UNIVERSITY OF PITTSBURGH
Claude D. Pepper Older Americans Independence Center

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CENTER DESCRIPTION

Gait and balance disorders in older persons are common, disabling and complex. In order to prevent and treat these disorders, a concentrated, multidisciplinary effort to understand causes and consequences, and to develop innovative treatments, is needed. The team of investigators at Pittsburgh offers complementary expertise, outstanding research productivity, and ongoing studies to address this need through a Claude D. Pepper Older Americans Independence Center. This program includes investigators from medicine, bioengineering, rehabilitation, epidemiology/public health, biostatistics, psychology, pharmacology, biology, imaging, informatics, and health services research. Our long range goals are: to address the critical need to improve mobility, balance, and falls risk, both through improved understanding of their causes and through development of preventive and therapeutic interventions.

Our specific aims for the current cycle are to:

1. Promote multidisciplinary research to elucidate the causes, consequences and management of age-related changes in mobility and balance.
2. Further extend our work into two high potential areas: a) translational investigations to examine interactions between multiple systems at the level of molecules, signaling systems, cells and their organelles, and tissues, as they impact mobility and balance in living organisms, and b) impact on individual older adults of novel interventions to enhance mobility and balance.
3. Train young investigators from multiple disciplines to become national leaders in age-related mobility and balance problems in a vibrant, collaborative environment and build a translational sciences workforce through collaborative basic and clinical sciences team mentoring.
4. Serve as a champion and invaluable resource for investigators, research programs, institutions, OAICs and the public in the area of mobility and balance in older adults.

The Program has 7 Cores:

- Leadership/Administration Core
- Pilot Exploratory Studies Core
- Research Career Development Core
- Clinical Populations Outcomes Core
- Integrative Systems Core
- Data Management, Analysis and Informatics Core
- Biology of Mobility and Aging Core

Training support is provided directly to Pepper Scholars and also to trainees in related programs.

Research strategies to achieve OAIC goals:

1. Use Resource Cores to share expertise among projects and investigators.
2. Use pilot and developmental funds to extend existing studies and develop new studies.
3. Promote and reward collaborative multidisciplinary teams of investigators with complementary expertise by prioritizing them for funds and support.
4. Encourage new partnerships with highly productive investigators and programs by offering to partner with our expertise and resources.
5. Reward development of new methods and techniques.
6. Facilitate the use of a common set of core measures of mobility, balance and falls in human studies so results can be merged or compared.
7. Leverage resources by collaborating with other Centers at Pitt, other OAICs, and Centers around the US.
8. Sponsor seminar series to promote general awareness of expertise and resources, review progress in ongoing projects and facilitate new collaborations.
9. Support the new OAIC career development program with salary-funded Pepper Scholars in addition to resource support for Novice, Transition to Independence, and Visiting Scholars, with a focus on multidisciplinary teamwork, thematic knowledge, and specific skills.
10. Promote national discussion through programs at national meetings and other dissemination methods.
11. Provide administrative infrastructure, intellectual leadership, and oversight.

CORES

Leadership and Administrative Core (LAC)

Leader 1: Susan Greenspan, MD greenspn@pitt.edu
Leader 2: Anne Newman, MD MPH newmana@edc.pitt.edu

The Leadership Administrative Core (LAC) is responsible for the organizational, communication and regulatory functions of the Pittsburgh Pepper OAIC. The LAC receives valuable input and direction from 5 advisory groups including 1) the External Advisory Board (EAB) (national experts), 2) the Institutional Advisory Board (multidisciplinary group of experts on aging from the University and the UPMC health system), 3) the Community Advisory Board (representatives from local health care agencies, IRB, media, and local leaders), 4) the REC Advisory and the PESC Advisory groups (both internal and external experts). These boards provide advice and insight to the Executive Committee composed of leaders and co-leaders of OAIC cores.

The specific aims of the LAC are to:

1. Foster communication and multidisciplinary collaboration among OAIC investigators, cores and projects.
2. Promote awareness and involvement in our work by relevant investigators and research programs in and outside the University of Pittsburgh.
3. Represent the OAIC to the University through the Institutional and Community Advisory Boards.
4. Represent the OAIC to other OAICs and the larger academic, NIH, clinical and lay communities.
5. Through the EAB, maintain independent oversight of OAIC processes, resources and progress.
6. Establish new independent REC and PESC oversight committees as requested by NIA.
7. Provide research oversight and safety monitoring for all OAIC human studies and help establish a Data and Safety Monitoring Board as necessary.
8. Sponsor a Research Seminar series, an Annual Retreat, Workgroups, a publication/communication committee, formal grant reviews, and new partnership initiatives.
9. Increase basic and translational research partnerships.
10. Provide administrative support and manage financial records for the OAIC as a whole.
11. Collaborate outside the Institution on OAIC related themes.

Research Education Component (REC)

Leader 1: Neil Resnick, MD resnickn@pitt.edu
Leader 2: Jen Brach, PhD, PT jbrach@pitt.edu

The goal of the Research Education Component Core (REC) of the Pittsburgh OAIC is to provide a comprehensive, individualized career development program to prepare future investigators for mobility, balance, and aging research. Our ultimate goal is to develop highly qualified investigators to conduct high quality and high impact research in the field of mobility, balance, and aging and who will become leaders in this field nationally and internationally. We continue to improve our programs with input from our trainees, mentors, Executive Committee, and External Advisory Committee.

Our specific aims of the REC are to:

1. Promote careers in mobility, balance, and aging research among junior investigators at 3 levels:

- Novices: research mentees at the pre-and post-doctoral level
  Goal: submission and funding of their first research award (F series, Foundation, etc.)
- Pepper Scholars: junior faculty with initial expertise who receive OAIC salary support
  Goal: submission and funding of a career or R-type award
- Transition to Independence Investigators: junior faculty with independent career awards
  Goal: submission and funding of an R-type award

2. Foster Trainee success with a comprehensive training program that:

- Prepares trainees to engage in translational teams across basic, clinical, and health services science
- Educates in aspects of basic and clinical research via the Clinical and Translational Science Institute (CTSI) and our complimentary sessions that focus on aging, mobility, and balance
- Creates and monitors individualized teams of experienced mentors
- Offers multidisciplinary research experiences involving OAIC Cores and investigators, as well as retreats, and a peer-led seminar series that includes sessions for manuscript and grant review, career development, and leadership with CTSI
- Sponsors a 2-semester intensive grant writing course resulting in a polished grant proposal
- Uses stipends to protect Scholar time for research and training and provides targeted financial support for initial pilot projects and other opportunities
- Provides individualized advice, feedback, career guidance, and support to trainees and mentors.

3. Manage all aspects of the training program, including promotion, recruitment, selection, scheduling, monitoring, and evaluation of trainees and the program. The REC helps every Scholar complete a Customized Career Development Plan (CCDP) that is used to plan activities and monitor progress.

4. Collaborate with other cores and units within and outside the institution for OAIC related themes.

5. Enrich Scholar training through participation in the OAIC Coordinating Center’s Visiting Scholar Program.

Pilot and Exploratory Studies Core (PESC)

Leader 1: Daniel E. Forman, MD formand@pitt.edu
Leader 2: Aditi Gurkar, PhD agurkar1@pitt.edu

The goal of the Pilot/Exploratory Studies Core (PESC) of the Pittsburgh OAIC is to promote and fund innovative multidisciplinary pilot research in the topic areas of mobility, balance and aging and their interfaces. The expected outcomes for funded pilot studies are their successful completion in a timely manner, that the findings be presented at a national scientific meeting and submitted for publication in the peer review literature. Moreover, the findings from these pilot studies are expected to support the development of mentored career development awards and independent federally funded grant applications.

