Since its inception in 2003, the Johns Hopkins University (JHU) Older Americans Independence Center (OAIC) has pursued a rigorous and distinctive scientific approach considering physical frailty as a biologically-rooted state of decreased resiliency and reserve, which induces a syndromic phenotype and specific etiological mechanisms. As evidenced by peer-reviewed publications and associated NIH grant funding, this specific conceptualization of frailty has provided a highly productive framework for population-based, clinical, and biological discovery, for the development of potential prevention and treatment strategies, and for the training of junior investigators for academic careers in frailty and aging research. This center’s mission remains, in many respects, as it has been throughout the life of our OAIC: To make fundamental etiological discoveries related to frailty, move these towards frailty-focused interventions, develop evidence-based guidelines for the prevention and management of adverse outcomes in frail older individuals, identify new investigators dedicated to these ends, and provide supported investigators with the expertise, resources, and training necessary to lead the next generation of frailty-related scholarship and practice. Given the rapidly growing interest in frailty, its detection, its management, and the critical mass of frailty-related knowledge that this OAIC has generated, we have launched an Information Dissemination Core (IDC) to enable our OAIC to more comprehensively disseminate frailty-related findings so as to better impact clinical and public health practice. We pursue our mission through the following specific aims:

1) To stimulate, lead and develop effective frailty-focused interdisciplinary research programs that promote the maintenance of independence. This has helped to create a vibrant and growing center with scientific vigor and a rich interdisciplinary milieu of experienced faculty and successful trainees focused on frailty research.

2) To translate the new knowledge generated in this OAIC into targeted prevention and treatment strategies that help older adults maintain independence. An existing clinical translational resource core, an IDC, and the national OAIC network facilitate this effort.

3) To provide the highest quality expertise, support, infrastructure and technology in biological, data analytic and clinical research methodologies to OAIC investigators.

4) To support the development of new and innovative methodologies, research strategies and technologies essential to the study of frailty. Aims 3 and 4 are organized through Biostatistics, Biological Mechanisms, and Clinical Translational cores.

5) To provide tailored training and mentorship to junior investigators interested in developing careers focused on frailty in older adults. We continue with a leadership team that has demonstrated expertise and commitment to training the next generation of investigators.

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

Aim 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 from these biological and clinical discoveries, and ensure effective, high impact utilization of each of the cores of the OAIC.

Aim 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.

Aim 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.

Aim 4. Prepare reports for non-competing renewal applications, annually, and administrative documents as needed, including data safety monitoring documentation.
**Aim 5.** 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.

**Aim 6.** Maximize JHU OAIC scholarly visibility locally and nationally via local programming and participation in the OAIC network, the annual OAIC scientific meeting and annual scientific meetings of aging or frailty-focused organizations, and through the new Information Dissemination Core described in section 8.

**Aim 7.** 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 Education Component.
- b. Progress towards OAIC goals, conducted annually by an External Advisory Board.

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, training and dissemination needed to identify, train and inspire the next generation of scholars interested in ameliorating frailty-related adverse outcomes and optimize their career development
- promoting frailty-related scholarship and investigators across JHU, the nation, and the 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. We continue to support relevant intervention studies including a recently completed anti-inflammatory intervention with rH lactoferrin. In the past year we have particularly actively fostered investigation into the potential usefulness of frailty as a marker of risk in clinical subspecialties addressing older adults, the role of multisystem dysregulation in frailty and resilience, and racial and socioeconomic disparities in frailty prevalence in the United States. Newer studies focused on diagnostic measures related to chronic inflammation and mitochondria biology continue as part of our core discovery mission.
We have been able to recruit at least two metabolomic experts to help us with relevant assay development.

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 have 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 leaders continue to convene the biweekly 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 been a significant engine for propelling frailty related projects, including funded UH2/UH3 grant on physical resiliencies in older adults as well as other R mechanism grants. In addition, it has provided organization to support the development of international leadership in the field of frailty via participation and leadership of important symposia in the International Conference on Frailty and Sarcopenia Research in February 2019, and at the annual meeting of the Gerontological Society of America in Boston in 2018. In addition, Drs. Bandeen-Roche and Dr. Walston, as well as many participating investigators, are frequent invited speakers at other academic institutions and at national and international Geriatric Medicine, Gerontology and frailty-related meetings where ongoing frailty research and research findings are disseminated and broader collaborations around frailty are initiated.

The JHU OAIC has continued its efforts on Roadmap Development for the Field of Frailty Research through the efforts of the LAC and OAIC sponsored investigators, with priority foci on: clinical integration and translation; multisystem dysregulation; biological discovery; and conceptualization and measurement of frailty. The OAIC led in the development of programs of research with particular importance for broadening its impact to promote independence for older adults. First, the conceptual framework outlined by the NIA and its partners with respect to physical resiliencies in older adults is highly consonant with the conceptual framework underlying the approach to frailty we have pursued through our OAIC. We continue to develop theory, partnerships, clinical research infrastructure, and methodologic approaches for investigating the measurement, etiology and implications of these resiliencies in collaboration with three clinical groups at Johns Hopkins as part of the pilot phase of a UH2/UH3 grant on physical resiliency. Secondly, in the biological development realm, we have continued to collaborate broadly with bioengineering experts who have helped us capture aging-relevant physical properties of cells and how these changes may drive physical frailty. This pilot sponsored work has been leveraged into a manuscript in Nature Medicine Bioengineering and
into a U01 biomarkers of aging grant. A new working group of interdisciplinary investigators has been established to further the development of this effort to include gene transcription and the development of related aging phenotypes; the first local retreat took place in May 2019. Thirdly, in the frailty measurement realm, we have had two major efforts. First, we have developed a paper, led by the Biostatistics Core and inclusive of the entire Frailty and Multisystem Dysregulation Working Group, to elucidate principles of frailty measurement. The paper argues that frailty instruments should be grounded in formal validation; illustrates the paradigm it recommends; identifies unresolved measurement issues for the frailty field; and raises issues for frailty measurement in clinical practice. It has been accepted for publication in the Journal of Gerontology: Medical Sciences. Secondly, our RC1 development project over the past year has sought to create improved statistical strategies, grounded in latent variable modeling, for identifying “differential item functioning” (DIF) in geriatric measurement. DIF occurs when individuals who have the same “health” targeted by the measurement exhibit symptoms or signs or respond to questions comprising the measurement differentially by personal characteristics. The current work was motivated when appearance of DIF for frailty criteria by race emerged in a study of racial disparities in frailty prevalence. There have been multiple presentations of the work and a manuscript is under development: See the RC1 section for more detail.

As part of the roadmap development efforts, the JHU OAIC co-sponsored, with the NIA Extramural branch, a day-long symposium on “Frailty Science: Moving Toward Utility in Clinical Practice.” The goal of this international workshop was to lay out a more specific roadmap for the research most urgently needed in order for frailty to be widely and beneficially integrated into clinical practice. Focus areas that emerged from this session included language to clarify conceptual differences between frailty definitions and measurement instruments; the development of randomized, controlled trials for interventions testing among frail and non-frail individuals; developing development of biologically targeted intervention and prevention strategies, and using deep learning and dynamical systems approaches to better translate findings from epidemiological studies. Conference proceedings, which represent state of the art thinking on the integration of frailty into clinical practice, were published online by the Journal of the American Geriatrics Society in May 2019.

In an attempt to standardize the practice of frailty assessment and the computing algorithm, the JHU OAIC Biostatistics Core continues to maintain, refine, and promote an online Physical Frailty Assessment Calculator. This instrument has facilitated the measurement of physical frailty at multiple sites around the world and helped to integrate the measurement of physical frailty into many clinical and research groups. 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 REC and Pilot Cores, as well as ongoing Core progress and accomplishments, and of the supported faculty who submit progress reports quarterly.

The OAIC’s External Advisory Board includes the following members: Dr. Joan Bailey-Wilson; Dr. Gerald Beck; Dr. Howard Bergman; Dr. Harvey Cohen; and Dr. Luigi Ferrucci. The EAB most recently convened on June 23, 2017 to primarily discuss the Center’s roadmap for its renewal application that was due in October 2017. This session was divided into two parts: 1) Proposed Aims and New Areas of Focus; and 2) Proposed Core Structure and Leadership. The EAB members and the JHU leaders discussed critical biological, clinical and methodological issues related to frailty and advancing the field in a new grant cycle. All five board members have enthusiastically agreed to continue to serve on the EAB for this grant cycle. The next EAB meeting is scheduled to occur August, 2019.

The OAIC’s Data and Safety Monitoring Board provides 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 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 most recent meeting took place in December 2018, with another slated to take place in early fall 2019.

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 a recent presentations by: Dr. Walston on “The Unifying Biology that Impacts Frailty, Resiliency, and Age-Related Phenotypes” (Nov 2018); and Dr. David Roth, OAIC Leadership Council member, on “Family Caregiving and Inflammatory Biomarkers: Clarifying Answers are Finally Emerging” (April 2019), for which Dr. Walston serves as a co-investigator. Recent external seminar speakers and topics have included Dr. Barbara Resnick (NIA) on cognition and resilience, and Dr. Christine Ritchie (UCSF) on dementia palliative care.

The OAIC continues to work together with the leadership of the University of Maryland OAIC 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. On November 1, 2018, 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 March 29, 2019 at the Johns Hopkins School of Public Health, with a keynote
presentation by Dr. Luigi Ferrucci. Trainees and fellows presented posters and our faculty from these institutions served as judges for this research showcase. Multiple half-day symposia co-sponsored by our Biostatistics Cores have been held over the years; a next, to address reproducibility in clinical and translational research, is under active development for autumn, 2019. Collaborations such as these create additional regional visibility.

**Funded Studies:** Table 1 below provides an overview of funded research projects and support from resource cores in the current reporting period. A summary of each project is provided in the core sections.

**Table 1: Summary of funded research projects in Year 15-16 (Oct 2017-June 2019)**

<table>
<thead>
<tr>
<th>JHU OAIC Funded Studies</th>
<th>Grant / Support Year(s)</th>
<th>Resource Cores (RC)</th>
<th>Progress / Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RC-1: Biostatistics Core</td>
<td>RC-2: Biological Mechanisms Core</td>
</tr>
<tr>
<td><strong>Junior Faculty Awarded Projects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tae Hwan Chung, MD; &quot;Involvement of Kynurenine and NAD Pathways in Frailty.&quot;</td>
<td>14-15</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Abdulla Damluji, MD, MPH; &quot;Consequences of Frailty in Older Adults after Acute Coronary Syndrome&quot;</td>
<td>15-16</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Orla Sheehan, MD; “Frailty and compensatory mechanisms for managing treatment burden, treatment adherence, and adverse outcomes in homebound older adults.”</td>
<td>16</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pei-Hsun Wu, PhD; &quot;Biophysical cellular characteristics in frail and non-frail older adults.&quot;</td>
<td>16-</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
| Bharath Ambale Venkatesh, PhD; "Pathways leading to frailty: a study of muscle, cardiovascular tissue, and energy utilizing whole- | 16- | X | X | X | In progress: Poster presented at 2019 OAIC Annual Meeting; K01
### Table 1: Summary of funded research projects in Year 15-16 (Oct 2017-June 2019)

<table>
<thead>
<tr>
<th>JHU OAIC Funded Studies</th>
<th>Grant / Support Year(s)</th>
<th>RC-1: Biostatistics Core</th>
<th>RC-2: Biological Mechanisms Core</th>
<th>RC-3: Clinical Translation and Recruitment Core</th>
<th>Progress / Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>body magnetic resonance imaging.†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>submitted (Feb 2019)</td>
</tr>
<tr>
<td>Reyhan Westbrook, PhD: “Metabolomic differences in energy utilization and Kyn/Trp metabolism pathways in mouse models of frailty: evidence-based implication for translational studies in humans.”</td>
<td>16-</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>In progress: Poster presented at 2019 OAIC Annual Meeting; Co-Inv, NIA UH2 Resiliencies grant</td>
</tr>
</tbody>
</table>

#### Pilot Studies

<table>
<thead>
<tr>
<th>JHU OAIC Funded Studies</th>
<th>Grant / Support Year(s)</th>
<th>RC-1: Biostatistics Core</th>
<th>RC-2: Biological Mechanisms Core</th>
<th>RC-3: Clinical Translation and Recruitment Core</th>
<th>Progress / Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kathy Wilson, PhD: “Laminopathy mechanisms as potential components of frailty.”</td>
<td>14-15</td>
<td>X</td>
<td></td>
<td></td>
<td>4 Publications.</td>
</tr>
<tr>
<td>Damani Piggott, MD: “Frailty and Angiotensin Receptor Autoantibody Activation among Persons Aging with HIV and Injection Drug Use.”</td>
<td>15</td>
<td></td>
<td>X</td>
<td></td>
<td>Funded NIA R01 (September 2018)</td>
</tr>
<tr>
<td>Bonnie Swenor, PhD: “Exploring the Relationship between Visual Impairment and Frailty in Older Adults.”</td>
<td>15</td>
<td>X</td>
<td></td>
<td></td>
<td>1 Publication.</td>
</tr>
<tr>
<td>Janiece Taylor, PhD: “Pilot Behavioral Intervention to Address Pain and Frailty in Older African-American Women.”</td>
<td>16-</td>
<td>X</td>
<td>x</td>
<td>x</td>
<td>In progress</td>
</tr>
<tr>
<td>Anne Le, MD: “Metabolomics Energy Signatures of Frailty.”</td>
<td>16-</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>In progress</td>
</tr>
<tr>
<td>Naresh Punjabi, MD, PhD: “Association between Sleep Deficiency and Frailty: What harms most?”</td>
<td>16</td>
<td>X</td>
<td>x</td>
<td></td>
<td>In progress</td>
</tr>
</tbody>
</table>

#### Development Projects and Supplemental Awards

<table>
<thead>
<tr>
<th>JHU OAIC Funded Studies</th>
<th>Grant / Support Year(s)</th>
<th>RC-1: Biostatistics Core</th>
<th>RC-2: Biological Mechanisms Core</th>
<th>RC-3: Clinical Translation and Recruitment Core</th>
<th>Progress / Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC-1 Development Project: Karen Bandeen-Roche, PhD, “Characterizing Longitudinal Interdependence among Multiple MSD Biomarkers.”</td>
<td>16</td>
<td>X</td>
<td></td>
<td></td>
<td>In progress</td>
</tr>
</tbody>
</table>
### Table 1: Summary of funded research projects in Year 15-16 (Oct 2017-June 2019)

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<th>RC-2: Biological Mechanisms Core</th>
<th>RC-3: Clinical Translation and Recruitment Core</th>
<th>Progress / Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC-2 Development Project: Neal Fedarko, PhD. Peter Abadir, MD: “Development of an aptamer to selectively target the angiotensin autoantibody”</td>
<td>16</td>
<td>X</td>
<td></td>
<td>x</td>
<td>In progress</td>
</tr>
<tr>
<td>OAIC Supplement: Jennifer Schrack, PhD. “Fatigability in Functionally Independent Older Adults.”</td>
<td>14-15</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Multiple publications; Funded R01 (February 2019)</td>
</tr>
<tr>
<td>OAIC Supplement: Peter Abadir, MD. Alzheimer’s disease supplemental award</td>
<td>16</td>
<td></td>
<td>X</td>
<td></td>
<td>In progress – analyzing samples</td>
</tr>
</tbody>
</table>

Our group continues to play important national and international scientific leadership roles. The OAIC has held several high profile symposia and keynote talks during this reporting period. Dr. Walston led a symposium, entitled “The Molecular and Organismal Basis of Resilience and Frailty” at the 21st IAGG World Congress of Gerontology and Geriatrics in San Francisco in July 2017. Dr. Walston also led a symposium on “Metabolomic Signatures of Frailty” at the 2018 International Conference on Frailty and Sarcopenia Research in Miami. At the 2018 Annual Meeting of the Gerontological Society of America in Boston in November 2018, Dr. Bandeen-Roche led a symposium on “Disparities in Frailty and Resiliency among Older Adults.” At the 2019 International Conference on Frailty and Sarcopenia Research (again in Miami), Dr. Walston presented a keynote presentation on “Biomarkers and the Biology of Frailty,” and Dr. Bandeen-Roche led a symposium on: “The Gap between Theory and Practice: A 360 Degree Consideration of Opportunities Remaining in Frailty Measurement.” Importantly, at least 10 OAIC supported investigators presented data from their OAIC sponsored research during all of these meetings.

