the Harvard T.H. Chan School of Public Health.

   - Dr. Jeremy Walston was recognized with a 2015 David M Levine Excellence in Mentoring Award by the Johns Hopkins Department of Medicine.

2. **Minority Research**: List activities with minority trainees and research focusing on hypotheses dealing with minority health. Clinical research that has an expected number of minority subjects (a NIH requirement) is NOT what is desired for this section. Only work that has a comparison of minority members to majority members such as work on health disparities should be included.
   - n/a