The specific aims of the PESC are to:

1. Promote innovative multidisciplinary research on mobility, balance and aging.
2. Act as a bridge to foster interactions between the basic geroscience, clinical and community-based research communities.
3. Encourage supplements to leverage ongoing basic, translational, clinical and community-based studies.
4. Promote innovative techniques and methods for research on mobility, balance and aging.
5. Partner with other University of Pittsburgh groups (e.g. Clinical and Translational Science Institute and Aging Institute) that also offer pilot study awards, in addition to the Division of Geriatrics, to increase overall funding for individual pilot projects.
6. Promote, evaluate, and select for funding Pilot projects ($40,000 per year), small REC Pilots (up to $10,000), and Developmental projects ($70,000 over two years).
7. Conduct post-award processes (e.g., monitor adherence to ethics, safety, privacy, tracking of subsequent productivity and other related matters) for pilot and developmental projects.

Biology of Mobility and Aging Core (BMAC)

Leader 1: Toren Finkel, MD, PhD FINKELT@pitt.edu
Leader 2: Stacey Rizzo, PhD RIZZOS@pitt.edu

Problems with mobility and balance with aging are due to changes in multiple systems that develop due to age-related alterations in basic biological processes. Insights accumulated over the last two decades in the basic biology of aging are poised to be rapidly translated into new interventions to promote a longer healthspan, which depends in large part on maintaining mobility and balance. However, significant barriers must be overcome before the approaches and technologies of basic science can be efficiently translated into clinical practice. While the OAIC partnered over the last 10 years with individual basic scientists

who study aging, there was not yet a critical mass of activity to justify a distinct Pepper Core. With a major new investment creating an Aging Institute dedicated to using biological sciences to advance aging basic discovery and translation, the OAIC now proposes a Biology of Mobility and Aging Core (BMAC). The goal of this new core is to promote both basic-to-human and human-to-basic translation. The BMAC will provide an engine of discovery and innovation to guide and enhance our clinical and translational efforts. Specific emphasis includes using basic science approaches to uncover novel biomarkers and compounds that might aid in the treatment of age-related alterations in mobility and balance. Moreover, the BMAC will assist in the development and characterization of innovative pre-clinical animal models that can be used to mechanistically explore the fundamental basis of age-related changes in mobility, gait and balance.

The specific aims of the BMAC are to:

1. Provide expertise in biomarker development as potential intermediate markers of the aging processes in human studies of aging. This will include the development of novel model systems to accelerate biomarker development.
2. Provide access and guidance to the design and analysis of high throughput screening (HTS) systems and 'omic' technologies for identifying potential molecular targets relevant for mobility, balance and aging.
3. Provide access to and interpretation of various preclinical model systems. This includes cellular (e.g. muscle stem cells), rodent, zebrafish, and drosophila organisms and establish a preclinical phenotyping platform that faithfully reflects age-related mobility impairment in humans to enable translational studies.
4. Support the research training mission of the Pepper Center by enhancing the capacity for Team Science and promoting basic-translational-clinical interactions.

Clinical and Population Outcomes Core (CPOC)

Leader 1: Steven Albert, PhD, MSPH smalbert@pitt.edu
Leader 2: Andrea Rosso, PhD, MPH alr143@pitt.edu

The Clinical and Population Outcomes Core (CPOC) is dedicated to promoting multidisciplinary research on mobility, balance, and aging through 1) access to human subjects for studies and advice on screening, recruitment, and consent, 2) access to existing data sets from Pitt aging studies for secondary analysis, and 3) resources and space for clinical assessment of mobility and balance. To meet these aims, we provide registries of interested community-dwelling older participants and a Long-Term Care (LTC) Registry of residents from participating institutions, a searchable database on existing Pitt Aging data sets from longitudinal and clinical trial studies, a library of tests and scales with instructions, scoring and advice on implementation, and information on use of our Senior Mobility in Aging Research and Training (SMART) Center space for clinical studies. We successfully launched the Platinum LTC Registry (seniors residing in assisted living and skilled nursing facilities who have consented to research contact). To date, over 40 facilities signed agreements to participate as recruitment sites, and over 400 residents consented to be contacted. Our Community Registry, with over 2500 older

participants, was a key recruitment source for 60 research studies. The CPOC SMART Center provided clinical research space for multiple pilot and external projects. Our Community Advisory Board (CAB) continued to foster community collaboration, stakeholder involvement and feedback on OAIC activities.

Our specific aims of the CPOC are to:

1. Engage older adults from the community and LTC settings in research by expanding large registries of consented and well-characterized older adults accessible to investigators.
2. Provide training to investigators on appropriate contact, screening, and consent strategies for research with older populations.
3. Recruit and maintain a diverse community advisory board of older adults and leaders in aging services to review proposed research and advise the OAIC.
4. Provide access to ongoing and completed Pitt cohort studies, specimens, clinical trials, and existing databases.
5. Provide expertise in clinical assessment methodology by providing a standardized set of forms and instructions to promote a common dataset of core assessments for mobility, balance, and falls.
6. Use noninvasive, portable technology to examine mobility, balance, and physical activity in clinics and in the field through our novel mobile laboratory.
7. Provide access to space and equipment for OAIC-related studies through our SMART Center.
8. Promote dissemination of our findings within and outside the Pittsburgh community.

Data Management, Analysis and Informatics Core (DMAIC)

Leader 1:	Subashan Perera, PhD	pereras@dom.pitt.edu
Leader 2:	Charity Moore Patterson, PhD, MSPH	CGP22@pitt.edu

The overarching goal of the Data Management, Analysis and Informatics Core (DMAIC) is to ensure data and analytic integrity, transparency and reproducibility by continuing to serve as a central source of methodological expertise and a service provider to the researchers of the Pittsburgh Older Americans Independence Center (OAIC). Methodological expertise is most beneficial when provided by a team such as DMAIC familiar with the balance and mobility in aging theme, specialized measures and methods of the OAIC.

Our specific aims of the DMAIC are to:

1. Meet data management requirements of Pittsburgh OAIC PESC, REC, developmental and external projects.
2. Support quantitative and facilitate qualitative analysis needs of Pittsburgh OAIC projects.

3. Provide informatics expertise to Pittsburgh OAIC projects.
4. Support the training mission of the Pittsburgh OAIC with Pepper Scholars and other trainees.
5. Develop new techniques, as wells as novel application of existing methods to address OAIC-related unmet needs and methodological challenges.
6. Collaborate with other cores and units within and outside the institution on OAIC theme-related activities.

Integrative Systems Core (ISC)

Leader 1:	Caterina Rosano, MD, MPH	car2350@pitt.edu
Leader 2:	Mark Redfern, PhD	mredfern@pitt.edu

Problems of mobility and balance in the aged require multidisciplinary study because they are complex and multifactorial. Advances require integrating expertise and technical resources from biomechanics, physiology, neural control of movement and biology. Thus, the goal of the Integrative Systems Core (ISC) is to provide integrative, multidisciplinary knowledge, skills and techniques that foster an understanding of the biomechanical, structural, functional, physiological and biological influences on age-related mobility and balance.