We organized strong participation from our OAIC at the National Pepper Centers Annual Meeting held in April 2019. Meeting participants included our PIs, Drs. Walston and Bandeen-Roche, and supported investigators, Dr. Ambale-Venkatesh (REC), Damluji (REC), McAdams-DeMarco (Pilot), Taylor (Pilot), Westbrook (REC), and Wu (REC). Dr. Walston moderated and
presented at the Biomarkers session and presented during the resiliency session, and Dr. Bandeen-Roche moderated the resiliency session.

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 REC and Pilot supported faculty through the successful support of K01/K23/K76 funding to Drs. Abadir, Wang, Lin, Kalyani, McAdams-Demarco, Agrawal, Mathur, Gross, Brown (Beeson award), Chung, and Swenor in the past several years. Most recently, Keenan Walker (REC) and Nancy Schoenborn (Pilot; Beeson award) received K-awards from NIA. Drs. Abadir, Agrawal, Leng, McAdams-DeMarco, Arking, Piggott, and Walston – all previous REC or Pilot supported investigators – have received R01 awards in the recent years with OAIC support. Dr. Dan Arking, OAIC RC2 Co-Director, received a R01 award from NHLBI that directly resulted from his OAIC developmental project research on mitochondrial copy number and frailty. Dr. Jennifer Schrack, OAIC supplemental awardee, has received a U01 award and, most recently, a R01 grant for her work related to energy reserves, sensory motor functions, and cognitive outcomes. Our leadership features former REC- and pilot-supported faculty, including Drs. Walston, Abadir, and Arking.

In the last two years, a UH2/3 grant application on physical resiliencies in older adults was funded by the NIA on July 1, 2017 based on dynamic systems work performed in this OAIC over the past several years. In addition, an NIA U01 grant was awarded to Bioengineers Dr. Wirtz and Pei-Hsun Wu (small pilot and REC investigators), in collaboration with Drs. Walston and Bandeen-Roche, to study biomarkers of aging related to measurable physical property changes in cells. We continue to support many other present and former scholars for R, K, and Center grant 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. Mentorship from OAIC was instrumental in the career development K application by Dr. Keenan Walker, an OAIC REC awardee in the current grant year. Dr. Walker’s application was successful, and his notice of award was recently received.

Back to top

II.B. RESOURCE CORE-1 (RC-1): BIOSTATISTICS CORE
Karen Bandeen-Roche, Ph.D., Core Leader
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Qian-Li Xue, Ph.D., Core Director
410-502-7808  410-614-9625 FAX  qxue1@jhu.edu

The Johns Hopkins Older Americans Independence Center (OAIC) has empowered by many-fold the creation of significant research, training and practice paradigms for addressing frailty in older adults. The functions supplied by Resource Core 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 15 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 RC1 Specific Aims to:
1) Mentor junior scholars supported by our Research Education Core (REC) 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 REC 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. The Core continues to provide such support to all investigators funded through our REC and Pilot Cores. We also support other junior faculty and external studies pursuing aims consonant with the Center’s mission: Recent examples include the provision of advice and support to investigators interested in investigating linkages between visual impairment and frailty, incontinence and frailty, and frailty and adverse outcomes in HIV/AIDS, as well as continuing collaboration to pursue research on frailty in the National Health and Aging Trends Study.

To accomplish (B), we develop and test new methodologies for data analysis needed to translate basic research into clinical practice—please see below.

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 aids 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 REC 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:

The first is work from our RC1 Development Project over the past year. The topic was motivated by research under development to further elucidate nationwide racial and ethnic disparities found in a 2015 paper led by Dr. Bandeen-Roche. There, it emerged that the physical frailty phenotype criteria appear to exhibit systematic differences in their ascertainment of frailty for different race/ethnicity group. Our development work has sought to create improved statistical strategies, grounded in latent variable modeling, for identifying such differences (“differential item functioning”) in geriatric measurement. The strategies developed have two advantages relative to existing methods; They better identify “anchor” items—criteria that do manifest equivalently for persons of the same, say, frailty status but different, say, race/ethnicity, and they validly contrast criterion distributions and inter-relationships between persons of different race/ethnicity groups but the same frailty status, when assessment (possibly falsely) assumes that measurements are invariant across groups. Dr. Bandeen-Roche has delivered multiple presentations on the work, and a manuscript is under development.

In the last report, we reported the work by Dr. Xue aiming to evaluate the discordance in frailty classification between the Frailty Index (FI) and the Physical Frailty Phenotype (PFP) and identify factors discriminating those with discordant frailty classification from each other and from those for whom the assessments agree. Using data from the Cardiovascular Health Study, we found that, while the overall prevalence of frailty was similar between the PFP and the FI, we found substantial discordance in individual-level classification. The greatest agreement tended to occur among the oldest old with a considerable disease burden and disability; in comparison, the observed discordance seemed to exist primarily among younger older adults with higher social economic status and better overall health, suggesting that the concept of frailty may help identify a subclinical subset who might not come under the radar using conventional geriatric risk assessment. Our analysis also revealed that age and disease burden were the strongest predictors of discordance pattern with people at younger age but with greater disease burden more likely be classified as FI-frail but not PFP-frail. This study highlighted the risk to advocating the use of the different frailty assessment tools without a better understanding of the degree of distinction in the identification of vulnerable older adults, as well as the heterogeneity of older adults identified as frail by either instrument.

This project was initially supported by Dr. Xue’s R03 award. As the funding ended in June 2017, the OAIC supplemented Drs. Xue and Bandeen-Roche’s effort to maximize research productivity and impact. The manuscript has recently been accepted for publication in JGMS.

With increased interest in the frailty syndrome and its relationship with brain aging, recent consensus papers have suggested expanding the definition of frailty to include cognition. Approximately 50% of the frailty instruments in the literature include a measure of cognition, although the type of measure varies across studies from global measures (e.g., MMSE) to clinical diagnosis (e.g., dementia). Such inclusion primarily aims to improve the predictive accuracy of
frailty for future adverse outcomes. Through a R03 award, Drs. Xue and Bandeen-Roche conducted a secondary data analysis of the National Health and Aging Trend Study cohort to examine the temporal ordering in physical frailty and cognitive impairment onset, and found that participants with incident dementia during the 5-year follow-up were at increased risk of developing cognitive impairment first, or frailty and cognitive impairment concurrently. In contrast, dementia onset was associated with reduced risk of physical frailty onset before cognitive impairment [92]. These findings suggest that dementia-related pathology is less likely to be the cause of cognitive impairment if preceded by physical frailty, therefore providing support for the current IAGG/IANA definition of “cognitive frailty.” As the funding for the R03 ended, the OAIC continued the support of Dr. Xue’s effort to bring this work to publication. The paper has recently been accepted for publication in JGMS.

A fourth project is a paper to elucidate principles of frailty measurement, led by Drs. Bandeen-Roche and Xue together with recent OAIC REC alumnus Alden Gross and longer-ago RCDC alumnus Ravi Varadhan. This paper synthesizes a series of scientific discussions among the Johns Hopkins Frailty Working Group, sponsored by this OAIC. The Working Group comprises approximately 20 regular attendees spanning geriatricians, clinicians in a variety of other fields, social scientists, epidemiologists, and biostatisticians, who reside at Johns Hopkins, University of Chicago, and University of Rochester. The recent paper argues that frailty instruments should be grounded in formal validation; illustrates the paradigm it recommends; identifies unresolved measurement issues for the frailty field; and raises issues for frailty measurement in clinical practice. The paper is under revision for publication.

In May 2018, Dr. Xue initiated a new collaborative relationship with the Johns Hopkins Physics Laboratory (APL). The goal is to develop and test a mobile app to incorporate quantitative, in-home sensor-based measurements of routine daily activities and patient reported outcomes to create a standardized tool to assess frailty and monitor its progression in elderly populations. The Hopkins team led by Dr. Xue worked closely with the APL team on the project application and successfully obtained intramural funding at the APL to develop the APP. The OAIC provided supplemental funding through a small pilot to conduct focus groups to better understand perspectives and preferences of older adults across the frailty spectrum, as well as their informal caregivers and medical providers, regarding the use of wearable and/or installed sensors at home to assess frailty. Currently, the focus groups are now completed. An abstract was accepted for the 2019 GSA meeting as part of a symposium co-chaired by Dr. Xue and Dr. Huisingh-Scheetz from University of Chicago.

The RC1 continues to play important national and international scientific leadership roles. Dr. Bandeen-Roche co-led, with Dr. Jeremy Walston and Dr. Luigi Ferrucci, “Frailty Science: Moving Toward Utility in Clinical Practice,” a workshop of international reach co-sponsored by our OAIC and the NIA in September, 2017. A paper reporting the findings has been accepted for publication in JAGS. Dr. Bandeen-Roche continues to serves on the External Advisory Boards for the Duke and University of Maryland OAICs, and in July 2018, joined the OAIC network-wide Coordinating Center as a co-leader. She continues to co-lead the CTSA Lifespan / OAIC Workgroup on Aging, together with Dr. Elena Volpi, and in fall of 2018, was elected to co-leadership of the overall CTSA Lifespan Enterprise Initiative. She was recognized with two awards in the field of Statistics during the last year—she was re-elected to the Executive Director
board for the International Biometric Society, and she was the Distinguished Women in Statistics keynote lecturer (Vanderbilt University, April, 2019): work from this OAIC was featured prominently in this lecture. Dr. Xue serves on the OAIC’s DSMB at University of Maryland at Baltimore. Dr. Xue is also initiating research collaborations with frailty researchers in China to help translate research finding into clinical practice. He was an invited speaker at the Chinese Congress on Gerontology and Health Industry and the 2018 JinSha Forum organized by the Sichuan University West China Hospital.

During the reporting period from May 2017 to present, the RC1 Biostatistics Core assisted 27 researchers in 22 projects and 16 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 14 publications to date in this reporting period. We were co-leaders (Dr. Bandeen-Roche, an MPI) in the successful Johns Hopkins application for the UH2-UH3 grant to study Physical Resiliency, sought via a special National Institute on Aging RFA. We additionally supported the development of a successful U01 application in response to the NIA RFA “Development of Valid Reliable Markers of Aging-Related Biologic Mechanisms for Human Studies” (D. Wirtz, PI). This study is evaluating cellular morphology and motility as potential aging biomarkers. Dr. Bandeen-Roche’s mentorship was instrumental to Bonnie Swenor (pilot awardee) in her successful application for a K01 award to study the potential role of vision impairment in cognitive decline, following on her highly successful work to elucidate implications of vision impairment for frailty (three papers submitted to date). She also has mentored two K awards whose disposition is still pending: For Nadia Chu (to continue in her study of frailty and cognitive decline) and Bharath Ambale-Venkatesh (to pursue his development of whole-body metrics that may illuminate frailty etiology and recognition). Drs. Bandeen-Roche and Xue continue to co-mentor Alden Gross’ K01 (with Jeremy Walston) which followed from his OAIC RCDC award.

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

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

**RC2 Specific Aims:**

1) To provide state-of-the-art scientific expertise, technology and infrastructure necessary to facilitate cost-effective and efficient use of molecular approaches and downstream computational technologies relevant to etiologic frailty research. Relevant technologies are offered to the investigator either by core-supported analysis (genetic, genomic, ELISA based), access to a specialized JHU laboratory (mitochondrial function, metabolomic) or through an outside vendor when necessary (proteomic, aptamer development). Technology, access to measurement and measurement expertise and training, study design, bioinformatics and integrative omics data analyses are supported.

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 assists in identifying the relevant samples and provide access, and provide 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 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 provide guidance on available technologies/assays, study design, technical training and technology transfer, access to the resources in aims 1-3, and mentoring on study objectives, data analyses, interpretation, and translation.

5) To continue to provide institutional, national, and international access and visibility for RC-2-related science and activities. This aim seeks to identify and further train biologically motivated junior faculty with frailty relevant interests to contribute to this area.

During this reporting period (Year 16), 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 new metabolomics data being generated by REC and PESC sponsored investigators, b) incorporate measurements of oxidative stress, mitochondrial function, inflammatory cytokines, senescent T-Cell markers, DNA methylation, autophagy, autoimmunity, apoptosis/necroptosis, 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 REC 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 related to tryptophan metabolism, as well as physical properties of cells (i.e. nuclear membrane variability and function in gene expression with increasing age). These efforts have greatly influenced subsequent scientific and grant developments, and have facilitated the funding of a U2/U3 grant to study physical resiliency in response to clinical stressors, as well as a new U01 to study age-related biomarkers. In this case, we are supporting a study that evaluates with high throughput technology the changes in physical properties of cells and how they might influence the development of frailty and the development of chronic illnesses in older adults. RC-2 funded staff continue to provide support to these and other studies related to frailty and late life decline.

Specific Aim 1: To provide state-of-the-art scientific expertise, technology and infrastructure necessary to facilitate cost-effective and efficient use of molecular approaches and downstream computational technologies relevant to etiologic frailty research. Relevant technologies are offered to the investigator either by core-supported analysis (genetic, genomic, ELISA based), access to a specialized JHU laboratory (mitochondrial function, metabolomic) or through an outside vendor when necessary (proteomic, aptamer development). Technology, access to measurement and measurement expertise and training, study design, bioinformatics and integrative omics data analyses are supported.

We supplied internal and external support in this area to many REC and PESC supported investigators, as well as additional time, with ongoing external support to Dr. Abadir’s R01, Dr. Walston’s R01, R21, U01 Wirtz, UH2/3 Resiliency, K23 to Tae Chung, K08 to Alden Gross, R01s to Mara McAdams Demarco, R01 to Damani Piggott, and the OAIC Year 16 supplement on dementia. 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. 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. A paper was published from this work in Nature Biomedical Engineering in July of 2017, and directly resulted in the successful competition for a U01 to study Biomarkers of Aging. In the metabolomics realm, we successfully collaborated with the Department of Pathology in order to successfully apply for a large equipment grant that enables more robust metabolomic measurements. We have also greatly informed the development of specific measures related to the Tryptophan metabolism that enabled successful applications for Dr. Chung’s K23 and is serving as the basis of K08 application for REC supported investigator Dr. Westbrook.
Specific Aim 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 assists in identifying the relevant samples and provide access, and provide assistance and training in sample procurement and processing, as needed by each supported investigator. 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, and the QRPT mouse in order to study the consequences of chronic inflammation on frailty and to further explore the tryptophan kynurenine pathway that may be driving frailty. We have developed a new partnership with Drs. Ahmet Hoke of Neurology and Johns Hopkins and with Robert Schwartz of the University of Maryland so that we can utilize and collaborate around very important biology. EP investigators include Abadir and Chung, AFAR supported investigators Westbrook, and multiple other external investigators. We continue to provide access to an institutionally supported mouse phenotyping database related to frailty in order to facilitate the identification and utilization of other mouse models with frailty or related chronic inflammation phenotypes. This includes mouse tissues to Enid Neptune, from Pulmonary Medicine, Linda Resar from Hematology, Denis Wirtz from Bioengineering, and Kathy Wilson from Cellular and Molecular Basic Biology.