Our specific aims of the ISC are to:

1. Provide cutting-edge resources and expertise to concurrently study both whole-body as well as multiple systems and physiologic mechanisms affecting mobility and balance during aging, both during study planning as well as during implementation and analysis.
2. Develop and test novel techniques and approaches to address gaps and needs for multi-system evaluation of mobility and balance.
3. Support the training mission of the OAIC by educating and supporting the work of Pepper trainees through workgroups, seminars, “field trips” and active involvement in trainee research projects.
4. Collaborate with other cores and Centers in and outside Pitt on OAIC-related activities.
5. Continuously monitor, evaluate and communicate about Core activities both within and among Core laboratory leaders, as well as with other Pepper Cores, Pepper leadership and NIA.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications
Aimee N. Pickering, MD, MS Assistant Professor / University of Pittsburgh School of Medicine implementation strategy for deprescribing inappropriate medications in older adults with diabetes	2023-2025 / 7 (total) 4 (1st/Sr)
Brendan McNeish, MD Assistant Professor / University of Pittsburgh, Physical Medicine and Rehabilitation aging related structural brain assessment using neuro-imaging	2023-2025 / 10 (total) 5 (1st/Sr)
Nami Safai Haeri, MD Assistant Professor / University of Pittsburgh School of Medicine A Novel Method to Examine Muscle Health in Frail Elderly	2022-2024 / 4 (total) 1 (1st/Sr)
Megan M. Marron, PhD Assistant Professor / University of Pittsburgh School of Public Health Using –omics to better understand the underlying biology of decline in muscle, liver, and physical functioning with aging	2022-2024 / 24 (total) 10 (1st/Sr)
Marcelo Rocha, MD PhD Assistant Professor / University of Pittsburgh School of Medicine Dimethyl-Arginine and Large Vessel Occlusion Stroke in Older Adults	2022-2024 / 28 (total) 7 (1st/Sr)

Past Scholars

Mary Kotlarczyk, PhD, University of Pittsburgh School of Medicine (2017-2020)
Emily Rocha PhD, University of Pittsburgh School of Medicine (2019-2021)
Lena Makaroun MD, MS, University of Pittsburgh/VA Pittsburgh Center for Health (2019-2021)
Samaneh Farsijani, PhD, MSc, University of Pittsburgh School of Medicine (2020-2021)

PILOT/EXPLORATORY PROJECTS (16 Pilot Projects Listed)

1. **Project Title:** **Medical Marijuana and Chronic Pain in Older Adults**
   Leader: **Neelesh NadKarni, MD, PhD, FRCPC; Debra Weiner, MD, FACP**

   Background: Challenges with conventional treatments for chronic pain have led to many older adults considering medical marijuana (MM) as a treatment option. Older chronic pain sufferers may be vulnerable to the effects of MM from age-related changes in pharmacokinetic and pharmacodynamic function, and from changes in the brain that control mobility and cognition. Whether potential benefits from alleviation of chronic pain with MM are counteracted by its adverse effects on mobility in older adults on MM is unknown.

   Specific Aims: We will compare adults 60 and over who are pain free (PF) to those with chronic pain not on MM (CP), and those with chronic pain on MM (CP-MM) on mobility, cognition, gait-cognitive dual-task measures, mood, anxiety, physical function and quality of life measures. The main hypotheses are that: 1) the CP-MM group will perform the worst on measures of gait speed, physical function, executive function and dual- task gait and cognitive performance (i.e., the interface between gait and cognitive function), and 2) the CP group will perform the worst on other measures of mood, anxiety and quality of life.

   Summary of Methods: This pilot will recruit 20 participants in each group, PF, CP and CP-MM. The CP-MM group will be recruited from Solevo Wellness, a Pittsburgh MM dispensary using targeted mailings. We will recruit the PF and CP participants from the Pepper Registry and pain clinics. We will assess mobility performance with the short physical performance battery (SPPB) and the Timed-up-Go. We will assess gait parameters with and without dual tasking on the Gait mat II. We will administer standardized tests of executive function, memory, language and visuospatial function. Accuracy and reaction time will be captured on working memory, response inhibition and motor sequencing tasks performed while standing and while walking (dual-tasking). Mood will be assessed with the PHQ-9 anxiety with the GAD-7, physical function with the late life function and disability index, and quality of life with the EuroQoL. We will also capture details of MM type, blood levels of active MM compounds, dosage, administration, and severity of pain on the BPI.

   Future use of data: This data will be used to support a prospective cohort study (R01 application) in response to the FOA from NIA/NIDA (PA-17-196) that will address the relative impact of MM as compared with chronic pain itself on mobility, cognitive function, and other geriatric-specific outcomes in older MM users.

   Core Collaborations: CPOC, DMAIC

2. **Project Title:** **Investigating Biological Aspects of Aging through Molecular Epidemiology: Linking Genes to Physical Function in Older Adults**

Leader: **Adam J. Santanasto, PhD MPH; Joseph M. Zmuda, PhD; Zsolt Urban, PhD; Ryan L. Minster, PhD, MSIS**

Specific Aims: To examine the association of RNA expression profiles of the transforming growth factor-beta (TGF-ß) pathway with baseline and 7-10-year change in physical function among older adults.

Brief Background: The TGF-ß signaling pathway is a strong biological candidate pathway that may negatively impact skeletal muscle and physical function with aging. TGF-ß induces pathogenic tissue fibrosis, negatively regulates skeletal muscle differentiation and repair, and contributes to mitochondrial dysfunction. TGF-ß is also implicated in inducing pathogenic fibrosis, muscle wasting and primary myopathies, all of which can impact physical function.

Methods: We propose to assay the expression of genes involved in the TGF-ß signaling pathway, using a custom-designed TGF-ß pathway expression array. We will examine the relationship between mRNA expression and the Short Physical Performance Battery, a comprehensive lower-extremity performance battery that includes gait-speed, balance and timed chair-rise tests.

Future use of Data: The data generated from the Pepper Pilot will be used in future NIH grant proposals to examine tissue-specific (skeletal muscle) expression of genes involved in TGF-ß signaling and their effect on age-related changes to physical function. Further, this dataset will be integrated with data from PI Dr. Santanasto's K01, which investigates the association of genome-wide genetic markers, circulating TGF-ß, and other biomarkers, to better understanding of biological mechanisms underlying age-related declines in physical function.

Core Collaborations: DMAIC, CPOC

3. Project Title: **Cellular senescence, SASP and Metabolites as biomarkers for early aging**

Leader: **Aditi U. Gurkar, PhD; Susan Greenspan, MD; Neil M. Resnick, MD; Subashan Perera, PhD**

Specific Aims: The aims of the current proposal are to (1) Design assays for measuring senescence and SASP in whole blood/ serum from the Solve-IT study. (2) Perform global metabolomics on serum to quantitate 600+ metabolites and estimate effects of sex, and physical aging using statistical and bioinformatics methods (3) Perform statistical analysis to identify differentiating biomarkers of interest and their co-occurrence patterns. These biomarkers will be selected from the measured metabolites, senescence and SASP markers.

Background: Aging comprises of a diverse array of phenotypes influenced by multiple factors including genetics, epigenetics, environmental influences, diet, exercise and the microbiome. Cellular senescence and senescence associated secretory phenotype (SASP) are known to correlate with age and ablation of such cells drastically improves health span, albeit in model organisms. This hints that cellular senescence can possibly drive aging-related degenerative change. Metabolites are

circulating small molecules that are supremely suited to account for biological aging influenced by a number of these factors. This study will simultaneously identify the metabolite profile, and the immune, as well as senescence markers that collectively play an important role in biological aging.

Methods: Cellular senescence and SASP markers will be measured by ELISA and Luminex based assays from whole-blood and serum samples from the Solve-IT study. Metabolomics profiling will be performed from randomly selected 60 participants. Using statistical and bioinformatic approaches we will analyze (a) which metabolites and combination of metabolites best discriminate the cohorts of interest; (b) which senescence markers and combination of markers best discriminate the cohorts of interest; (c) which combinations of metabolites and senescence markers best discriminate the cohorts of interest. By constructing co-occurrence networks we will identify groups of features/phenotypes that co-occur, potentially suggesting the entities that are be involved in a
biological model for aging.