Specific Aim 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 usually differ in matters of scale and access to biological materials. We continue to focus on the development of clinical research studies that focus on the development and translation of new biological measurements related to frailty and frailty-related outcomes in specific clinical studies that we have helped to support. These efforts are supporting 2 of the 3 ongoing PESC studies as well as the 3 of the 4 REC supported scholars (see other core reports) and ongoing RC2 development projects. We have provided inflammatory measurement expertise to a R21 and R01 led by Dr. Walston that is attempting to identify the most robust and predictive cytokine for chronic inflammation observed in frailty and aging. This has resulted in the elevation of TNF-R1 as the most stable and consistently predictive marker of the commonly measured cytokines. The RC2 continues to facilitate the development of a novel wound care technology that targets diabetic and chronic non-healing wounds in older adults, including the leveraging of prior intellectual property developed in RC2 into a successful SBIR application with Gemstone Biotherapeutics, LLC. A major manuscript reporting some of these findings was published in Investigative Dermatology in 2018, and has been leveraged into a new SBIR award to Gemstone from the NIH. In addition, as previously reported above in overview, collaborative efforts of the RC2 has helped to facilitate the successful procurement of the U2U3 grant to study physical resilience (measurements of senescent cells, inflammatory biomarkers, T cell markers, metabolomic markers) and a U01 to develop improved biomarkers of aging related to age-related physical properties of cells.
Specific Aim 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 provide guidance on available technologies/assays, study design, technical training and technology transfer, access to the resources in aims 1-3, and mentoring on study objectives, data analyses, interpretation, and translation. We have continued to work with all REC and PESC supported investigators, and with Drs. Gross and Chung, recent K awardees who were previously REC supported investigators, and Dr. McAdams DeMarco, a prior PESC and REC supported investigator who now holds 2 R01s related to frailty. We continue to provide relevant technology, laboratory supplies, measurement expertise, critical reviews, and career guidance to these individuals as they develop scientific protocols, perform experiments, develop manuscripts, and apply for new grants. We also provide ongoing support to External Project (EP) investigators Leng, Abadir, Wirtz, Resar, Franco, Gross, Piggott, Brown, Neptune, McAdams Demarco and Walston, as they develop manuscripts related to frailty, aging, inflammation, mitochondrial biology, and the renin angiotensin system. We also continue to provide a conduit to the Johns Hopkins Technology Ventures office, where new technologies can be vetted by trained personnel for intellectual property development and for possible transfer into start up or established companies. Dr. Abadir and Walston have done these on prior occasions, and continue to provide advice and assistance to all investigators who have developed new biotechnologies that could possibly be transferred into commercial technologies.

Specific Aim 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 and senior faculty who are interested in the development of new biological knowledge relevant to frailty and aging, especially if that knowledge has translational potential and can be utilized in future clinical practice settings. RC2 continues to be the ‘go to’ place for the development of interdisciplinary biological collaboration and expertise development. Collaborative efforts continue to grow across the Johns Hopkins Medical Institutions and increasingly with Biomedical Engineering and Applied Physics programs. The core works very closely with the Biology of Healthy Aging program, which brings considerable mitochondrial, renin angiotensin, and immune-senescent cell measurement expertise to many collaborators across the institution. On the national and international stage, RC2 leaders developed major symposium at the 2018 and 2019 International Conference on Fraility and Sarcopenia as well as at the 2018 Gerontological Society of American meeting, and at the 2018 and 2019 OAIC Annual Meeting. Dr. Walston and Dr. Abadir both frequently talk at international Gerontological meetings and present RC2 supported data in other national and international conferences in Atlanta and Porto, Portugal (related to wound care technology development) and in Sao Paulo Brazil and Madrid Spain related to energetics and biology of frailty and late life decline.

RC2 Development projects:

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. Dr. Westbrook collaborated extensively with Dr. Rafael De Cabo of the NIA extramural branch in Baltimore to more extensively characterize the metabolic and metabolomic phenotype of this mouse model. A manuscript was published in 2017 in the Journal of Gerontology detailing these findings. Metabolomic profiling has identified marked differences in tryptophan metabolism, in TCA cycle components, and in lipid metabolites between chronically inflamed and control mice have been identified. Working with Dr. Abadir and previous REC supported scholar Chung, 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 has become a core component of the successful renewal effort that started in July 2018. This work has resulted in the awarding of the 2016 AFAR Translational Research Post-Doctoral Fellowship Award to Dr. Westbrook, and a subsequent K-23 award to previously supported (by REC) investigator Tae Chung. Dr. Westbrook has in collaboration with Dr. Abadir translated these important findings into human subjects, and is in the process of developing a manuscript and a K-08 application.

Year 13-14 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. Using a targeted metabolomics approach, this development project 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 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 are 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 is used to support a future NIH grant application on sarcopenia and frailty. Progress Updates: For plasma, we had measured plasma metabolites in a cross-sectional analysis of 508 adults, aged 50-95 y, who participated in the Baltimore Longitudinal Study of Aging (BLSA). Using a targeted metabolomics approach, we identified 126 plasma metabolites. We found that plasma concentrations of all three major branched-chain amino acids were significantly associated with muscle quality. For skeletal muscle, we had conducted targeted metabolomics of 37 BLSA subjects and skeletal muscle samples are still in collected from hospital. Our metabolomics studies demonstrate that muscle quality shows a linear decline with older age, and the low muscle quality is associated with a reduced incorporation of all three major branched-
chain amino acids (BCAA). The high concentration of lipid molecular species that have been previously associated with a high-fat diet as well as impaired mitochondrial function. Based upon the work supported by the OA IC, they have published 3 articles to date and an R01 grant submission is under review.

Year 14-15 project: IL-6 knock in mouse development. Funds were provided to develop an IL-6 knock-in mouse model with a mitophagy reporter. The purpose of this developmental effort is to study the impact of IL-6 on the development of mitochondrial changes observed in aging. The project has been successful to date with several breeding pairs now reproducing litters that can be aged and utilized in future grant and study development efforts. An R01 has been submitted for review later in 2019. Dr. Abadir is leading this effort.

Year 16-17 project: Autoantibody aptamer development efforts. This project commenced in the fall of 2018 with the recruitment (in collaboration with RC3) of 6 frail subjects. Blood was drawn and autoantibodies were extracted. The antibodies are being sequenced and utilized to design aptamer synthesis.

Externally Supported projects:
- Sean Leng, MD, PhD. NIH/NIAID R01 AG108907. Influenza Vaccine Failure in Adults over Age 75: Role of Chronic CMV Infection. Funded 2014. This project receives ongoing support.
- Peter Abadir, MD. NIH/NIA R01AG046441: Age-Related Change in Mitochondrial Angiotensin System and Mitochondrial Decline. This project receives ongoing support.
- Jeremy Walston, MD. NIH/NIA R01: Enhancing Mobility in Older Adults by Treating Chronic Inflammation: Pilot Phase. Grant support and lab support ongoing through 2017-2019.
- Jeremy Walston, MD. NIH/NIA R21: Recombinant Human Lactoferrin for the Treatment of Chronic Inflammation in Older Adults. This project received ongoing support during the 2017-2019 period.
- David Roth, PhD. NIH/NIA RF1: Transitions to Family Caregiving and its Impact on Health Indicators. Provided provides biomarker measurement support.
- Dan Arking, PhD. NIH/NHLBI R01: Mitochondrial DNA Copy Number and Genetic Variation in Coronary Heart Disease. RC1 Development project provided infrastructure and development support.
- Ravi Varadhan, PhD, PhD, Jeremy Walston, MD Karen Bandeen-Roche, PhD, co PIs, NIA UH2/UH3, Funded 2017: Characterizing Resiliencies to Physical Stressors in Older Adults: A Dynamical Physiological Systems Approach.
- Denis Wirtz, PhD. NIA U01, Funded 2018: Validation of Nuclear Morphology as a Biomarker of Aging and Aging-related Phenotypes.

Back to top

II.D. RESOURCE CORE-3 (RC-3): CLINICAL TRANSLATION AND RECRUITMENT CORE
Todd Brown, M.D., Ph.D., Core Leader
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. **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 600 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 core is led by Dr. Todd Brown, an endocrinologist and long-standing active participant in our OAIC Working Group on Frailty and Multisystem Dysregulation, who has substantial human subjects research expertise and plays a leading role in the CTSA entity at Johns Hopkins. 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 funded in part by philanthropic resources from the Division.

The goals of this core are outlined in the following **RC-3 Specific Aims:**

1) To provide OAIC-supported investigators with mentorship and training in all aspects of human subjects research, including study conceptualization, study design and outcomes, definition of interventions, measurement, data analysis, protocol development and implementation, regulatory approval, quality assessment, and standard operating procedures related to frailty and the maintenance of independence.

2) To ensure optimal and safe performance of clinical studies supported by this OAIC by providing oversight regarding regulatory issues involving human subjects, including human subject protection, IRB and FDA applications, and data safety and monitoring plan (DSMP) development.

3) To provide all OAIC-supported investigators with the clinical research infrastructure and services necessary to successfully conduct frailty-related clinical studies, together with RC1 and RC2, including
   a) Space to perform clinical research
   b) Direct assistance with protocol development, standard operating procedures, regulatory documentation preparation, data safety and monitoring plan development by an experienced clinical research program manager.
   c) Direct assistance, and training for clinical research staff, in data collection in human subjects, including study advertising, recruitment from a registry and from the community, clinical measurement assistance for frailty, function, cognition, and phlebotomy services.
   d) Direct expert assistance with all aspects of human subjects research articulated in Aim 1.
4) 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 frailty. The utilization of this registry is prioritized to OAIC-supported investigators.

The Healthy Aging Studies Unit and the Frailty Registry provide the bulk of support for human subjects research in this OAIC. The following section describes these research resources that are articulated in the specific aims, as well as specific studies that are supported by this RC3.

**Healthy Aging Studies Unit**: The central hub of RC-3 is the Healthy Aging Studies Unit (HASU) located on the Johns Hopkins Bayview Medical Center. The well trained personnel, the expertise that has been developed in the measurement of frailty and other aging phenotypes, the expertise in recruitment of older adults, and a large pool of older adults (registry) willing to participate in clinical research provides the human resources necessary to support the development, implementation, and finalization of a wide range of clinical studies that have a wide range of needs. Indeed, the space and personnel in this unit, including those supported by RC3 funding, provide resources for the conduct of frailty-related clinical and clinical intervention studies that facilitates 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 that are crucial to the function of RC2. Importantly, this unit provides the physical space necessary to interview and examine subjects for a wide range of studies. It provides touch down points for multiple clinical coordinators working across several studies.

**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 database to store data and enable database inquiries. Most OAIC supported investigators have utilized this resource since its inception. Over the past several years, we have had over 1300 older adults who have been active in the registry. Currently, there are currently over 650 active participants in registry database who have been characterized for frailty, all of whom have agreed to be re-contacted for additional research studies.

**Projects supported by the RC-3 during this reporting period:**

**OAIC Pilot Study: Anne Le, MD**: “Exploratory Study of Metabolomics Energy Signatures in Frailty.” Please see full description provided in the Pilot Core report. RC-3 to provide recruitment, scheduling and evaluation support.
OAIC REC Study: Pei-Hsun Wu, PhD: “Biophysical cellular characteristics in frail and non-frail older adults.” Please see full description provided in the REC report. RC-3 provides recruitment, scheduling and evaluation support.

OAIC REC Study: Bharath Ambale-Venkatesh, PhD: “Pathways leading to frailty: a study of muscle, cardiovascular tissue, and energy utilizing whole-body magnetic resonance imaging.” Please see full description provided in the REC report. RC-3 provides recruitment, scheduling and evaluation support.

OAIC REC Study: Reyhan Westbrook, PhD: “Metabolomic differences in energy utilization and Kyn/Trp metabolism pathways in mouse models of frailty: evidence-based implication for translational studies in humans.” Please see full description provided in the REC report. RC-3 provides recruitment, scheduling and evaluation support.

OAIC RC-2 Development Project: Neal Fedarko, PhD, and Peter Abadir, MD: “Autoantibody aptamer development efforts” Please see full description provided in the RC2 report. RC-3 provides recruitment, scheduling and evaluation support.

OAIC Small Pilot Study: Qian-Li Xue, PhD: “Focus Group Discussion of Developing a Sensor-Based Mobile Application for In-Home Frailty Assessment.” Please see full description provided in the Pilot Core report. RC-3 provided recruitment assistance via registry access.

R01: Sean Leng, MD, PhD: “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.

R01: J Walston, MD: “Enhancing mobility in older adults by treating chronic inflammation.” RC3 personnel were responsible for the implementation and recruitment of this study.

R21: J Walston, MD: “Recombinant Human Lactoferrin for the Treatment of Chronic Inflammation in Older Adults.” RC3 personnel were responsible for the implementation and recruitment of this study.

U01, Denis Wirtz, PhD: “Validation of nuclear morphology as a biomarker of aging and aging-related phenotypes.” RC3 personnel are responsible for recruitment of this study.

UH2 / UH3, Karen Bandeen-Roche, PhD, Ravi Varadhan, PhD, Jeremy Walston, MD: “Characterizing resiliencies to physical stressors in older adults: a dynamical physiological systems approach.” RC3 personnel support recruitment efforts and IRB tasks for 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. The NIA Program Officer has previously approved all members. 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 meets semi-annually, or more frequently as needed, to review progress, findings and all potential safety issues related to OAIC sponsored human subjects research projects. Reports and minutes from each meeting have been submitted to the NIA Program Officer.

Back to top

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

1) To develop a state-of-the-art online platform to efficiently disseminate current information on frailty-related science, practice, and implications. We collect, create, organize, synthesize, and keep up-to-date documentation on: current evidence-based frailty knowledge, best-practice recommendations from national and international organizations, frailty assessment instruments and apps, and other resources of interest to researchers and clinicians who are engaged in frailty research or who are seeking guidance on how to incorporate frailty into their work, as well as patients, policy-makers, and other stakeholders.

2) To create a series of low-cost or free online courses and other materials that provide in-depth knowledge and training on key aspects of frailty, including biology, measurement, interventions, treatment options, prevention, clinical impact and policy impact. These will be accessible from the web platform articulated in Aim 1.
3) To partner with professional societies (e.g., Gerontological Society of America), foundations (e.g., AFAR), and colleagues worldwide to promote high-impact frailty findings, and their translation through collaborative activities for information exchange, briefings for policymakers and key health care organizations, and participation in the development of evidence-based practice guidelines.

4) To promote scientific interaction on frailty so as to accelerate the field’s progress and implementation to the benefit of older adults. We will develop pre-conference workshops to accompany the meetings of professional societies, expert conferences, webinars, and communities of practice to this end. The translation of frailty to clinical settings is a primary area of focus.

Website development: During the first year of our renewal and initiation of the IDC, the Core’s leader and staff from CCP have worked in close coordination with the JHU OAIC Leaders to develop a go-to online, up-to-the-moment hub for frailty-related science. This website aims to catalog state-of-the-art knowledge, provide highly relevant resources related to frailty ascertainment, measurement, prevention and treatment, and present novel findings and innovations. It will serve as the central platform for information storage, organization, and dissemination and will provide online access to comprehensive program information and resources. This website will primarily target academic researchers and clinicians; it will also feature more general news and announcements for public audiences.

Development of this website has followed the system development life cycle procedures. CCP began development of the website with knowledge acquisition sessions. The web development team met with the JHU OAIC leaders to understand the intended audiences, types of content and resources to include, and current and future plans for this site. This has allowed the web developers to build in appropriate flexibility to accommodate future additions and/or changes to the website. Procedures have been developed and followed, to include guidelines for programming, change management, change control, testing and approval, and posting changes in the production environment. The procedures have also covered the submission of requests or suggestions, maintaining compliance with guidelines on the public site, and periodic website review and updates. We will seek the guidance of our EAB in the development and implementation of these important procedures.

We aim for this website to serve as a central repository for the JHU OAIC frailty information resources available to academics, clinicians, and the public. Its software developers employ rigorous procedures for backup, version control, testing, and workflow. The Drupal content management software (https://www.drupal.org/about) is being used as the foundation for the website. Advantages of Drupal include: a) It is built on the leading technologies that power the Web—Linux, Apache, MySQL, and PHP, making it flexible, powerful, and reliable. b) It implements rigorous security measures, including enforcement of strict coding standards and a review process, a database abstraction layer that performs security checks on data as it is written to and retrieved from the database, c) It is an open source Web framework supported by a community of thousands of developers. d) It integrates readily with existing and leading edge technologies. e) Its content architecture is flexible, thus allows a site to grow and evolve based on user needs. f) It affords very granular permissions, which allows content managers to present
the most appropriate content to the right group of users. CCP and OAIC jointly manage the backend of the website and the server on which it is hosted, sharing equal access.

The types of features that have been designed for the website are:

- An **engaging, mobile—responsive design** that orients visitors and draws them in.
- A "scrolling marquee" on the homepage, which allows content managers to highlight particular aspects of the site or link to other relevant content in an appealing slideshow format.
- A **Twitter feed, or other social media outlets** into the sidebar of the homepage
- A dynamically driven "**Latest Updates**" section, which keeps the homepage fresh by featuring newly-posted content (e.g., new publications, new blog posts, new resources, new events)
- A “**Blog and commentary**” section with multiple contributor profiles, permission-controlled commenting, and tagging
- A **resources** section, easily filterable by **resource type**, for sharing program documents, meeting notes, presentation slides, etc.
- A **custom logo** with site name and tag line
- Robust **search** functionality based on Apache Solr.

As described above, once launched, this website will serve a number of essential dissemination functions, including the broadcast of press releases and newsletters; the promotion of publications, awards, and events; presentation of curated frailty knowledge; and the gateway to online resources (online Hopkins Frailty Assessment Calculator, frailty instruments database, and more). The IDC is working closely with the OAIC leadership to develop and finalize site content, and with members of the Frailty & Multisystem Working to develop blog and commentary pieces to be posted in the coming year. In addition, Dr. Abadir (RC2 co-leader) and Mr. Buta (administrator) have mentored a master’s student in the JHU Department of Art as Applied to Medicine during the past year, who has developed a series of animated video modules that will serve as educational resources to be included on the Frailty Science website.

With guidance from the JHU OAIC Leaders, CCP has registered a domain name (URL), ensuring that the project retains all rights to this name for its duration: [http://frailtyscience.org](http://frailtyscience.org). The site is currently in the production environment, and we aim to launch in the coming months. A screenshot of the website design is provided below.
Workshop / webinar development: A key goal of the IDC is to offer in-person workshops that will gain further visibility for the OAIC and its collaborators, articulate areas where advances are needed in research on frailty and aging, and support network building across these groups. During this reporting period, we submitted a pre-conference workshop to the Annual Scientific Meeting of the Gerontological Society of America, to be held in Austin, TX in November 2019. The workshop, titled “The translation of frailty to clinical settings: a state-of-the-art workshop on measurement, etiology, and intervention” focused on four main topics (Frailty Ascertainment and Epidemiology, Present Use in Clinical Practice, The Biology of Physical Frailty, Possible Interventions) and include discussion and brainstorming sessions. Though not selected, we are now working with GSA to reformat as a webinar series to present and disseminate this information. Themes for the webinars / workshops will developed based on input from the OAIC leaders and individual presenter preferences.

II.F. RESEARCH EDUCATION CORE (REC)

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The major goals of the JHU OAIC Research Education Component (REC) are to increase the cadre of experts dedicated to scholarship on frailty and provide them the training and skills required to develop, perform and eventually translate research into clinical management and preventive strategies that enhance and maintain independence in older adults. The REC accomplishes these goals by identifying and selecting outstanding junior faculty investigators to pursue frailty-related discovery and by providing them with the comprehensive training and support necessary to develop independent research careers focused on such discovery. The in-depth support we provide includes material, intellectual, and mentorial elements. Material
support in the form of salary secures protected research time. Comprehensive resource core support facilitates and enhances research. Individually-tailored intellectual support and training are provided through one-on-one instruction, the wealth of research coursework available at the JHU Bloomberg School of Public Health, off-site workshops, and training modules and symposia developed and delivered by this OAIC. Mentorial support comes through easy access to the network of highly expert, interdisciplinary scholars who comprise the OAIC leadership, their dedicated time, oversight and provision of guidance and advice, and the creation of a community of scholars from among current and former OAIC-supported junior and senior investigators. Salary and full-service resource core support is prioritized to “K-eligible” individuals for whom REC funding can optimize the likelihood of obtaining major career development awards. These individuals are our highest priority because of the very significant positive impact of these awards at a key career transitional point. In addition to this priority set of trainees, investigators as junior as pre-doctoral and as accomplished as having already received career award funding (“R-eligible”) can also benefit from REC support. In addition, mentorship, research resources and participation in our community of scholarship are provided to as many qualified individuals as research core capacity allows, with R-eligible faculty given priority for pilot awards and external project support that can enhance their prospects for further funding and solidify their transition to becoming independent investigators.

This REC provides (i) a focus for frailty- and aging-related training activities for junior investigators from the entire University, and (ii) more extensive support, training and mentorship to a select few whose careers we can pivotally aid, and who will become aging and frailty-focused independent investigators who will apply their learned expertise across disciplines and lead research whose application is expected to improve and maintain independence in older adults. Support we provide aims to facilitate the junior investigators’ ability to discover and understand basic research principles, to apply these to clinical investigation and intervention strategies, to explore responsible mechanisms, and to disseminate the relevant results to the health provider and broader communities. They also learn to master the leadership and communication skills required to become academic leaders with independent research careers who can easily work across disciplines to pursue and conduct the highest quality, frailty-focused science.

To accomplish these goals, we propose the following REC Specific Aims:

1) To provide a research education program which develops, for each supported individual, a portfolio of subject-area, methodological and leadership training, mentorship individualized to his or her needs, a mentored research project, and monitoring of the progress of the program, research project, and career development.

2) 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.

3) 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 ensure protected time and access to core resources necessary to successfully conduct outstanding research and advance their interdisciplinary training.
4) 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.

This REC serves as a center of training, mentorship and networking for talented junior investigators spanning three levels of development: 1) K-Eligible Investigators: The highest priority of the REC is given to junior faculty members deemed to have promise for K or other career development awards. At least 3 individuals in any given year receive salary and 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 Pilot Core resources as needed. They also receive ongoing mentorship and education to facilitate successful applications for 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. They are also provided with mentorship by this OAIC and encouraged to develop research and career goals that enable them to be eligible for formal OAIC support. Over the past 3 years, such trainees have made substantial contributions to the scientific progress of this OAIC and many have become REC, Pilot Core, external project, and diversity supplement supported scholars.

REC awardees, October 2017 – June 2019:

1) Rani Hasan, MD, MHS. “Frailty in Elderly Patients Undergoing Transcatheter Aortic Valve Replacement (TAVR) for Symptomatic Severe Aortic Valve Stenosis (AS): Impact on Outcomes, Effect of TAVR on the Frailty Phenotype, and Association with Inflammation.” Mentors: Drs. Jon Resar, Gary Gerstenblith, and Bruce Leff.

Project description. This study: 1) evaluates 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) evaluates 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) investigates inflammation as a pathophysiologic link between frailty and TAVR outcomes in aortic stenosis patients undergoing the procedure by evaluating pre- and post-TAVR levels of traditional and novel inflammatory markers.

Progress Updates: Dr. Hasan has an approved IRB protocol for his studies: IRB00054646, which has been renewed. There have been no adverse events to date. Dr. Hasan has met and reviewed statistical plans and study progress with Biostatistics Core Leader, Dr. Bandeen-Roche. Dr. Hasan and colleagues have completed a preliminary analysis and have collected 1-year clinical follow-up data (N=89). Dr. Hasan has met with Dr. Bandeen-Roche regarding final data analysis, which is underway. As part of the prospective study, Dr. Hasan has worked collaboratively with Drs. Karin Neufeld and Atsushi Kamiya of the Department of Psychiatry to study delirium and its impact within the same patient population. Dr. Hasan has also conducted a sub-study to compare subjective frailty assessment by both providers and patients as compared to standardized
frailty assessment using the Fried criteria within the prospective study. Four papers are planned / in preparation (Physical frailty pre- versus post-TAVR, inflammation and physical frailty in TAVR patients, objective versus subjective frailty assessment in TAVR patients, and frailty and delirium in TAVR patients), an R21 grant was submitted in October 2018 with collaborators in the Department of Psychiatry but was triaged; we plan to resubmit this after completing some of the aforementioned planned manuscripts. An abstract was accepted for presentation at the American Association of Thoracic Surgeons Annual Sessions.

Awards and presentations to date include:

- Research grant from the Hitachi Medical Corporation, with Drs. Neufeld and Kamiya to support evaluation of novel near-infrared spectroscopy for diagnosis of delirium as part of a collaborative effort.
- JHU Division of Cardiology Grand Rounds. Dr. Rani K Hasan, "Frailty and Delirium in Elderly Patients undergoing TAVR: Moving beyond the “Eyeball Test.” May 24, 2017.
- JHU Division of Cardiology Fellows' Research Conference, Dr. Rani K Hasan: “Frailty and Delirium among Patient Undergoing Transcatheter Aortic Valve Replacement (TAVR).” April 4, 2019.

2) Tae Hwan Chung, MD: "Involvement of Kynurenine and NAD Pathways in Frailty.”
Mentors: Drs. Ahmet Hoke and Jeremy Walston.

Project description: Age-related muscle weakness is a critical component of and contributor to frailty in older adults, and reliably predicts morbidity and mortality in late life. From a biological standpoint, age-related muscle weakness is likely multi-systemic, involving nutritional, metabolic, immune, and central nervous system changes. Emerging evidence indicates that degeneration of the neuromuscular junction (NMJ) is one of the earliest findings of age-related muscle weakness, with muscle atrophy (sarcopenia) occurring at a later stage. Dr. Chung’s lab recently demonstrated a dying-back distal axonopathy in the motor axons of aged animals, which may explain early degeneration of the NMJ. Dying-back axonopathy is a form of neurodegeneration that occurs when a neuron is under a metabolic stress, with the most distal part of the neuron, such as the
NMJ, starting the neurodegeneration in a centrifugal fashion. However, the metabolic pathways responsible for such neurodegeneration with aging are not known. In a recent collaboration with OAIC investigators, the frail mouse model (IL-10 -/-) was used to identify alterations in the kynurenine and NAD pathways in a metabolomic study. Interestingly, the kynurenine and nicotinamide adenine dinucleotide (NAD) pathways generate potent neurotoxic metabolites, and have been extensively studied in many age-related neurodegenerative diseases, such as Alzheimer and Parkinson diseases, while the role of these pathways in frailty is largely unexplored. Therefore, Dr. Chung hypothesized that a shift towards neurotoxic metabolites in the kynurenine and NAD pathways drives a dying-back distal axonopathy, and ultimately sarcopenia and frailty. To support the hypothesis, he used quantitative real time PCR (qRT-PCR) and demonstrated that most enzymes involved in kynurenine and NAD pathways are significantly down-regulated in the spinal cords of aged wild type animals, as compared to muscle and liver tissues. To further explore the roles of kynurenine and NAD pathways in the context of frailty, he plans to: 1) characterize NMJ and peripheral axons of the frail mouse model (IL-10 -/-), and 2) profile the kynurenine and NAD pathways in the nervous tissues of the IL10 -/- frail mice. The study aims are: Aim 1: To characterize NMJ function in IL10 -/- frail mice. Hypothesis: Age-related dysfunction of NMJ is greater in frail IL10 -/- mice than in wild type old mice. Subaim 1: to evaluate the morphological differences in NMJ innervation between IL10 -/- and wild type mice and correlate these with markers of frailty and strength. Subaim 2: to evaluate the electrophysiologic differences in NMJ function between IL10 -/- and wild type mice and correlate these with markers of frailty and strength. Aim 2: To investigate kynurenine and NAD pathways in the nervous tissues of IL10 -/- frail mice and wild type mice. Hypothesis: The kynurenine and NAD pathways are altered in the nervous tissues of IL10 -/- mice to a greater extent than in wild type mice. Subaim 1: to compare the enzyme expressions of the kynurenine and NAD pathways in IL10 -/- and wild type mice and correlate these with the NMJ abnormalities and dysfunction identified in aim 1. Subaim 2: to compare the levels of kynurenine and NAD pathway metabolites between IL10 -/- and wild type mice and correlate these with the NMJ abnormalities and dysfunction identified in aim 1. We anticipate that the results from the above experiments will provide a strong rationale for further studies of the relationship between age-related metabolic changes in the kynurenine and NAD pathways, distal motor axonopathy, and ultimately sarcopenia and frailty. Importantly, these pathways have not been extensively studied and hold great potential for both risk assessment and intervention development in future translational studies. We anticipate that the results of this study will eventually lead to the development of targeted, biological approaches to aging and frailty. Dr. Chung applied for a received aK08AG058483: “Alterations in Kynurenine Pathway in Age Associated Muscle Weakness” based on the pilot data and assistance that he received while he was an OAIC funded REC scholar. He continues to attend REC meetings and continue to receive RC1, 2 and 3 support as necessary for his K award. Progress Updates: For Aim 1, sub-aim 1: The investigators collected and stained NMJ of 11 IL10 -/- old and 10 wild type old mice, and process confocal images (20 images per mouse). They are currently in the process of analyzing the images for semi-quantitative comparison between IL10 -/- and wild type B6 mice. For Aim 1, sub-aim 2: The investigators have completed the single fiber EMG and grip strength measurements from
the above 11 IL-10/- old and 10 wild type old mice. As they study more young IL-10/- and wild type mice, they plan to perform the same functional tests. For Aim 2: they recently discovered that gas chromatography-mass spectrometry (GC-MS) with triple quads is needed to measure all the metabolites from the kynurenine pathway, and requested collaboration with Dr. Schwarcz’ lab at University of Maryland for mass spectrometry. Dr. Ratnam Bandaru perform the mass spectrometry.

Publications/presentations:
- JHU Peppers Scholars Research in Progress Presentation, February 6, 2019: “Alteration of Kynurenine Pathway in Sarcopenia and Frailty”.


3) Abdulla Damluji, M.D., MPH. “Consequences of Frailty in Older Adults after Acute Coronary Syndrome.” Mentors: Jeremy Walston, M.D., Karen Bandeen-Roche, Ph.D., Mauro Moscucci, M.D., M.B.A., Gary Gerstenblith, M.D. Advisors: Jodi B. Segal, M.D., M.P.H., David L. Roth, Ph.D., Orla Sheehan, M.D., Ph.D.

Project description: Frailty is a predictor of adverse outcomes after acute myocardial infarction (AMI). Objectives: To estimate the prevalence of frailty among adults age 75 years admitted with AMI and examine the relationship between frailty, interventions, and mortality. Methods: We used the Premier Healthcare Database to identify older adults with primary diagnoses of AMI. We classified individuals as frail or not using the validated Claims-based Frailty Index (CFI). We described patients’ characteristics and receipt of percutaneous coronary intervention (PCI) stratified by frailty status. The primary outcome was hospital mortality.

Progress updates: From 2000 to 2016, we identified 469,390 encounters for older patients admitted with AMI. The median age was 82 years, 53% were women, and 75% were Caucasian. The prevalence of frailty was 19%. Frail patients were less likely to receive PCI than non-frail (15% vs 33%, <0.001) and much less likely to receive CABG (1% vs 9%, <0.001). There were far fewer interventions in individuals over age 85 years. Frailty was associated with a higher unadjusted mortality during AMI admission (OR 1.43, CI 1.39-1.46). While there was a differential benefit of the interventions due to frailty, frail patients had reduced hospital mortality with PCI (Frail: OR 0.59, CI 0.55-0.63; Non-Frail: OR 0.49, CI 0.47-0.50, p for interaction <0.001) and with CABG (Frail: OR 0.77, CI 0.65-0.93; Non-Frail: OR 0.74, CI 0.71-0.77, p for interaction <0.001) relative to no intervention. Conclusions: In the U.S., frailty is common among older patients admitted with AMI. While these vulnerable patients are at an increased risk for mortality, judicial use of revascularization with PCI in frail older patients still confers immediate survival benefit.
Publications / Presentations:

- Damluji AA et al. Frailty among Older Adults with Acute Myocardial Infarction and Outcomes from Percutaneous Coronary Interventions. J Amer Heart Assoc. Accepted.
- Additional papers are in progress (analysis phase).
- Abstracts (two) in American College of Cardiology 2018 (March 2018); 2 abstracts in American College of Cardiology 2019 (March 2019); 2 abstract in American Heart Association 2018 (Nov 2018). One oral presentation and one symposium in ICSFR 2019 (Feb 2019).