Future Uses: The assays can be applied to other patient cohorts to determine if the unique signature obtained here significantly correlates with falls, mobility, frailty, critical care patient outcome, risk of aging-related degenerative diseases, healthy aging, etc. In particular, this pilot study will provide critical data for a grant application to fund a larger study to understand the relationship of these measures to outcomes of aging. Our approach has the potential to identify metabolic pathways that may drive cellular senescence, immune system and aging, thus providing a mechanistic insight into healthy aging. This will provide an opportunity to develop novel strategies to modulate aging and simultaneously delay the onset of multiple chronic degenerative diseases.

Core Collaborations: CPOC, DMAIC, BMAC

4. Project Title: Association of Social Determinants of Health with Functional Status, Mortality, and Healthcare Use in Older Adults Who Survive Critical Illness

Leader: Leslie Scheunemann, MD, MPH, Eric Roberts, PhD

Rationale: More than half of older critical illness survivors develop new or worsened dysmobility and functional impairments. While suspected to influence critical illness outcomes, there is little evidence about how social determinants of health (e.g., income, education, and environmental characteristics such as housing quality, transportation access, and social support) affect functional outcomes and healthcare utilization in this important and currently highly relevant older population.

Approach: This study uses data from the well-established and locally available Health and Retirement Study, which is linked to Medicare claims. It will identify older critical illness survivors, characterize important baseline individual social determinants of health (SDH), and link to their subsequent survival, pre-and post-illness function (including self-reported walking, stair climbing, falls, and activity level), and use of healthcare resources. Aim 1 will examine the relationship between SDH measured the

year prior to critical illness and post-critical illness health outcomes. Aim 2 will assess the relationship between SDH and healthcare utilization.

Relevance to the Pepper theme: Loss of physical function and mobility among older adults after critical illness is highly relevant to the OAIC theme.

Core Collaboration: CPOC (population studies), DMAIC (analysis), includes REC members

5. Project Title: **Mechanisms underlying changes in inflammation in mobility limited older adults**

Leader: **Rachel Gottschalk, PhD, Maria Chikina PhD; Co-Is: Drs. Daniel Forman, Anne Newman, Toren Finkel**

This pilot examines gene regulatory networks in macrophages from older adults with impaired mobility and elevated IL-6 levels in the Reducing Inflammation for Geriatric Healthspan Therapy (RIGHT) Study, a clinical trial which will test the effects of an IL-inhibitor.

Significance: Persistent inflammation is associated with aging and the onset and progression of mobility disability and fatigability. Monocytes and macrophages play a pathological role in age-related inflammation and disease,1,2 and there is substantial person-to-person variation in their gene expression and regulation of inflammatory responses, resulting from age, sex, and genetic factors.This variation is key to understanding mechanisms behind healthy vs non-healthy aging, and how therapies may impact inflammation in mobility limited older adults.

Hypotheses: We expect that 1) inter-person variation in macrophage basal gene expression will predict stimulus-induced macrophage inflammatory responses and 2) these measures will be associated with elevated serum IL-6 and impaired mobility across people.

Approach: (Aim 1) We will utilize pre-treatment blood collected from the RIGHT trial to assess inter-person variation in inflammatory regulatory networks across 50 elderly subjects with high serum IL-6 (>2.5 pg/ml), an inflammatory cytokine associated poor clinical outcomes,7 and 20 controls (IL-6 <2.5pg/ml). Readouts will include (i) basal serum protein quantification, (ii) macrophage responses to microbial stimuli (inflammatory cytokine output across a range of stimulus concentrations), and (iii) basal and stimulus-induced macrophage gene expression (RNAseq). Using these data and novel computational methods (graphical lasso and causal inference algorithms), we will infer regulatory relationships that govern inflammatory control and identify regulators associated with macrophage responsiveness, elevated serum IL-6, and impaired mobility. (Aim 2) We will analyze a subset of 10 subjects treated with IL-6 inhibitor for 6 months to determine whether serum proteins, macrophage responses, or gene regulatory networks are impacted by therapy.

Innovation: Our preliminary data suggest that person-to-person variation in

inflammatory regulation is most apparent in response to weak stimuli. By using computational and quantitative experimental approaches to elucidate network connectivity and its impact across a broad range of stimulus strengths, this proposal provides a framework for both conceptual and methodological innovation in understanding mechanisms underlying age-associated inflammation.

Core Collaborations/grants: ISC (Dr. Forman's Lab), CPOC (Community Registry), DMAIC (statistical analysis).

Future Proposals: This study will inform a planned R01 grant proposal to further our basic understanding of how gene regulatory networks change with age and impact of IL-6 inhibition.

6. Project Title: **A lysosomal-based, small molecule approach to prevent and reverse mobility decline**

Leader: **Emily Rocha, PhD, Stacey Rizzo, PhD; Co-Is: Drs. Toren Finkel and Daniel Forman**

This Pilot leverages the Pitt/UPMC program in drug development to target critical age-related pathways affecting mobility. A small molecule that activates TFEB will be tested, which can lead to Phase I human testing in 18-24 months.

Significance: Aging is the main risk factor for neurodegenerative disease and loss of mobility. Aging lysosomes undergo impaired volume and pH regulation, accumulation of indigestible materials, and reduced functional degradative enzymes. Age-related autophagy-lysosomal dysfunction may be responsible for the observed incidental ?-synuclein pathology that occurs at a frequency of 8-22.5% and up to 34.8% in centenarians; thus may play a role in age-related mobility loss. TFEB is a master regulator of autophagy and lysosomal biogenesis and regulates the expression of Coordinated Lysosomal Expression and Regulation (CLEAR)-network proteins, which include many autophagy proteins. Our data indicates that exposure to a novel, small-molecule (BC18630) prolongs nuclear TFEB activation, and can prevent age-related lysosomal dysfunction, ?-synuclein accumulation, neurodegeneration and loss of mobility.

Hypothesis: Improving lysosomal function using TFEB activator can prevent or delay age-related neuropathology and mobility decline.

Approach: This pre-clinical study evaluates BC 18630 (a small-molecule that selectively prolongs TFEB activation) to 1) prevent the progression of age-related neuropathologies and mobility decline in healthy aging male and female C57BL/6J mice; and 2) attenuate or reverse neuropathology and mobility decline in advanced aged mice. Following baseline assessments of mobility-related phenotypes, BC18630 will be administered via chow to middle aged (6-8 month) and aged (16-18 month) male and female mice for several months and compared to young ~3-4 month vehicle treated sex- and age-matched controls. Based on data in C57BL/6J mice, the dose will be equivalent to 5 mg/kg/day. A battery of behavior tests before and after treatment will assess aging-related gait and motor coordination in addition to hearing, vision, body mass,and frailty index score. Discrete brain regions will be microdissected from the left hemisphere and used for lysosomal enzymatic activity assays. Right hemisphere

regions will be used for histological assessment of autophagy-lysosomal function.

Innovation: This proposal outlines a unique therapeutic strategy to improve lysosomal function and prevent age-related mobility loss that may prevent accumulation of aggregated proteins and delay the onset of mobility disability.

Core Collaborations/grants: DMAIC (statistical analysis), BMAC (Greenamyre), ISC (Forman), REC (Scholar)

Future: This pilot will provide data for a NIA R21 or R01 grant.