Grant development: K23 grant to be submitted in the next 2019 cycle.

Project description: Most older adults now live with MCCs, requiring constant care from health services and patients themselves. For many the burden of treating MCCs negatively affects quality of life and leads to decreased medication adherence and serious adverse events. Dr. Sheehan is building on her prior work to understand challenges vulnerable older adults experience in managing their MCCs by investigating the hypothesis that frailty reduces compensatory mechanisms for managing treatment burden, resulting in decreased treatment adherence and increased adverse outcomes vs comparable non-frail older adults. Her study has three specific aims—to: 1) characterize the prevalence of frailty among the homebound; 2) determine associations of frailty with treatment burden; and 3) determine the effect of frailty on a) adherence in the year after...
NHATS interview, and on b) adverse outcomes of Emergency Department visits and potentially avoidable hospitalizations, accounting for previously established predictors of these outcomes. Potential research experiences and mentorship: Dr. Sheehan has taken two workshops in understanding and analysis of CMS data run at the Centers for Medicare and Medicaid Services headquarters Baltimore, MD. She continues to meet regularly with her mentors about this project and has drawn in additional expertise as needed (e.g. from Dr. Christine Ritchie on the homebound and Dr. Karen Bandeen-Roche on imputation of the frailty phenotype in NHATS).

Progress to date: Data use agreements have been executed with both The National Health and Aging Trends Study (NHATS) and CMS to allow Dr. Sheehan access to the NHATS linked CMS dataset to study the issues outlined above. IRB approval was also obtained for this work. Aim 1: Prevalence of frailty was calculated among the homebound using both the physical frailty phenotype (PFP) and the Segal index designed to approximate the PFP using claims data. As predicted, frailty prevalence is high in this population. Population weights have been applied to account for the oversampling of the oldest old in NHATS many of whom are homebound. Further study is ongoing to understand why the population weights appears to affect the claims based frailty prevalence more than the frailty phenotype (possibly due a differential use of Medicare fee for service among the homebound population) and also to understand why non-frail older adults are homebound.

- **CFI frailty (unweighted):** Homebound sample (n=361): 58.2% (95% CI: 53.1%-63.3%)
- **CFI (weighted):** Homebound sample (n=361): 45.0% (95% CI: 38.9%-51.0%)
- **PFP frailty (unweighted, imputed):** Homebound sample (n=361): 71.3% (95% CI: 66.1%-76.5%)
- **PFP (weighted, imputed):** Homebound sample (n=361): 69.2% (95% CI: 64.2%-74.2%)

Aims 2 and 3: Extensive work has been done to operationalize and define the variables used in the analysis. Two continuity of care (COC) indices are being used, the traditional Bice-Boxerman COC index and the more recently developed Known Provider of Care Index, which may be more applicable to older adults with multiple chronic conditions. Adherence is measured using both the NHATS self-report adherence question and the Medication Possession Ratio which calculates the amount of medication a person has filled over a given time period. We had originally planned to use the Medication Regimen Complexity Index as a measure of treatment complexity; however, the Part D Medicare data does not contain all the variables necessary to accurately calculate the index. We chose to use the daily dose (Quantity prescribed / Days supply) as a surrogate measure of complexity. Analyses are ongoing but initial results indicate a relationship between treatment burden and the frailty phenotype and but not with the claims based frailty index.

Publications/Presentations/Funding: Dr. Sheehan presented at the JHU OAIC Pepper Scholars Program Research in Progress meeting on May 1, 2019. Abstract submitted and accepted for presentation at the American Academy of Home Care Medicine Annual Meeting October 2019 on the prevalence of frailty in the homebound. Manuscript on Frailty in the Homebound being drafted with a plan to submit to the Journal of the
American Geriatrics Society (JAGS). Career Development Award applications: Planning to submit a Beeson K76 Career Development Award this fall.

5) Pei-Hsun Wu, PhD, Assistant Research Professor, Institute for NanoBioTechnology. “Biophysical cellular characteristics in frail and non-frail older adults.” Mentors: Denis Wirtz, PhD, Professor of Engineering; Jeremy Walston, MD, Professor of Medicine. Dr. Wu received his BS at National Taiwan University and PhD at the University of Florida in Chemical Engineering. He then pursued a post-doctoral fellowship at JHU in Biophysics and Cell Biology—primarily, at the Institute of NanoBioTechnology (INBT) laboratories of RC-2 internal collaborator Denis Wirtz. Dr. Wu is a co-author on 38 papers and a first author on eleven, mostly related to cancer cell motility. He has considerable expertise in high throughput measurements of single cells, and has recently worked to measure cell phenotypes and motility in aging and frailty. In a recent study supported by PESC and RC-2, and published in the Nature Biomedical Engineering, dermal fibroblasts were characterized with high-throughput single cell studies. Cell morphology, mechanics, and migration predicted chronological age with a significantly higher level of certainty than more conventional biochemical properties such as secretomic profiles, DNA repair, and nuclear organization. In particular, biophysical phenotype-features such as nucleus size and roughness of cell shapes, together with cellular morphological heterogeneity were shown to have strong predictive value. Further, multivariate models using these phenotypes were established that provide an accurate prediction of biological aging at the cellular level.

Project description: Aging-related biological changes as observed in tissue and cellular dysfunction are thought to be central to the development of chronic diseases and functional decline. Building on the prior PESC findings described above, Dr. Wu hypothesizes that buccal cells and lymphocytes from frail, older adults express similar phenotypes of altered physical characteristics seen in dermal fibroblasts that differentiate them from those from a robust subset of older adults. Building on prior findings, and on the analytical, molecular and clinical translational, and recruitment infrastructure (RC1-3) available in this OAIC, we pursue the following specific aims: Specific Aim 1) To further develop physical cellular phenotyping assays described above using buccal cells and lymphocytes in order to investigate whether these readily accessible cell types differentiate younger from older adults based on biophysical cellular characteristics. Specific Aim 2) Building on findings in Aim 1, to investigate whether the described cell types can be utilized to differentiate frail from robust older adults. Study design: For Specific Aim 1, 20 volunteers age 25 years or younger and 20 over age 60 years are recruited. For Aim 2, 30 frail and 30 age and gender matched robust volunteers are recruited. RC-3 staff recruit participants from the registry or through newspaper advertising. Research plan: Cells are obtained from participants, processed in RC-2 space, and transferred to the Wu/Wirtz lab in the INBT for further characterization as described below. The samples from both aims are be stained with Hoechst 33342 and HCS CellMask dyes for fluorescent imaging of cell nuclei and cytoplasm, then imaged on a fluorescent microscope equipped with a motorized stage and a multi-slide holder for fast imaging. For lymphocytes, additional cell surface markers for CD4 and CD8 are stained for identification of lymphocytic subpopulation in silico. A novel high-throughput, microscopy-based phenotypic assay quantitatively and reproducibly
characterizes high-content information about individual cells— including cell morphology, cell cycle, molecular content and pattern for more than 1,000 individual cells. Leveraging expertise in the Wu lab, a comprehensive analysis pipeline will be utilized to profile the complex nature of cell morphology, i.e. curvature analysis, roughness analysis, skeleton structure analysis and shape mode clustering analysis. Nuclear morphological features associated with donor aging will be identified; these will be assessed for their ability to differentiate the cells from young from old participants using t-tests, multiple linear regression, and area under receiver operating characteristic curves (AUC). The most relevant cell biophysical phenotypes will be measured in each sample collected in Aim 2, and differences between frail and robust cell phenotypes will be identified using similar (albeit paired) analyses. Research Experiences, Mentorship: Dr. Wu is extensively biologically trained but benefits from further exposure to clinical science and statistical analysis. To further his understanding of clinical issues, RC-3 allows the opportunity for him to shadow personnel conducting frailty-related measurements and to gain exposure to older clinical populations. Dr. Wu also aspires to implement machine-learning techniques in a confirmatory study of his diagnostic methods: RC-1 provides him with a mentored learning experience including readings to learn the mechanics of machine learning and practice in applying predictive machine learning models. He also continues to interact in the rich scientific and measurement milieu of INBT. Contributions of OAIC Resources: Dr. Wu’s project requires full collaboration with all three resource cores. He interacted with RC-3 to develop a clinical research protocol and seek IRB approval and reviews potential subjects from the registry. He benefits from meeting participants for his study in RC-3 space, and is able to take buccal swabs of the participants. He works closely with research staff in RC-3 and RC-2 to ensure protocol continuity regarding sample collection and processing. He also works closely with Drs. Hansen (RC-1) and Arking (RC-2) regarding statistical analysis. Progress updates: We continue to collect and process patient samples from clinics. We now have PBMC and buccal swab cells from more than 20 participants. We are now using the participant derived B-lymphocytes cells from different aging group as our model system to optimize and test our cell motility and cell phenotyping assays. We also identified the molecular probe set that can be used to fluorescently label nucleus and cells particularly for buccal sample swabs for high-throughput microscopy imaging and analysis. Our preliminary study has shown that B-lymphocytes nucleus morphology and cell motility are associated with aging and can be detected from our assay. As for buccal cells, our preliminary analysis reveals that the cell subpopulation distribution are associated with both aging and frailty. Publications/Presentations: A manuscript is in preparation on Dr. Wu’s aging B-lymphocyte study. He presented at the JHU OAIC Pepper Scholars Program Research in Progress meeting on April 3, 2019 on: “Characterization of the motility and morphology of lymphocytes as biomarkers for aging and frail.” He presented a poster on this topic at the 2019 OAIC Annual Meeting on April 25, 2019.

6) Bharath Ambale-Venkatesh, PhD, Assistant Professor, Department of Radiology, Co-Director CAIRS. “Pathways leading to frailty: a study of muscle, cardiovascular tissue, and energy utilizing whole-body magnetic resonance imaging.” Mentor: Joao Lima, MD, Professor in Department of Medicine, Division of Cardiology and Department of
Radiology, Co-Director Center for Advanced Imaging and Research Sciences (CAIRS). Dr. Ambale-Venkatesh received his PhD in Electrical / Computer Engineering from Auburn University. He completed a postdoctoral fellowship in Radiology at JHU in 2013 and was appointed to the faculty of that Department that year. He specializes in quantitative analysis for data-intensive technical platforms, with specific foci of quantifying cardiac deformation from magnetic resonance imaging (MRI) of the heart, and intra-muscular fat properties from magnetic resonance spectroscopy. He has performed mechanistic research in several NIH-funded studies, notably the Multi-ethnic Study of Atherosclerosis (MESA) and the NIH-sponsored Patients with Intermittent Claudication Injected with ALDH Bright Cells (PACE) trial.

**Project description:** The overall research goal is to identify potential pathways leading to frailty—and that might delay frailty onset if addressed—related to muscle, cardiovascular tissue, and energy. Dr. Ambale-Venkatesh hypothesizes that frailty is characterized by (a) decreased lean muscle mass, increased skeletal muscle fat percent, and cardiovascular tissue stiffness and (b) increased fatigability. He assesses (a) via whole-body MRI and (b) via accelerometry and physical activity testing, seeking to identify links among subclinical CVD, inflammation and frailty, imaging phenotypes that differentiate frail from non-frail individuals, and tissue characteristics that are hallmarks of physical frailty and inflammatory and aging pathways. Specific aims: 1) Perform a pilot study with (a) whole body MRI on 25 frail and 25 age- and gender-matched robust volunteers, and assess differences, variability and covariation in body composition and skeletal muscle morphology (Dixon imaging), cardiac fibrosis (T1 mapping), peripheral vascular plaque assessment (fresh-blood imaging) and vascular stiffness (phase-contrast imaging based pulse wave velocity and aortic distensibility), (b) fatigability and activity assessed using accelerometers and physical activity tests, (c) biomarkers of inflammation (C-reactive protein, interleukin-6, and tissue necrosis factor-α) and mitochondrial function (mitochondrial DNA copy number); 2) Utilize feasibility and pilot data generated to design a proposal for a large scale ancillary (to main exam) study in the MESA population. Research plan sketch: As a pilot study, Dr. Ambale-Venkatesh (under the mentorships of Dr. Walston, Dr. Lima, and Dr. Bandeen-Roche) aims to perform a 1-hour whole-body MRI in 25 frail and 25 age- and gender-matched robust volunteers. MRI acquisitions are performed on a dedicated 3-Tesla MRI system situated at the Toshiba-JHU CAIRS using specifically developed contrast-free high-resolution protocols. Measures and protocols for phenotypes relating to muscle mass, fat content, vascular properties, and fatigability are as referenced in the previous paragraph. Phenotypes will be assessed for their ability to differentiate frail from robust using paired t-tests, paired-difference regression adjusting for comorbidities, and area under receiver operating characteristic curves (AUC). Those that best do so, and their feasibility / tolerability, are catalogued, and preliminary data generated for aim 2. For Aim 2, information obtained in Aim 1 is leveraged to design a MESA ancillary study. In the last MESA follow-up exam 3045 participants underwent cardiac MRI exams We expect to recruit 1500-2000 participants for a study on frailty after accounting for drop-off and increased participant age. In this study, the plan will be twofold: To rigorously evaluate pathways suggested by the pilot study, and to use machine-learning techniques to identify, and cross-validate, multiple-marker profiles that characterize frail older adults as compared to their non-frail counterparts. To identify needed sample size and other design
features for this complex analysis, simulation studies are performed using pilot estimates, and sensitivity settings around these, as inputs. **Anticipated Training Activities:** Dr. Ambale-Venkatesh receives training in (a) human subjects research, particularly as it pertains to safety and feasibility of imaging in elderly individuals, (b) introduction to frailty research - to understand the various components of frailty assessments and pathophysiological pathway studies, (c) statistical analysis methods as applied to multi-system dysregulation, mechanistic pathway research, and design of epidemiological studies. We also integrate Dr. Ambale-Venkatesh in the Wearable Information Technologies (WIT) working group—led by Dr. Ciprian Crainiceanu, internal consultant to the Biostatistics Core. Dr. Crainiceanu’s specialty expertise is the analysis of data from advanced research technologies such as Dr. Ambale-Venkatesh proposes, and he is experienced in studies of older adults. **Contributions of OAIC Resources:** Dr. Ambale-Venkatesh receives material support from RC-1 for development and implementation of his study, development of analytical plans, and for planning for future population study. He receives biomarker analyses support for aim one from RC-2. Human subjects training, IRB development, and recruitment and study coordination assistance is provided by RC-3 personnel.

**Progress updates:** We have made progress on several fronts:

1) We have scanned a total of 6 frail and 4 age-matched robust individuals (3 more scans scheduled this coming week) in addition to the 10 normal healthy volunteers (ranging from 20-70 years of age) that we had previously scanned as a means to set up and optimize the imaging protocol.

2) Using these datasets, we have continued to implement improvements in our post-processing and quantifications methods which include –
   a. identification and quantification of muscle fat and volume from over 80 different muscle tissues in the normal human body;
   b. identification and quantification of fat depot volumes based on their location in the human body;
   c. calculation of overall atherosclerosis burden based on vessel imaging from over 15 main vessels in the human body;
   d. calculation of organ fat and fibrosis of the liver and myocardium.
   e. Newly added parameters looking at aortic tortuosity as a marker of aging. We have completed analysis on all the studies acquired so far.

3) Our preliminary findings show that in normal volunteers, the difference in muscle fat percent and atheroma burden is only slightly higher in older individuals (50-65 years) as compared to younger individuals (20-50 years). In the comparison of robust vs frail - The entire scan was performed within 55 minutes for each of the participants and involved no contrast administration. All participants were recruited through the JHU OAIC registry. The atheroma score, aortic length, and aortic tortuosity were higher in frail as compared to robust, indicative of higher atherosclerotic burden and vascular stiffness. Subcutaneous and visceral adipose tissue volumes were lower (large variability observed) in frail as compared to robust. However, myocardial, liver and skeletal muscle T1 times were higher, indicative of a likelihood of greater interstitial diffuse fibrosis. Intramuscular fat content was measured across five different regions – pelvis, forearm, pectus, thigh, and calf; the average intramuscular fat percent was
higher in frail compared to robust individuals, indicative of higher fatty infiltration of muscles in this small sample size.

4) We have also started work on inter- and intra-reader reproducibility with the 10 participants to get an idea of variability to enable sample size assessments and precision of the techniques.

5) We are also in constant contact with the OAIC to recruit more frail and robust non-frail individuals to participate in our imaging study.

6) We have also been collecting measurement of physical activity using accelerometers (Fitbits).

Publications: Two manuscripts are in preparation: (1) a paper detailing the study findings is awaiting study completion; (2) a paper assessing the determinants of frailty and reduced physical capacity in the Multi-Ethnic Study of Atherosclerosis (MESA) is underway (the MESA Study Steering Committee approved the proposal).

Grant Development/Submissions: A K01-award proposal was submitted during the February 2019 submission cycle; this grant will be formatted for resubmission in the next cycle. Dr. Venkatesh attended the 2019 OAIC investigators meeting which provided further insights regarding grant submissions in the field of aging and gerontology.

Abstracts/Presentations:

- Presented at the 2018 International Conference on Frailty and Sarcopenia Research in Miami, FL, March 2018: “Aging-associated changes in skeletal muscle morphology assessed by intramuscular adipose and connective tissue.”
- Presented at the 2019 American College of Cardiology Annual Scientific Sessions meeting: “The Role of Atherosclerosis and Left Ventricular Structure and Function in Frailty Development: Results from the Multi-Ethnic Study of Atherosclerosis (MESA).”
- Dr. Sesso (the first author of the paper, I was the last author) was also invited to present the same in a special member session on “Geriatric Cardiology”.
- Presented at the International Society of Magnetic Resonance in Medicine 2019 to be held in Montreal, on the development of the whole-body MRI protocol including providing the technical background. The first author (Jason Ortman, our chief technologist; Dr. Venkatesh was senior author) was awarded the young investigator award at this conference for his work.
- Abstract accepted to the 2019 Gerontological Society of America meeting.
- Abstract with some of the technical details of the post-processing to be submitted to the International Society of Magnetic Resonance in Medicine 2020.

7) Reyhan Westbrook, PhD, Instructor, Division of Geriatric Medicine & Gerontology.

“Metabolomic differences in energy utilization and Kyn/Trp metabolism pathways in mouse models of frailty: evidence-based implication for translational studies in humans.”

Mentors: Anne Le, MD, Department of Pathology; Jeremy Walston MD, Division of Geriatric Medicine and Gerontology. Dr. Westbrook is an Instructor in the Department of Medicine, Division of Geriatric Medicine & Gerontology. He led the effort to characterize the body composition, metabolic and metabolomic features of the aging Interleukin 10^(-1)Cgn (IL-10 ko) mouse. This mouse model of frailty was previously
developed by RC-2 investigators to study the intersection of aging, chronic inflammation, mitochondrial decline, and frailty. Dr. Westbrook has established a broad network of collaborators at the intramural branch of the NIA in Baltimore and at JHU to facilitate metabolic and metabolomic studies. Building on this network, he identified frailty-related alterations in energy metabolism in the TCA cycle, and in the kynurenine-tryptophan (Kyn/Trp) pathway, a highly conserved pathway critical for de novo NAD+ generation and known for having neurotoxic intermediates linked to age related diseases. He built these preliminary findings into a successful proposal for the highly competitive American Federation for Aging Research (AFAR) Postdoctoral fellowship for Translational Research on Aging. This preliminary metabolomic study enabled him to confirm the Kyn/Trp findings in human subjects and supports the underlying hypothesis for this REC proposal, namely that shifts in the Kyn/Trp ratio and alterations in specific TCA cycle intermediates result in the accumulation of potentially neurotoxic metabolites, lower energy production, and ultimately frailty.

**Project description:** Dr. Westbrook proposes to identify metabolomic differences in energy utilization and Kyn/Trp metabolism pathways in three mouse models of frailty and identify common differences associated with frailty across these groups (Aim 1), and then pursue the best-evidenced findings in humans (Aim 2). The frail mouse models are: (i) the quinolinate phosphoribosyltransferase knock out (QPRT ko) mouse that develops increased levels of potentially toxic Kyn/Trp pathway intermediates (69;70); (ii) the superoxide dismutase 1 knock out (SOD1 ko) mouse, which has recently been identified as a frailty model due to its propensity to develop chronic inflammation (71) (see Richardson support letter); and (iii) the IL-10 ko mouse characterized for frail features in this OAIC (63;64). **Specific aims:** Aim 1: To identify common energy-related metabolites in IL-10 ko, QPRT ko, and the SOD 1 ko mouse using high performance liquid chromatography and mass spectrometry (LC-MS) based targeted and untargeted metabolomic profiling. Based on prior metabolic and mitochondrial differences identified in frailty, focus is on tryptophan degradation, TCA cycle metabolism, mitochondrial function, and energy substrate utilization. Aim 2: To determine if distributions of the most discriminatory metabolomic markers from Aim 1 are replicated in frail and robust older adults. Studies for Aim 1 include 10 12 month old and 10 22 month old mice of each sex per frail mouse model, for a total of 40 mice per frailty model paired with a background, age, and gender matched control group. **Anticipated training experiences:** Dr. Westbrook continues to receive primary mentorship in the areas of chronic inflammation, metabolism, and aging mouse model research from Drs. Walston and De Cabo; clinical translational research from Dr. Walston; and metabolomic measurement training and mentoring from Drs. Le and Moaddel (section 5C.4). Analytical training takes place through ongoing biostatistics course work at JHU School of Public Health, and in close collaboration with RC-1 faculty member Hansen. To deepen his appreciation of clinical issues, RC-3 creates a program in which he shadows personnel in conducting frailty-related measurements and gains exposure to older clinical populations recruited for his studies. **Progress updates:** For Aim 1, we have collected plasma samples from the QPRT ko and IL 10 ko mice at the twelve month old time point, and will collect the plasma for the 20 month time point when the mice mature. We have received the SOD1 ko mice samples from the Richardson lab (although there was some unfortunate and potentially
compromising delay in delivery of the package due to FedEx shipping). When the remainder of the IL 10 ko and QPRT ko mice reach 22 months we will collect samples from them and begin metabolomic profiling. For Aim 2 we have begun sample collection from 20 frail and 20 robust subjects. Additionally, we have explored in vivo phenotypic characteristics in the QPRT ko mouse including body composition, indirect calorimetry, locomotor activity, and glucose tolerance. QPRT ko mice have decreased lean mass, activity, and glucose handling capabilities at 12 months of age indicating that these mice may develop characteristics similar to those seen in frail humans. We have also recently performed *in vivo* and *in vitro* experiments to explore the impact of increased kynurenines on neuromuscular integrity and motor neuron cell metabolism and have found evidence supporting the hypothesis that kynurenines have an etiological role in the development of functional decline in frailty and aging. For the *in vivo* experiments, we have used a force transducer system to explore the muscle contractility of old aged IL 10 ko mice and saw that maximal rate of contraction is decreased and the muscle of these mice is more fatigable. For the *in vitro* studies we exposed MN-1 motor neuronal cells to 3-hydroxy kynurenine and/or quinolinic acid at physiological concentrations for 48 hours and saw that the axonal processes ‘die back’ as indicated by lowered ATP levels when the two toxic metabolites are increased together indicating there is some potentiation of toxicity. Additionally, we have examined presynaptic and postsynaptic areas of neuromuscular junctions from quadriceps muscle from chronically inflamed IL 10 ko mice and controls and saw that IL 10 ko mice have reduced presynaptic coverage relative to postsynaptic coverage. Together this data supports the hypothesis that the increased levels of cytotoxic and neurotoxic levels of tryptophan degradation metabolites may play an active role in neuromuscular integrity and functional decline associated with chronic inflammation and frailty.

**Publications:** We are currently writing up our results for a manuscript to be submitted in the next month.

**Grant Development/Submissions:** We submitted a grant to the American Thoracic Society looking at chronic inflammation related changes to lung structure and function in the IL 10 ko mouse. We also plan to submit a K-08 application in June of 2019.

**Abstracts/Presentations:**
- JHU OAIC Pepper Scholars Program Research in Progress meeting, January 2, 2019: “Chronic Inflammation-related Metabolomic Profile Discovery and Translation into Older Adults.”
  Won first prize for poster presentation at the 2019 JHU Department of Medicine Research Retreat, March 1, 2019.
- Submitted abstracts & presentations to the 2019 Gerontological Society of America meeting, November 2019.

Investigators supported by the JHU OAIC Research Education Core have published a number of articles important to advances in the field of frailty research in the past year. These include:
The JHU OAIC REC helped to establish the careers of many of its REC-supported faculty and to receive the successful support of K01/K23 funding. Former junior faculty awardees Drs. Peter Abadir, George Wang, Frank Lin, Rita Kalyani, Mara McAdams-DeMarco, Yuri Agrawal, Alden Gross, and Charles Brown (Beeson Scholar) all received NIH career development awards in the past several years. During this reporting period, REC awardee Dr. Tae Chung received a K08 award, for his project “Alteration of Kynurenine Pathway in Age-Associated Muscle Weakness” that began in May 2018. Additionally, Drs. McAdams-DeMarco and Agrawal, both former REC supported scholars, received their first R01 awards. We continue to support many other present and former scholars for R award development. We effectively utilize our Pepper Scholars Program, a monthly research in progress series, and the Frailty Working Group as mechanisms to stimulate and develop a ‘farm team’ of investigators committed to developing research in this area, and ensuring that they are able to generate the data necessary to successfully advance their science and careers.

Back to top

II.G. PILOT / EXPLORATORY STUDIES CORE
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The major goal of Pilot and Exploratory Studies Core (PESC) is to cultivate and support innovative pilot and exploratory studies that are needed to develop crucial larger scale and
confirmatory studies to advance the development of effective prevention and/or therapies for frailty, and hence facilitate independence in older adults. The PESC provides funding, access to biostatistical, biological, and clinical research core resources, and mentoring and oversight pilot and exploratory studies. Because of the importance of these studies to the development of new scientific priorities, additional resources are provided to this core to help maximize flexibility, efficiency, and rapid development of areas of focus for this OAIC. The PESC Core, in close collaboration with the OAIC Leadership Council, sets ideas the next stages of research most essential to advancing science on frailty, and then works to identify investigators whose expertise and career goals are applicable to furthering knowledge in these target areas. The leadership and resources of these cores are then focused on the development, conduct and eventual translation of high impact pilot studies. The proposed studies must be novel and either hypothesis-driven or focused on development of methods needed to validly address hypotheses: they ideally address potential mechanisms, etiologies, or screening approaches for frailty, or lay groundwork for evaluating potential therapies to prevent or treat the frailty and its consequences and hence maintain independence. It is expected that PESC-supported studies establish preliminary data that will lead to substantive, long term external funding that can bring the research initiated to completion. Given our roadmap goals of accelerating translation of frailty to increase healthspan in clinical and public health settings, elucidating the biological underpinnings and role of multisystem dysregulation in frailty and resilience, and improving ascertainment of frailty measurement in settings that challenge measurement, special focus was given to these areas for the PESC studies articulated in this application. We intend the same in future years of this cycle. The specific aims of this core are:

1) To solicit, and select support pilot and exploratory studies (PES) that advance the biological understanding of frailty, studies that move OAIC discoveries towards clinical practice or intervention development, or studies that improve frailty measurement. This enables the PESC and other core leaders to identify areas of focus consistent with the goals and frailty-related priorities of the OAIC and that are crucial to accelerating frailty-related research progress.

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 for junior investigators, assistance in helping awardees 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 in other OAIC cores and using relevant resources at Johns Hopkins University.

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 by placing awardees in contact with other investigators whose interests intersect, and by encouraging discussion of frailty and the potential application of the pilot studies. This aim is further encouraged by a new Information Dissemination Core (IDC).

Pilot Studies supported during this reporting period:

Katherine L. Wilson, PhD: “Laminopathy mechanisms as potential components of frailty.” (Funded September 1, 2016-June 30, 2018).

**Project description:** Nuclear structure protects the genome and supports most nuclear activities including tissue-specific signaling and gene expression. Mutations in LMNA, which encodes two abundant “A-type” nuclear intermediate filament proteins named lamin A and lamin C, cause a spectrum of dominant heritable diseases including cardiomyopathy, muscular dystrophy, insulin resistance, diabetes, and progeria (‘accelerated aging’). LMNA missense mutations are also reported in so-called metabolic syndrome, in which patients with three or more factors (abdominal obesity, high fasting plasma glucose, high blood pressure, high serum triglycerides) have higher risk of cardiovascular disease, stroke or type 2 diabetes. A-type lamins are major components of nuclear ‘lamina’ structure, with key roles in tissue-specific signaling and 3-dimensional chromatin organization and gene silencing in specific tissues. Hence, even subtle mutations that perturb their posttranslational regulation or interactions can disrupt gene regulation in specific tissues, through mechanisms that are poorly understood. Certain laminopathy phenotypes and affected tissues appear to overlap frailty in normal aging. We hypothesize that frailty may arise, at least in part, from perturbed expression or pro-inflammatory misregulation of wildtype lamin A. This hypothesis is tested using tissues from the IL-10 knockout ‘frail’ versus control mice, in collaboration with Jeremy Walston. The specific aims are as follows: **Aim 1** evaluates potential nuclear dysmorphology in frail vs control mouse in primary fibroblasts and selected tissues (skeletal muscle, heart, endothelial cells, vascular smooth muscle). **Aim 2** tests potential accumulation of the lamin A precursor (associated with progeria) by Western blot analysis of proteins from primary fibroblasts and selected tissues from frail vs control mice. **Aim 3** tests potential changes in the level of O-GlcNAcylation or functionality of lamin A by immunoprecipitation and western blotting with antibodies specific for O-GlcNAc or key partners.

**Progress Updates:** Dr. Wilson was awarded a second year of pilot funding. She continues to collaborate with Dr. Walston and OAIC RC2. **Updated Aim 1:** Western blot analysis of lamin A O-GlcNAcylation in five organs. Aim 1 is complete for three organs (liver, heart, skeletal muscle). Kidney was discontinued after discussion with Dr. Walston due to inconsistent detection of lamin A in western blots attributed to multiple cell types in kidney and differential modifications that blocked epitope(s) recognized by our lamin A antibodies. We found that O-GlcNAcylation of lamin A was significantly increased in frail hearts. We immunoprecipitated lamin A/C from all five sets of tissues and submitted them for mass spectrometry to test potential frailty-associated changes in the lamin A proteome. Results for heart and brain tissues will be analyzed soon. **Updated Aim 2:** Test human ExAC variants for defects in (A) prelamin A processing, or (B) O-GlcNAcylation. Project 2A is complete: we generated 12 LMNA missense variants for co-expression with human ZMPSTE24 in yeast cells. We found that proteolytic cleavage was significantly reduced in the most-frequent human LMNA variant, p.R644C, but was unaffected by novel variants. Project 2B tested the effects of 12 missense variants on lamin A modification by OGT in vitro. The tail domains of precursor and mature lamin A (wildtype vs
missense) were purified from bacteria as recombinant proteins and then: (a) O-GlcNAc-modified in vitro, (b) western blotted to quantify O-GlcNAcylation, and (c) analyzed by mass spectrometry to identify O-GlcNAc-modified sites. We hypothesized that the extended tail of the precursor might 'fold back' and block access to known O-GlcNAc sites. We also tested triple-substitutions in prelamin A residues with potential homology as OGT recognition sites. These residues are retained in mature lamin A, but occupy the region essential for ZMPSTE24-dependent cleavage of prelamin A, suggesting these two regulatory enzymes might compete. Since prelamin A accumulation is dominantly toxic, we hypothesize cells have a mechanism to ensure that ZMPSTE24-dependent cleavage happens first. Auto-inhibition would be supported if Aim 2B shows that prelamin A is a poor substrate for OGT. Mass spectrometry results are now being analyzed.