7. Project Title: **The relationship between dietary protein intake, gut microbiome and mobility in older adults**

Leader: **Samaneh Farsijani, PhD; Co-Is: Drs. Anne Newman and Subashan Perera**

This study builds on the NIA-funded Study of Skeletal Muscle and Mobility in Older Adults (SOMMA), with an add-on study focused on the role of nutrition and the microbiome in influencing muscle health and mobility.

Significance: The imbalanced composition of gut microbiome(dysbiosis), in aging is associated with gait speed and frailty. Protein intake is an important anabolic stimulus for muscle protein synthesis and may influence the gut microbiome, which can in turn affect muscle function and walking ability. Despite emerging evidence supporting the roles of amount, source and pattern of protein intake in promoting muscle health and mobility, associations with age-related dysbiosis are unclear. This study will determine the relationships between dietary proteins and gut microbiome and help inform development of age-specific dietary recommendations to maintain muscle health and mobility by promoting a healthy gut microbiome.

Hypothesis: Higher amount and even within-day distribution of protein intake, as well as higher quantity of plant-based proteins are independently associated with increased diversity of the gut microbiome.

Approach: Two 24-h food recalls, a food frequency questionnaire, and fecal samples (for 16S rRNA analysis) will be collected from 200 SOMMA participants (age ? 70-y) residing in Pittsburgh at baseline, for 80% power with ?=0.05 for detection of R2=0.065 between protein intake measures and microbial diversity.

Innovation: This is the first study to address associations between dietary protein parameters and gut microbiome composition in older adults and will provide preliminary data to test associations with gait speed and mobility in SOMMA.

Core Collaborations/grants: ISC (Forman and SOMMA), DMAIC (analysis), REC (Scholar).

Future: Findings will support Dr. Farsijani’s K01 application.

8. Project Title: **Increasing gait automaticity in older adults by exploiting locomotor adaptation**

Leader: **Gelsy Torres-Oviedo, PhD; Co-Is: Andrea Weinstein, PhD, Andrea Rosso, MPH, PhD , Douglas Weber, PhD**

This study integrates the insights of 4 dynamic investigators with complementary expertise in a pilot study of mechanisms and clinical effects of locomotor adaptability training.

Significance: Age-related deficits in locomotor adaptation are common and linked to disability and falls. Older adults are slower at adjusting movements when interacting with a new environment and have difficulty switching motor patterns when transitioning across walking conditions. While locomotor training using split-belt walking (SBW), in which legs move at different speeds, has known efficacy, neither the underlying mechanisms nor clinical relevance of improvements are known.

Hypothesis: SBW-related improvements in locomotor adaptation will translate to increased community mobility activity in older populations by reducing the high cognitive load associated with walking.

Approach: Locomotor adaptation will is studied with a novel SBW protocol. Initial walking automaticity is assessed with wireless functional near-infrared spectroscopy (fNIRS) during dual-task treadmill walking. Mobility performance is evaluated with instrumented walking surfaces and portable sensors recording body motion and muscle activity. Community mobility is assessed with integrated analysis of accelerometry and global positioning system (GPS)-based measures of walking in-home and in the community. We focus on two measures of adaptability: 1) rate at which individuals adapt to SBW and 2) capacity to switch between context-specific walking patterns. We also determine if improving locomotor adaptability changes the neural and cognitive characteristics post-training. We plan for 30 participants for sufficient power.

Innovation. SBW targets locomotor adaptability. We characterize the relation between locomotor adaptability and GPS-based measures of community mobility, and functional gait assessment predicting fall risk.

Future: This will provide needed data for an NIH grant.

Core Collaborations: ISC (Torres-Oviedo and Redfern labs), DMAIC (analysis).

9. Project Title: **Small Pilot for Pepper Scholar: Function, falls and injuries as risk factors and outcomes of elder abuse in the VA**

Leader: **Drs. Lena Makaroun , Debra Weiner, Scott Beach, Ann Marie Rosland**

Significance/Approach: Little is known about physical function and falls as risk factors and outcomes for elder abuse (EA).37-43 With VA administrative data, 2 national cohorts of veterans over age 60 will be compared including one that received services for abuse/neglect and one that did not. Logistic regression and mixed modeling will be used to assess candidate variables including demographics, social status,

physical/cognitive function, falls and injuries. EA will be the independent variable for outcome analyses, and similar statistical methods will be used to explore the association with outcomes, including change in physical/cognitive function, fall and injuries, health service utilization and placement.

Innovation: Exam of a vulnerable population.

Core Collaboration: ISC, PESC, and DMAIC.

10. Project Title: **Continuous Real-world Sensing of Physical Function in Older Cancer Survivors**

Leader: **Carissa A. Low, PhD, Grace B. Campbell, PhD, MSW, BSN**

Specific aims: (1) To examine the association between continuous wearable and smartphone sensor data and commonly used clinical measures of physical function in cancer survivors aged 65 and older (2) To develop a preliminary machine learning model using mobile sensor data to differentiate older cancer survivors with impaired physical function, poor performance status, frailty, or history of falls from more physically robust participants. Brief background: Impaired physical function is common among older cancer survivors and is an important predictor of clinical outcomes. Mobile sensors that passively capture continuous objective data provide new opportunities for quantifying physical function in real-world settings during routine daily activities. Summary of methods: We will recruit cancer survivors aged 65 or older (n = 40) to complete a battery of validated performance-based and patient-reported physical function measures. Participants will also collect four weeks of continuous data from wearable devices and personal smartphones that will include physical activity, geographic mobility, sleep, and heart rate. We will evaluate associations between performance-based and patient-reported measures and daily behavioral features and will develop a preliminary model to classify participants into impaired physical function vs. high physical function groups. Future use of data: Data from this project will inform a NIH application assessing physical function longitudinally in a larger sample of older cancer survivors and evaluating the ability of mobile sensing to detect functional decline. This Pepper pilot project will provide important feasibility and effect size data and will help to identify which functional assessments and mobile sensors to use in future work. Core Collaborations: CPOC, DMAIC

11. Project Title: **The muscle-brain axis: Exploring the effect of skeletal muscle activity on the connectome and transcriptome of aging animals**

Leader: **Amrita Sahu, PhD**

Aims: The overarching goal of these studies is to test the central hypothesis that skeletal muscle contractile activity promotes a more youthful cognitive connectome (Aim 1) and spatially defined transcriptomic profile (Aim 2), ultimately contributing to enhanced cognitive capacity. Background: Physical activity attenuates age-related declines in neurostructual, neurofunctional, and neuromolecular profile of the brain. However, the mechanisms that underlie this beneficial effect of physical activity on aging brains are poorly understood. Individual approaches of cognitive testing, brain architecture analyses, and neuromolecular probing are often used to understand the aging process within the brain. In order to gain a comprehensive mechanistic understanding of aging brain and its response to physical activity, an integrated approach combining behavioral testing (cognition), connectomics

(neuroimaging), and spatial –omics (neuromolecular) analyses are warranted. Methods: All animal experiments will be performed with prior approval from the Institutional Animal Care and Use Committee of the University of Pittsburgh. Young and aged male C57BL/6 mice will be used in the studies (Young: 3-6 months, Aged: 21-24 months,). For inducing physical activity in animals, mice will be subjected to a neuromuscular electrical stimulation (NMES) protocol to elicit repetitive skeletal muscle contractions. Mice will receive five stimulation sessions over a period of two weeks, with each session consisting of 20 repetitions. Two days after the last session, animals will be subjected to behavioral testing (spatial memory, short-term memory, and motor activity) or neuroimaging (connectomics). After neuroimaging, the brains will be probed for spatial transcriptomic. Future use of data: We anticipate that using this integrated approach we will be able to identify mechanisms that underlie the benefit of skeletal muscle contractile activity on brain health. Findings from this study will lay the groundwork for developing targeted rehabilitation protocols designed to enhance cognitive functioning in an older population. Preliminary results from this study will also be leveraged to apply for larger funding to determine the effect of NMES on cognitive connectome based on sex. Core Collaborations: BMAC, ISC