**New Aim:** Test the hypothesis that mutations in ‘laminopathy’ genes, previously thought to be exceedingly rare, are relatively common in human populations and might therefore predict genetic risk of heart disease, muscular weakness or metabolic disorders. Our results support this hypothesis for two known ‘laminopathy’ genes, *LMNA* (lamins A/C) and *EMD* (emerin), alleles of which were identified at frequencies of ~0.3% in specific ethnic groups. We also investigated *SIGMAR1*, which encodes the pharmacologically and physiologically important integral membrane protein named Sigma-1 Receptor. Sigma1R binds many hydrophobic neuroactive drugs—therapeutic and addictive. One agonist (cocaine) enhances Sigma1R association with emerin and lamin A/C and causes emerin-dependent silencing of a gene, *MAOB1*, needed for dopamine removal from synapses. However, Sigma1R has many other roles (e.g., at ER-mitochondrial contact sites) and is expressed in all tissues. We identified two *SIGMAR1* missense variants of special interest due to their prevalence in human populations (overall allele frequencies of 0.8% and 18%) and their potential to impact Sigma1R association with nuclear lamina proteins. This is an unexplored area of nuclear envelope biology for which the molecular mechanisms are entirely unknown, and deserves further study. Dr. Wilson is also now participating in a bigger forum on nuclear membrane changes related to aging with REC scholar Dr. Wu and former pilot funded scholar Dr. Wirtz, as well as with the PI Dr. Walston. This broad interdisciplinary working group is planning to develop a program project that will help to further the investigation into this important area of aging biology, and further its translation into clinically relevant diagnostic and treatment modalities.

**Publications and Presentations:**

Submitted manuscript: Arun A, Eddings CR, Wilson KL. Novel missense alleles of SIGMAR1 as tools to understand emerin-dependent gene silencing in response to cocaine.

Dr. Wilson, presented "Misregulation of cardiac lamin A as a potential mechanism of frailty" at the March 2019 meeting of the JHU OAIC Pepper Scholars Program Research in Progress sessions.

Dr. Wilson presented a poster on “Misregulation of Nuclear Lamin A as a Potential Mechanism of Frailty in Heart and Skeletal Muscle of IL10-Knockout Mice” at the 2018 annual meeting of the Pepper Centers.

Damani Piggott, MD: "Frailty and Angiotensin Receptor Autoantibody Activation among Persons Aging with HIV and Injection Drug Use." Collaborating Investigators: Gregory Kirk, MD, PhD, Peter Abadir, MD. (Funded 7/1/2017-6/30/2018).

Project description: With increased access to antiretroviral therapy (ART), HIV-infected patients are living longer worldwide. Yet, survival gains have been accompanied by a rising burden of aging-associated disease and adverse aging phenotypes. Frailty is a critical aging-related phenotype, heightened with HIV infection, and predictive of increased hospitalization and death in HIV-infected and uninfected adults alike. Inflammation is central to frailty and HIV pathophysiology; with heightened inflammation persistent even with effective ART that is strongly associated with aging-related morbidity and mortality. Emerging data support a role for the renin-angiotensin system as a putative key precursor pathway to inflammation. Agonistic autoantibodies to the angiotensin II type 1 receptor (AT1R) have been characterized to increase with age and have recently been found to be strongly associated with both heightened inflammation and important aging outcomes including frailty in the HIV uninfected population. Elevated AT1 receptor autoantibodies may be a critical precursor to the inflammation associated aging phenotype frailty in HIV, and consequently its associated pathway a key putative target for amelioration of this critical aging-related condition. This proposal seeks to assess AT1R autoantibody levels among HIV-infected persons with injection drug use (PWID) and to investigate the relationship of these levels to frailty, inflammation and HIV disease stage in the aging HIV-infected PWID population. The specific aims are: Aim 1: To determine the relationship of HIV clinical parameters to angiotensin II receptor type 1 autoantibodies among aging PWID. Aim 2: To evaluate the association of agonistic angiotensin II receptor type 1 autoantibodies with inflammation among persons with HIV infection and injection drug use. Aim 3: To assess the relationship of agonistic angiotensin II receptor type 1 autoantibodies with frailty among persons with HIV infection and injection drug use.

Progress Updates: AT1R autoantibody testing was completed and initial analyses performed for Aims 1 through 3: the relationship of HIV clinical parameters to AT1R, the relationship of AT1R to the inflammatory markers interleukin-6 and soluble TNF receptor 1, and the relationship of AT1R to the physical frailty phenotype. Initial results presented at the Biology of Healthy Aging working group. Additional analyses are ongoing.


Publications:


Presentations:

- Damani A. Piggott. “Aging with HIV.” University of the West Indies/Barbados Association of Medical Professionals Conference, Bridgetown, Barbados, November 2018

Bonnie Swenor, PhD: "Exploring the Relationship between Visual Impairment and Frailty in Older Adults." Mentor: Dr. Karen Bandeen-Roche. (Funded 7/1/2017-6/30/2018).

**Project description:** There is limited research examining the relationship between vision loss and frailty in older adults. Prior studies indicate that visually impaired older adults have lower grip strength, slower walking speeds, and less physical activity – all physical frailty phenotype components – than their normally sighted counterparts, but only a few studies have used these measures to examine the association with frailty. Additionally, both vision loss and frailty put older adults at an increased risk of disability, comorbidity, and mortality. However, the relationship between vision loss and frailty remains largely unknown. This project aims to explore the visual impairment-frailty relationship by testing two hypotheses: (1) visually impaired older adults are at increased risk of developing frailty, and (2) visual impairment is a stressor to which frail older adults are particularly vulnerable, leading to an increased risk of negative health outcomes in those with both vision loss and frailty. In this exploratory study, we analyzed merged data from the Women’s Health and Aging Study I and II studies, as these cohorts objectively measured visual function, assessed all the components to define the physical frailty phenotype, and measured multiple negative health consequences (including disability, comorbidity, and mortality). The specific aims of the proposed research are: (Aim 1) Examine the longitudinal relationships between visual impairment and frailty to determine if: (a) visually impaired older women have a greater risk of incident frailty than those who are not visually impaired, and (b) if worse visual functioning is associated with an increased risk of incident frailty; and (Aim 2) Explore the interaction between frailty status and visual impairment on
health outcomes in older women to determine if those with both frailty and visual impairment, synergistically: (a) have a greater incidence of mobility disability, (b) are more likely to have a fall during follow-up, (c) have a greater increase in difficulty score for instrumental activities of daily living (IADL) and activities of daily living (ADL) tasks, and (d) have a greater risk of mortality than older women who are visually impaired or frail alone. Results from this exploratory research will be foundational for developing future studies aimed at elucidating the mechanism that underlies the relationship between visual impairment and frailty among older adults.

**Progress updates:**
1. Association between visual impairment and frailty using WHAS III and NHANES data (published in Journals of Gerontology; a second paper provisionally accepted in the American Journal of Ophthalmology). 2. Associations between uncorrected refractive error and frailty using NHANES data (submitted to Age and Aging). 3. Association between near visual acuity and frailty using NHANES is being finalized. 4. Currently examining interaction between visual impairment and frailty on mortality, ADLs, IADLs in WHAS III combined cohort. We are in the process of exploring using a propensity score approach for these analyses.

**Grants:** A follow-up Internal grant proposal using the NHATS/Medicare linked data files to explore the effect of cataract surgery on frailty outcomes has been funded and research is underway.

**Publications:**

**Presentations:**
- B. Swenor, presentation to the JHU Frailty Working Group / Pepper Scholars Program, June 6, 2018.

Janiece Taylor, PhD, RN: “Pilot Behavioral Intervention to Address Pain and Frailty in Older African-American Women.” Co-Investigators: Mary Catherine Beach, PhD; Sarah L. Szanton PhD, ANP, FAAN, and Roland J. Thorpe Jr., PhD. (Funded July 1, 2018).

**Project Description:** Older African American women are crucial to target for intervention not only because of their heightened frailty prevalence, but because they are at higher risk of pain than other racial/ethnic groups and African American men and have exacerbated relationship and outcomes of frailty and pain. They often experience difficulties communicating with health care providers, moreover, that may interfere with treatment of symptoms related to pain and frailty (49-52): Communication intervention has well documented potential to lessen these difficulties and result in better disease management. **Specific aims of this study are: 1) To pilot a tailored**
behavioral activation intervention focused on improving frailty, chronic pain, and depressive symptoms among community dwelling older African American women and collect summary data needed to design a confirmatory intervention trial. Strategies are non-pharmacologic and aim to improve communication, physical activity and education. 2) To determine a) feasibility and acceptability of the intervention b) if strategies and evaluation techniques were appropriate. To this end, we conduct focus groups and/or qualitative interviews with participants before and after completing the intervention to elicit their perceptions. The proposed intervention is modified from interventions known to be effective in treating chronic pain and physical function in older community dwelling older adults (56-59) to address pain and depressive symptoms in older African American women with frailty. In brief, it employs nurse visits to the participants’ homes: participants set goals and work with the nurse using strategies that are evidence-based (e.g. communication strategies, physical activity, education on pain and frailty symptoms and management), and individualized to their needs and environments, to address pain and frailty. Standing strategies are augmented by strategies to address low energy and nutritional deficits — specific additional concerns in frailty. Community-dwelling African American women who reside in their homes and/or assisted living facilities, age 50 and older, are screened for frailty; 40 are to be recruited from community practices and RC-3 registry. The women are randomized to the intervention group or wait list control group. Data is collected for both groups pre-intervention and at the completion of the 4-month intervention, and then final post data collection is completed in both groups after wait list control group completes intervention, approximately 4 months after last data collection. Data collected includes pain (Patient Reported Outcomes Measures Pain Intensity and Interference), the physical frailty phenotype (PFP), and inflammatory cytokines (e.g. IL-1β, IL6, IL8 and TNF-alpha) from salivary samples, and on comorbid diseases, social support, and socioeconomic status.

**Updates:** The first goal of the proposed project, Depression and Pain Perseverance through Empowerment and Recovery (DAPPER) is to understand and receive training in the communication process between African American women ages 50 and older with pain and depressive symptoms. The second goal is to test feasibility of a behavioral activation intervention that utilizes communication and non-pharmacological tailored strategies to target the pain depression cycle among community dwelling older African American women. 1) To conduct an analysis of communication between older African American women with depression and pain and their primary care providers. 2) To explore older African American women’s beliefs of the pain depression cycle and perceptions of strategies to address it. 3) To evaluate feasibility of a tailored behavioral activation intervention focused on improving the pain depression cycle through communication and non-pharmacological strategies among older African American women. The second leg of this study (DAPPER for Frailty) targets African American women with pain, depressive symptoms and frailty. A cycle can occur in women that further exacerbates frailty.

**Progress to date:** The study protocol has been submitted to the IRB and is in revision. DAPPER is being adapted from Dr. Laura Gitlin's Get Busy Get Better/ Beat the Blues. Training from Beat the Blues has been completed. Four focus groups have been completed to assist with the adaptation for the intervention. Two nurses have been hired to work as interventionists and one research assistant to assist with recruitment and data collection. Dr. Taylor attended the 2019 Annual Pepper Centers Meeting, and she presented at the July 2019 JHU OAIC Pepper Scholar Program Research in Progress meeting.

**Publications/Presentations:** Manuscripts: Dr. Taylor currently has three manuscripts in review and one in preparation, focused on topics closely related to this project. She will complete
manuscripts from this supported study once preliminary data is completed. Abstracts/Presentations: She presented on the development of this intervention, “Development of DAPPER (Depression and Pain Perseverance through Empowerment)” at the 2019 American Association of Geriatric Psychiatry conference in Atlanta, GA on 3/2/2019. She has two abstracts accepted for the 2019 Annual Meeting of the Gerontological Society of America:


Funding:


Anne Le, MD: “Exploratory Study of Metabolomics Energy Signatures in Frailty.” (Funded July 1, 2018).

Project description: Building on a small PES awarded in 2016 to Drs. Le and Westbrook that utilized a frail mouse model previously characterized in RC-2 (64;66-68), altered metabolomics signatures were identified that suggest that TCA cycle processes are a component of dysregulated energy utilization in frailty. Given this background, we hypothesize that specific patterns of altered energy metabolites linked to glucose metabolism through mitochondrial bioenergetics, biosynthesis, and redox homeostasis pathways can help to distinguish frail from non-frail older adults, and that the circulating concentrations of metabolites related to glucose metabolism are measurably different between frail and non-frail older adults. Utilizing research resources from all three resource cores, and Dr. Le’s established metabolomics measurement infrastructure (Metabolomics facility) and expertise in energy metabolism measurement (69;70), we propose the following specific aims: 1) To utilize metabolomics measurement to reconstruct the relevant metabolic pathways of glucose metabolism related to bioenergetics, biosynthesis, and redox homeostasis, and determine differences between frail and non-frail participants, and 2) To identify the most promising biomarkers for a frailty-related energetic signature and plan for a future targeted validation study of diagnostic utility and biological discovery. Subjects and Methods: 20 frail and 20 non-frail age- and gender-matched adults over age 65 without diabetes will be recruited from the RC-3 maintained subject registry, and receive a 10 grams uniformly labeled 13C intravenous glucose tolerance test (71-74) with plasma samples taken at baseline, and 1 and 3 hours post glucose infusion in the Johns Hopkins ICTR clinical studies unit. 13C has been proven safe to humans (72;74-76); the use of fully labeled 13C6-glucose facilitates the identification precisely of which metabolites from glucose (rather than lipids or amino acids) are metabolized differently between frail and non-frail older adults. Samples will be processed according to standard protocol by RC2 personnel, stored at -80 C, and later transferred to Dr. Le’s lab for further processing and metabolic measurement as per standard protocols utilized in her laboratory (see facilities and resources). Frozen plasma will be subjected to metabolite extraction and data acquisition protocols as previously described. Using stable isotope-resolved metabolomics (SIRM) with the use of liquid chromatography-mass spectrometry (LC-MS), three
main categories of glucose metabolism will be assessed: bioenergetics, biosynthesis and redox homeostasis. Metabolic pathways will be reconstructed in the three main categories listed above to better understand the differences between frail and non-frail, according to methods developed in prior studies. These analyses will be guided by RC1 faculty—particularly, metabolomics expert Kasper Hansen. At the end of this study, we will have a better understanding of TCA cycle and glucose metabolism differences between frail and non-frail older adults, and utilize this information to better identify specific etiologies of decline and potential to components of glucose metabolism to target for intervention development.

**Progress updates:**
- Obtained IRB approval and approval for amendments.
- Finalized the 13C6-glucose injection with Clinical Research Pharmacist: Lisa Ruppel and Jim Monolakis.
- ICTR application under review
- Ordered 200g of 13C6-glucose from Sigma which is expected to ship mid-late September directly to Lisa Ruppel.
- Confirmed the final protocol (10 grams of labeled 13C6 glucose in 100 mL (100g/L) sterile normal saline solution via bolus IV infusion over 10 minutes; 2mL whole blood collection right before and every 30 minutes after glucose administration for the 3 hours) with experts: Elisabet Borsheim, and Mathiew Cotter.
- Identified 10 potentially eligible frail subjects and 10 matched controls
- Dr. Abadir received Meditech Physician’s Order Form.
- Started recruitment.
- Dr. Le will present to the Pepper Scholars Program on October 2, 2019.

**Naresh Punjabi, MD, PhD: “Association between Sleep Deficiency and Frailty: What harms most?” Co-Investigator: Jiawei Bai, PhD. (Funded July 1, 2018).**

**Project description:** Epidemiologic surveys show that at least 50% of adults over 65 years in age have sleep-related complaints. Sleep disturbance has been associated with neurohormonal, circadian, and homeostatic alterations: As many such changes have been evidenced by this OAIC and others to also underlie frailty, it reasonable to expect interconnections between sleep quality and frailty. We hypothesize that disordered sleep heightens risk for frailty onset and believe that intervention to improve sleep can prevent or buffer frailty. Prior studies indicate that poor sleep quality is associated with frailty. These predominantly have assessed sleep, however, by either self-report or relatively crude summaries (e.g. time in sleep states) of actigraphy or polysomnography data. This project uses data from the community-based Sleep Heart Health Study (SHHS) to extract power spectral “curves” summarizing the history of the overnight sleep EEG, by *functional principal components analysis* (fPCA), and identify sleep EEG signatures highly associated with frailty prevalence, incidence and transitions. The physiologic changes underlying frailty may also impact subsequent sleep quality: Therefore we also study frailty as a predictor of change in sleep. Our specific aims are to: 1) Derive functional PCs to characterize primary sleep EEG features in SHHS; 2) Identify sleep EEG dimensions that are associated with frailty and frailty-related inflammatory biomarkers cross-sectionally and can accurately predict frailty onset and remission; 3) Estimate cross-associations between baseline sleep and subsequent frail status, and between baseline frailty status and subsequent sleep disturbance.

**Approach:** Dr. Punjabi leads this effort. He co-led the SHHS and was supported by this OAIC in its first cycle. He works closely with PESC, RC1 and RC2 leadership to develop, refine, and
implement his proposed analysis. He oversees analyses to derive functional PCs from the SHHS EEG data, and fPCA scores characterizing individuals’ sleep profiles, using methodology to study EEG delta-wave power in the SHHS. Dr. Jiawei Bai, a PhD biostatistician who pursued his dissertation in the lab that produced this work, conducts these analyses as a co-investigator. This project aims to determine associations of prevalent frailty to: (a) conventional metrics of sleep quality such as sleep stage percentages, arousal index, and frequency of sleep stage transitions, and (b) measures of sleep quality derived from the quantitative power spectral analysis of the EEG subjected to fPCA, independent of potentially confounding covariates (e.g., age, race, BMI, smoking status, and prevalent medical comorbidity), using logistic (frail vs. not) and multinomial logistic (non-frail, pre-frail, frail) regression. Model building proceeds from single sleep parameters, to include potential confounders, to finally include multiple sleep parameters at once. We then examine, longitudinally, associations of sleep quality measures with incident frailty and with frailty transitions (over three rounds in which frailty was measured), using discrete time proportional hazards models (incidence; and longitudinal multinomial logistic regression (transitions). Finally, we explore that prior frailty may influence subsequent sleep deficiency. Cross-sectional multiple linear regression is used with frailty as independent variable and our panel of sleep measures as dependent variables (separately, and as a multivariate outcome). Then, again using multiple linear regression, we examine whether baseline frailty status is independently associated with a longitudinal deterioration in sleep parameters, controlling for potential confounders. Change in our sleep variables are derived from the two assessments of sleep available in the SHHS data (visit 1: 1994-96; visit 2: 2000-02). To fully distinguish longitudinal prediction from cross-sectional association: as a final step, baseline sleep parameters also are included in the sleep change models. Sample size for analyses using baseline sleep assessment includes all CHS participants that were part of the SHHS: n=1248. Prevalence and year 0-3 incidence of frailty both were estimated at 7% in the seminal 2001 CHS paper.

Significance and Innovation: Our project seeks to provide new information about the cross-sectional and longitudinal associations between measures of sleep and frailty. These findings delineate the interplay between sleep and the development of frailty, and possibly inform novel prevention and intervention strategies. This study informs better understanding of sleep quality as a potential determinant, or marker, of frailty in older adults, and provide clues as to dysregulation in specific biological systems that impact sleep and frailty.

Progress updates: To address the above specific aims, we have completed several key milestones. First, the data from the Sleep Heart Health Study (SHHS) has been accessed along with the data on frailty measures in the Cardiovascular Health Study (CHS). A one-to-one link was used to connect the data from the SHHS to the CHS measures on frailty. EEG data during sleep from the SHHS data set were used to derive the power spectrum during sleep using the discrete Fast Fourier Transform. These power spectrum data were then subjected to functional principal components analysis. The derived principal components for specific bandwidths of the EEG were then related to the assessment of frailty, which was categorized into three levels. Preliminary analyses reveal that in the most frail the EEG spectrum during sleep has greater power in the theta band (8.0-12.0 Hz). In addition to the approach of using EEG power spectral analysis, we have also extracted epoch-by-epoch sleep stage data on each SHHS participant and subjected the data to multi-state survival analysis. These preliminary analyses show that with frailty there is an increase in sleep stage instability with an increased risk for sleep stage transition between NREM sleep and wake. Ongoing analyses need to include potential
confounding covariates to tease out the independent association between frailty and sleep stage instability.

Small Pilot Award: Qian-Li, PhD: “Focus Group Discussion of Developing a Sensor-Based Mobile Application for In-Home Frailty Assessment.” Co-PI: Sara Gravelyn from the Johns Hopkins Applied Physics Laboratory (APL); Co-investigators: Marcela Blinka, Brian Buta, Matthew McNabney, Nancy Schoenborn.

**Project description:** This project is a key component of a larger project to enable real-time frailty assessment in free-living environment by developing and testing a mobile application using sensor-based technology. By combining assessment, communication, health alert and data collection into one unit, this mobile app will greatly facilitate frailty assessment for research and clinical monitoring purposes. This is a two-phase study. Phase 1 (12 months) includes (a) literature review, (b) focus-group discussion, (c) protocol development, (d) App and database design and development, and (e) system testing. Phase 2 (12 months) will implement a field test of the mobile app among older adults following the conclusion of Phase 1 to further evaluate feasibility and usage. The proposed small pilot supports Phase 1 items (b) and (c). Separate funding has been secured to support Phase 1 items (a), (d), and (e) through the APL’s Independent Research and Development (IRAD) program. Specifically, in collaboration with the ALP team, this small pilot aims to:

1. Design and conduct focus group sessions with app users. Goal: Collect feedback from study subjects and medical professionals to assist app design. Deliverables: Complete a written report summarizing focus group findings and recommendations.
2. Develop study and IRB protocols. Deliverables: Complete protocol development and submission.

**Progress Updates:** The IRB protocol was approved to investigate user perspectives for use of sensor-based technologies and mobile applications. To date, we have held eight focus groups with community-dwelling older adults (n=14), their informal caregivers (n=12), and medical professionals (n=14). We are planning to interview two caregivers that were unable to participate in the focus group due to unforeseen circumstances. All completed focus group meetings have been transcribed, and we use qualitative inductive analysis to organize thematic content. An abstract was submitted and accepted for the 2019 GSA meeting as part of a symposium on qualitative methods and technology use among older adults.

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Overall, investigators supported by the JHU OAIC Pilot and Exploratory Studies Core have published a number of articles important to advancements in the field of frailty research. These include the following publications that have directly resulted from their OAIC funded projects:


We have helped to establish the careers of Pilot supported faculty through the **successful support of K01/K23 funding** to Drs. Kalyani, McAdams-Demarco, Agrawal and Mathur in the past several years. Most recently, Bonnie Swenor (Pilot) received a **K-award** from NIA. Drs. Abadir, Agrawal, Leng, McAdams-DeMarco, Piggott, and Walston – all previous Pilot or small pilot supported investigators – have received **R01 awards** in the recent years with OAIC support. 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 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.

*Back to top*

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**II. OAIC Supplement Award to Dr. Peter Abadir (P30AG021334-16S1)**

*Funded July 2018.*

The investigators have signed and executed a Material Transfer Agreement between RUSH university and Johns Hopkins University to obtain the samples. Dr. Abadir and collaborators have identified and obtained samples from 670 unique patients in the RUSH Alzheimer’s disease study that meet the study’s inclusion and exclusion criteria. These patients are divided into three categories of cognitive function: normal cognition, mild cognitive impairment and Alzheimer’s dementia. They complete yearly follow-up visits with physical and cognitive assessments and the collection of blood samples. Dr. Abadir and team have worked with Dr. Alden Gross, a biostatistics collaborator, to identify appropriate cross-sectional and longitudinal time points to obtain blood samples and study in these patients.

They have received 959 samples (670 unique individuals at initial visit, with an additional 289 samples from a second visit) from RUSH. They measured the circulating cell-free DNA fragments (genomic and different mitochondrial fragments) in the samples. They have also started preparing statistical analysis tables and formulas for the study population in order to expedite the analysis process once bench experiments are complete. Initial data analysis is showing significant association for these fragments with survival and physical frailty outcomes.

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

**Subsequent funding by supported investigators:**

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

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

**Arking, Dan (Pilot)**
- Dan Arking. Functional Dissection of the Sudden Cardiac Death Associated BAZ2B Locus, NHLBI, 12/15/2011-12/14/2016
  Dan Arking. R01, NHLBI, Mitochondrial DNA Copy Number and Genetic Variation in Coronary Heart Disease, 2016-2020

**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. NIA K24: Patient-Centered Care for Older Adults with Multiple Chronic Conditions: Research and Mentoring Program. Funded Sep 2017.
Brown, Charles (RCDC)
- Charles Brown. Awarded an Johns Hopkins inHealth grant to evaluate mobility after cardiac surgery, 2016-2017
- Charles Brown. Awarded a Johns Hopkins Clinician Scientist Award, 2016

Carlson, Michelle (RCDC)

Chaves, Paulo (RCDC/CTU)
- Paulo Chaves. Cardiovascular Health Study: Events. NHLBI (Subcontract to Dr. Bruce Psaty, University of Washington). Funded 12/16/06 – 5/31/14.

Chung, Tae (REC)

Gross, Alden (RCDC)

Hasan, Rani (REC)

Kalyani, Rita (RCDC/Pilot)

Leng, Sean (RCDC/Pilot)

- Sean X Leng. R01, NIAID: Influence Vaccine Failure in Adults Over Age 75: Role of Chronic CMV Infection. Funded January 2014.
- Joshua Hare, Sean Leng, Anthony Oliva. NIA R42: A Randomized, Blinded, Placebo-Controlled Clinical Trial to Evaluate Longeveron Mesenchymal Stem Cell (LMSC) Therapy for Treating the Metabolomic Syndrome. Funded Sep 2017.
- Sean Leng, Sabra Klein. NIA U54: Sex Differences in the Impact of Frailty on Vaccine-Induced Immune Responses in Community-Dwelling Older Adults. Funded Sep 2018.

Lin, Frank R. (RCDC)


Makary, Martin (RCDC)


Mathur, Aarti (Pilot)


McAdams-Demarco, Mara (RCDC/Pilot)

Mielke, Michelle (Pilot)
- Michelle Mielke. NIA R01: Sphingolipids and Inflammation in the Development and Progression of Alzheimer’s. Funded Sep 2015.

Neptune, Enid (Pilot)

Piggott, Damani (External Project)

Polotsky, Vsevolod (RCDC / Small Pilot)
- Vsevolod. Polotsky. NHLBI R01: Sleep Apnea and Dysregulation of Lipid Metabolism (R01 renewal). NIH. Funded 4/1/10 – 3/30/15.

Punjabi, Naresh (External Project)

Roy, Cindy (RCDC)

Schoenborn, Nancy
• Nancy Schoenborn. NIA K76 (Beeson Award): Improving Cancer Screening in Older Adults with Limited Life Expectancy. 2018-2022.

Schrack, Jennifer (Supplement awardee)

Segev, Dorry (External Project)
• Dorry Segev. JHU Clinician Scientist Award. JHU. 2008.

Semba, Richard (Pilot)

Seplaki, Christopher (RCDC)

Swenor, Bonnie (Pilot)

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.

Walston, Jeremy (Pilot/Genetics)
• Jeremy Walston. NIA Long Life Family Study (LLFS). Subcontract to University of Pittsburgh U01AG023744. Funded 5/1/05 – 5/31/10
• Jeremy Walston. R01, NIA, Enhancing Mobility in Older Adults by Treating Chronic Inflammation: Pilot Phase, 2016-2018
• Jeremy Walston. R21, NIA, Recombinant Human Lactoferrin for the Treatment of Chronic Inflammation in Older Adults, 2016-2018

Wang, George (RCDC)

Weiss, Robert (Pilot)

Westbrook, Reyhan (Diversity Supplement)
• Reyhan Westbrook. 2016 AFAR Translational Research Post-Doctoral Fellowship Award.

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.

Yuh, David (RCDC)

Back to top
2019


26) Xue QL, Tian J, Walston JD, Chaves PHM, Newman AB, Bandeen-Roche K. Discrepancy in Frailty Identification: Move beyond Predictive Validity. J Gerontol A


Older but Previously Not Reported


Back to top
### Section V. External Advisory Board Members Names, Institutions and Years of Service

<table>
<thead>
<tr>
<th>EAB Member</th>
<th>Affiliation</th>
<th>Years of Service</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joan E. Bailey-Wilson,  Ph.D.</td>
<td>Head, Statistical Genetics Section; Co-Branch Chief, Inherited Disease Research Branch; National Human Genome Research Institute; National Institutes of Health</td>
<td>11</td>
</tr>
<tr>
<td>Gerald Beck, Ph.D.</td>
<td>Section Head, Clinical Trials; Design and Analysis, Department of Quantitative Health Sciences, Cleveland Clinic Foundation</td>
<td>6</td>
</tr>
<tr>
<td>Howard Bergman, M.D.</td>
<td>Chair, Department of Family Medicine, Professor of Family Medicine, Medicine and Oncology, Dr. Joseph Kaufmann Professor of Geriatric Medicine, McGill University</td>
<td>6</td>
</tr>
<tr>
<td>Harvey J. Cohen, M.D.</td>
<td>Division Chief of Geriatrics, Director of the Center for the Study of Aging and Human Development, Duke University Medical Center</td>
<td>16</td>
</tr>
<tr>
<td>Luigi Ferrucci, M.D.,  Ph.D.</td>
<td>NIA Scientific Director, Senior Investigator and Chief, Longitudinal Studies Section</td>
<td>16</td>
</tr>
</tbody>
</table>
1. **Recognition and Awards:** Prize or honors, NOT grant awards, should be a listing of all major scientific awards received by your center’s personnel in 2018-2019

Dr. Bandeen-Roche was recognized with two awards in the field of Statistics during the last year—she was re-elected to the Executive Director board for the International Biometric Society, and she was the Distinguished Women in Statistics keynote lecturer (Vanderbilt University, April, 2019): work from this OAIC was featured prominently in this lecture.

Pilot investigator, Dr. Janiece Taylor received the Harold Amos Medical Faculty award for her work on “Communication Behaviors and Development of a Pain and Depression Intervention among Older African American Women” in July 2018.

REC investigator, Dr. Reyhan Westbrook, won the W. Leigh Thompson Excellence in Research Award, Basic Research Faculty, for his work on “Altered Metabolome in Frailty Link Chronic Inflammation to Functional Decline” at the 2019 Johns Hopkins Department of Medicine Research Retreat.

Dr. Walston served as an editor for the Oxford Textbook of Geriatric Medicine, 3rd Edition; this text won the coveted notation: *Highly Commended* in the Medicine category at the British Medical Association Book Awards in 2019.

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.

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

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