12. Project Title: **Interplay between Balance, Gait and Sleep in Older Adults with Glaucoma**

Leader: **Rakié Cham, PhD, Shachi Tyagi, MD, MS**

Background. Falls are a major health risk for adults with glaucoma. While glaucoma-related changes in vision certainly contribute to falls, other well established risk factors for falls occurring at a greater rate in glaucoma than in older adults need to be considered. Poor sleep, an example of such risk factors, is well documented in glaucoma. In older adults without glaucoma, poor sleep negatively impacts falls risk and postural control, and causes other adverse health outcomes. Yet, we do not know if poor sleep function and disruption in sleep architecture associated with glaucoma, i.e. beyond aging-related symptoms, contribute to the increased prevalence of falls and reduced postural control in this clinical population. The overarching goal of the proposed project is to understand the interplay between sleep and postural control in glaucoma. Specific Aims. Three specific aims will be pursued. In Aim 1, participants with undergo detailed sleep assessments. In Aim 2, the relationship between sleep metrics and postural control function during standing and walking will be examined. In Aim 3, dual-task paradigms will also be used during balance/gait testing to examine attentional influences on postural control. Methods. Adults with advanced glaucoma and controls will participate in the proposed experiments. Our well-established balance/gait assessment protocols including dual-task experiments will be conducted to assess postural control function in various sensory challenging conditions. These protocols probe the ability to integrate multisensory information relevant for mobility through dynamic computerized posturography and gait analyses. In addition, rigorous assessments of sleep will be performed, including validated self-reported measures of sleep function and in-home EEG-based sleep testing. This state-of-the-art sleep assessment technology will provide detailed information related to sleep architecture by recording objective measures of various sleep stages duration. Appropriately constructed mixed linear statistical models will be used to test the hypotheses associated within each aim. The potential mediating effects of sleep on postural control impairments in glaucoma will be of primary interest. Future use of data. The findings can be used to identify specific sleep domains as potentially modifiable risk factors to improve balance/gait and reduce falls-related adverse health outcomes in glaucoma. The data collected

in the proposed project may be used to plan larger-scale intervention studies. Core Collaborations: DMAIC, ISC

13. Project Title: **Continuous Real-world Sensing of Physical Function in Older Cancer Survivors**

Leader: **Low, C; Campbell G**

Specific aims: (1) To examine the association between continuous wearable and smartphone sensor data and commonly used clinical measures of physical function in cancer survivors aged 65 and older (2) To develop a preliminary machine learning model using mobile sensor data to differentiate older cancer survivors with impaired physical function, poor performance status, frailty, or history of falls from more physically robust participants. Brief background: Impaired physical function is common among older cancer survivors and is an important predictor of clinical outcomes. Mobile sensors that passively capture continuous objective data provide new opportunities for quantifying physical function in real-world settings during routine daily activities. Summary of methods: We will recruit cancer survivors aged 65 or older (n = 40) to complete a battery of validated performance-based and patient-reported physical function measures. Participants will also collect four weeks of continuous data from wearable devices and personal smartphones that will include physical activity, geographic mobility, sleep, and heart rate. We will evaluate associations between performance-based and patient-reported measures and daily behavioral features and will develop a preliminary model to classify participants into impaired physical function vs. high physical function groups. Future use of data: Data from this project will inform a NIH application assessing physical function longitudinally in a larger sample of older cancer survivors and evaluating the ability of mobile sensing to detect functional decline. This Pepper pilot project will provide important feasibility and effect size data and will help to identify which functional assessments and mobile sensors to use in future work.

14. Project Title: **A Novel Method to Examine Muscle Health in Community-Dwelling Elderly**

Leader: **Safai Haeri, N**

Background: The assessment of muscle mass in elderly is challenging. This information is important as we try to characterize sarcopenia (loss of muscle) in older adults to improve muscle mass, strength, and function. Although we can measure lean mass by dual X-ray absorptiometry (DXA), DXA is a controversial measure for characterizing sarcopenia and is not well-correlated with strength or function. The deuterated creatine (D3-creatine) dilution method is a novel assessment of total body muscle mass based on the knowledge that nearly all creatine is stored in skeletal muscle, creatine is converted to creatinine at a steady rate, and creatinine is excreted in urine. Muscle mass measured by this method is associated with gait speed, physical function, serious falls and mobility limitation in ambulatory community-dwelling older men. However, the usefulness of this measure has not been established in frail older adults, who have the largest loss of muscle mass and would have the greatest benefits from assessments. Longitudinal measures are also sparse. Rate of muscle loss or gain would be a key determinant for future therapeutic modalities to preserve muscle function and strength in older adults. Aims: Aim 1: Obtain preliminary data on the impact of two different classes of osteoporosis medications on longitudinal changes in skeletal muscle function, muscle strength and lean mass in older adults. Hypothesis 1.1: Older adults on

denosumab (a RANKL inhibitor) will exhibit greater preservation or improvement in lean mass (D3-creatine; primary outcome, whole-body DXA, muscle ultrasound), grip strength and muscle function (Short Physical Performance Battery) over 12 months compared to zoledronic acid (an osteoclast inhibitor). Aim 2: Explore associations between measures of bone mass and skeletal muscle health. Hypothesis 2.1: Measures of bone and muscle health will be associated both cross-sectionally and longitudinally. From previous studies in patients with osteoporosis who took denosumab or zoledronic acid and had their lean mass measured by whole-body DXA, patients who took denosumab, unlike zoledronic acid, preserved their lean mass. Nevertheless, this effect has not been assessed by the D3-creatine method which is a much better surrogate for lean mass compared with the whole-body DXA. This pilot study addresses an important knowledge gap regarding muscle mass assessment in older adults and fits well with the mission of the Pepper OAIC that focuses on mobility, gait, falls and function. Most importantly, for many other Pepper investigators interested in muscle health, this study will lay the groundwork to establish a feasible and novel muscle mass measurement for participants under treatment for osteoporosis. The data will be directly used for sample size and power computations involving Pepper studies that propose to use the measure. Therefore, other investigators who want to use this measurement technique will have it established within the Pepper center. Methods: We propose to perform the D3-creatine test in 20-30 community-dwelling older adults. We have measures of DXA lean mass, grip strength, gait speed and function. In an IRB-approved study, we will perform the D3-creatine method in addition to our standard assessments. Participants will ingest 30 mg D3-creatine, and a fasting spot urine sample will be collected 3-6 days later. D3-creatinine, unlabeled creatinine, and creatine will be measured by liquid chromatography and tandem mass spectroscopy. Total body skeletal muscle mass will be calculated using established algorithms based on the ratio of labeled to unlabeled urinary creatinine. We will repeat the D3-creatine, DXA and function measures, 6 months later to estimate rate of muscle loss. Future Use of Data: These data will demonstrate that this assessment is feasible in older adults, and can be added to 2 other R01-funded ongoing osteoporosis trials. This study will provide preliminary data for a career development award for Dr. Nami Safai Haeri, MD. Finally, if successful, this method will establish a new assessment for many other Pepper investigators with a focus on muscle health.

15. Project Title: **Interplay between Balance, Gait and Sleep in Older Adults with Glaucoma**

Leader: **Cham, R; Tyagi, S**

Background. Falls are a major health risk for adults with glaucoma. While glaucoma-related changes in vision certainly contribute to falls, other well established risk factors for falls occurring at a greater rate in glaucoma than in older adults need to be considered. Poor sleep, an example of such risk factors, is well documented in glaucoma. In older adults without glaucoma, poor sleep negatively impacts falls risk and postural control, and causes other adverse health outcomes. Yet, we do not know if poor sleep function and disruption in sleep architecture associated with glaucoma, i.e. beyond aging-related symptoms, contribute to the increased prevalence of falls and reduced postural control in this clinical population. The overarching goal of the proposed project is to understand the interplay between sleep and postural control in glaucoma. Specific Aims. Three specific aims will be pursued. In Aim 1, participants with undergo detailed sleep assessments. In Aim 2, the relationship between sleep metrics and postural control function during standing and walking will be examined. In Aim 3,

dual-task paradigms will also be used during balance/gait testing to examine attentional influences on postural control. Methods. Adults with advanced glaucoma and controls will participate in the proposed experiments. Our well established balance/gait assessment protocols including dual-task experiments will be conducted to assess postural control function in various sensory challenging conditions. These protocols probe the ability to integrate multisensory information relevant for mobility through dynamic computerized posturography and gait analyses. In addition, rigorous assessments of sleep will be performed, including validated self-reported measures of sleep function and in-home EEG-based sleep testing. This state-of-the-art sleep assessment technology will provide detailed information related to sleep architecture by recording objective measures of various sleep stages duration. Appropriately constructed mixed linear statistical models will be used to test the hypotheses associated within each aim. The potential mediating effects of sleep on postural control impairments in glaucoma will be of primary interest. Future use of data. The findings can be used to identify specific sleep domains as potentially modifiable risk factors to improve balance/gait and reduce falls-related adverse health outcomes in glaucoma. The data collected in the proposed project may be used to plan larger-scale intervention studies.

16. Project Title: The muscle-brain axis: Exploring the effect of skeletal muscle activity on the connectome and transcriptome of aging animals

Leader: Sahu, A

Aims: The overarching goal of these studies is to test the central hypothesis that skeletal muscle contractile activity promotes a more youthful cognitive connectome (Aim 1) and spatially defined transcriptomic profile (Aim 2), ultimately contributing to enhanced cognitive capacity. Background: Physical activity attenuates age-related declines in neurostructual, neurofunctional, and neuromolecular profile of the brain. However, the mechanisms that underlie this beneficial effect of physical activity on aging brains are poorly understood. Individual approaches of cognitive testing, brain architecture analyses, and neuromolecular probing are often used to understand the aging process within the brain. In order to gain a comprehensive mechanistic understanding of aging brain and its response to physical activity, an integrated approach combining behavioral testing (cognition), connectomics (neuroimaging), and spatial –omics (neuromolecular) analyses are warranted. Methods: All animal experiments will be performed with prior approval from the Institutional Animal Care and Use Committee of the University of Pittsburgh. Young and aged male C57BL/6 mice will be used in the studies (Young: 3-6 months, Aged: 21-24 months,). For inducing physical activity in animals, mice will be subjected to a neuromuscular electrical stimulation (NMES) protocol to elicit repetitive skeletal muscle contractions. Mice will receive five stimulation sessions over a period of two weeks, with each session consisting of 20 repetitions. Two days after the last session, animals will be subjected to behavioral testing (spatial memory, short-term memory, and motor activity) or neuroimaging (connectomics). After neuroimaging, the brains will be probed for spatial transcriptomic. Future use of data: We anticipate that using this integrated approach we will be able to identify mechanisms that underlie the benefit of skeletal muscle contractile activity on brain health. Findings from this study will lay the groundwork for developing targeted rehabilitation protocols designed to enhance cognitive functioning in an older population. Preliminary results from this study will also be leveraged to apply for larger funding to determine the effect of NMES on cognitive connectome based on sex.

DEVELOPMENT PROJECTS (4 Development Projects Listed)

1. **Project Title:** **Multi-system measures of mitochondrial dysfunction as early biomarkers of future aging-related mobility impairment**

   Leader: **Sarah Berman, MD, PhD, J. Timothy Greenamyre, MD, PhD, Daniel E. Forman, MD, Caterina Rosano, MD, MPH**

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

   Significance: Mitochondrial dysfunction in both the brain and periphery occurs with aging. This hallmark of aging is multifactorial and affects muscle-skeletal, central nervous, and cardiovascular systems. The multi-system co-occurrence in heart-brain-muscle systems (HBM) likely influences aging-related healthspan outcome measures including the multidimensional syndrome of frailty. Dr. Greenamyre has shown mitochondrial dysfunction in HBM in animal models of Parkinson's Disease *in vitro* and *in vivo*. However, mitochondrial function in humans has been difficult to measure, particularly in brain. Magnetic resonance spectroscopy (MRS) is able to estimate levels of ATP production via monitoring high-energy phosphates, but resolution in brain is poor. Therefore, correlating mitochondrial dysfunction within each independent component of the HBM system with functional outcome measures has not been possible. The ability to predict mobility impairment by non-invasive biomarkers of mitochondrial function may provide a window for intervention prior to the onset of frailty.

   Aims: Our goal is to develop the in-human use of a novel mitochondrial Complex I (Mito-CI) ligand for brain, heart and skeletal muscle using PET imaging to assess mitochondrial function in older adults. Thus, our primary aim is to characterize the pharmacokinetics of 18F-BCPP-EF in human brain, heart and quadriceps and optimize PET data analysis. Our secondary aim is to test the hypothesis that co-occurrence of mitochondrial dysfunction in more than one system plays a synergistic role in the pathogenesis of mobility impairment (e.g. 3>2>1). Conversely, preserved mitochondrial function in any one of these systems may lead to mobility resilience, even in the presence of deficits in the other two.

   Approach: The novel PET imaging ligand, 18F-BCPP-EF is a specific ligand of mito-C1 optimized for brain imaging. 18F-BCPP-EF has been successfully utilized to detect mitochondrial dysfunction in animal PD models and has been safely used in preliminary human studies[19] We have established a collaboration with the developer at Hamamatsu Photonics, and we have synthesized and purified the ligand in preparation for human studies at our center. Benefitting from our combined extensive expertise at the University of Pittsburgh in PET radioligand development, in mitochondrial biology, and in geriatric medicine, we propose to perform the first fully dynamic 18F-BCPP-EF PET imaging and analysis in 20 older adults aged >65 free from neurological diseases. Dr. Berman is currently funded to collect PET brain data of mitochondrial complex I in 10 older adults with mobility disorders and 10 age-matched controls. With this DP, we will expand the sample of control participants to 20 (recruited from the Pepper Registry) and add scan time in the cardiac and skeletal muscles (quadriceps). Measures of mobility will also be obtained.

Future Studies: This study will provide proof-of-concept of the utility of this PET ligand in aging, and will serve to inform future larger studies to delineate the mechanisms of frailty and possibly early risk of mobility disability. Imaging Complex I *in vivo* in multiple systems has the potential to 1) provide an early and specific biomarker of mitochondrial dysfunction in multiple systems; and 2) indicate mechanisms underlying the syndrome of physical frailty in aging.

2. Project Title: **Joint Modeling of Longitudinal and Survival Data for Dynamic Prediction of Mortality Risk with Gait Speed Serially Collected over Time**

Leader: **Robert Boudreau, PhD, Charity Patterson, PhD, MSPH, Subashan Perera, PhD**

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

Significance: One-time physical performance measures are associated with many future outcomes in older adults. It is not clear how to predict future outcomes when serial measures of performance are available, which is a more realistic situation created by subsequent clinic visits. A prediction of an outcome should be updated with any new information about performance. Short term current vs long term trends, the experience of others who have exhibited similar trends, and how to incorporate those, if useful for prediction, need to be considered. Our prior work has shown decline (improvement) in gait speed is associated with worse (better) survival and rate of decline in gait speed over time is related to brain changes. However, they focused on associations and not individual-specific predictions. We are not aware of any other work that has addressed the problem specific to gait speed in a systematic and integrated way. A survival analysis model with time dependent covariates is not appropriate due to the endogenous nature of serial measurements.

Approach: We propose a novel application of the recently developed joint modeling of longitudinal and survival analysis technique to comprehensively address the question. The method makes use of the distribution of trajectories of all the subjects to better estimate individual trajectories, while allowing the latent local, slope and spline-trended mixed model random effects that characterize the trajectories to be potential predictors of survival risk. The joint distribution of the trajectories and survival model are consequently correlated and model fitting is based on optimizing the joint distribution. The survival component acts as a source of informative censoring and addresses the endogenous quandary discussed above. The model can be applied to make individual-specific short and/or long term mortality and gait speed future-trend predictions with confidence/prediction intervals. The predictions can be based on the actual measurements historically collected during a routine clinic visit and currently available along an individual's trajectory. And predictions are updated over time as new gait speed measurements are obtained. The method has been successfully applied in many other areas of medicine. We will use serial 20m "usual pace" gait speed measures of 3075 older adults in Health ABC (Years 1-6, 8 & 10), and convert them to 4m speeds using a linear or quadratic regression model. Such conversions can be

done with a high R2. We will develop the model using Health ABC data and will include 20 years of mortality data, then independently validate it using the CHS (N =5888) cohort who had annual 15' gait speed assessments and 20 years of mortality data. Briefly, ith participant's survival component of the joint model is given by , where is the true unobserved value of gait speed at time is the history of such information up to time are covariates, and is the baseline hazard function, typically approximated with a piecewise-constant form where 's define a partition of the time scale. The longitudinal component for observed gait speeds is, where and are design vectors for fixed and random effects. The model can be fit using the R package jm.

Innovation: Apart from scientific innovation, we will enlist a graduate student researcher to train and perform analyses (MS/PhD thesis) adding a new core-specific dimension to the OAIC training mission. With CPOC, we will disseminate to put the resulting risk calculator on the Pitt Pepper website and/or create a smartphone app.

Core Collaboration: CPOC and DMAIC. If successful, mobility-predicted risk could be considered a standard outcome to be used across the OAIC studies.

Future Direction: The STAR trial (Irrgang & Patterson, DoD) has serial measurements of quality of life and time to return to duty/activity/work in a knee surgery population presenting an immediate future application related to balance & mobility.

3. Project Title: **Automated Neighborhood Walkability Audits by Machine Learning**

Leader: **Andrea Rosso, PhD, MPH, Ervin Sejdik, PhD**

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

Significance: In-person environmental audits provide important information on physical barriers to mobility7 but can be time-consuming. Google Street View now provides access to free, online street-level images. We recently used Google Street View's historical images to add environmental data retrospectively to the Health ABC cohort (R21 AG054666-01, PI: Rosso). Use of these images for environmental audits has been demonstrated to be valid and reliable for street-level characteristics.14-19 Because Google Street View images are in the public domain and will not be linked to individual data, this research is not considered human subjects research.

Innovation: No automated methods for environmental features relevant to mobility and falls in older adults currently exist for use in research studies.

Aims: 1) Identify the environmental components most relevant to falls using existing published literature, and 2) Based on findings in Aim 1, develop computer methods to assess these features in an efficient, reliable, and automated way.

Approach: We will develop computer-based, automated methods for auditing Google Street View images for environmental features most relevant to mobility and falls in older adults. We first determine the most relevant environmental features through a systematic literature review. We then use machine learning methods to develop automated auditing processes. Since Google Street View images provide visuals of house exteriors, nature, landscaping, and vehicles on the street20, we can use deep

learning to identify environmental features by looking for key urban design qualities; walkability: imageability, enclosure, human scale, transparency and complexity.21 Prior studies used several methods to detect and estimate pedestrian volume, visual enclosure, automotive vehicles, and curbsides. Since overlapping images are taken from different perspectives and have different levels of color and illumination, deformable part models (DPM) can be used22-27. Each "deformable part" represents an object model by taking on the appearance properties of the object. The deformations are then linked. Histogram of Oriented Gradient (HOG) is also used to capture the image's region's gradient's intensity and direction23,25,26. Algorithms such as the Aggregated Channel Features (ACF) algorithm can increase computational efficiency by large-scale estimating of HOG and then discarding parts in small-scale images23. Artificial Neural Networks (ANN) can be used to analyze color and texture in Google Street View images27. Feature extraction and segmentation can be performed to isolate regions such as the sky, objects that obstruct the view, and other environmental features of interest22. Extracted features from HOG-ACF or ANN can be used for classification using Support Vector Machine, Decision Trees, Adaboost, or other supervised classification algorithms,23,26,27. Convolutional Neural Networks (CNN) may be able to recognize a wide variety of environmental objects that may affect walkability due to CNN's ability in object classification20. However, CNN is a supervised machine learning method that requires a training set of labeled images. Another method is to use a combination of Region Proposal Networks (RPN) and Fast Region-CNN (RCNN)25. RPN is also a convolutional network that can propose areas or regions in the image, while detection of these regions is done by Fast RCNN. The results of the machine learning audits will be validated against human audits.

Core Collaborations: CPOC, DMAIC

Future Uses: These methods would be made available through the CPOC for wide general research use to expand efficient research assessments into community risk factors for any study focused on mobility and falls.

4. Project Title: **Targeting age-reprogrammed activity of methionine and tyrosine metabolism to delay frailty, improve motor function, and suppress age-predicting 'epigenetic clock'.**

Leader: **Andrey Parkhitko, PhD, Stacey Rizzo, PhD**

Core(s): Biology of Mobility and Aging Core (BMAC)

Metabolic reprogramming represents one of the major driving forces in aging and leads to impaired organismal fitness, an age-dependent increase in susceptibility to diseases, decreased ability to mount a stress response, and increased frailty. Although targeting methionine and tyrosine metabolism has been shown to increase lifespan in different species, at present, no data exist to demonstrate their effects on composite measures of health in general and on muscle health in particular. In addition, MetR in human patients has been only tested in the settings of methionine deprivation from food, which is hardly achievable in clinical settings and results in a moderate decrease in plasma methionine, potentially limiting its efficacy.

Rationale: Our preliminary data demonstrate that metabolism in general and methionine/tyrosine metabolism particularly are reprogrammed during aging in Drosophila (Parkhitko et al., 2016; Parkhitko et al., 2019) and (Parkhitko et al., eLife under revision). We also identified two novel anti-longevity genes in the methionine metabolism pathway that can improve the age-dependent decline in climbing activity (indicator of neuromuscular function in flies) and extend health- and lifespan (Parkhitko et al., G&D 2016). Similarly, we demonstrated that aging and mitochondrial dysfunction activate the tyrosine degradation pathway and that downregulation of tyrosine aminotransferase, the first and rate-limiting enzyme in the tyrosine degradation pathway, upregulates the production of tyrosine-derived neuromediators and extends lifespan (Parkhitko et al, eLife, under revision). Both methionine and tyrosine metabolism pathways can be targeted with FDA-approved drugs or drugs that are under current development for human applications. For example, we demonstrated that Methioninase, a bacterial enzyme capable of degrading methionine, efficiently depletes methionine and downstream metabolites (Figure 1) and dramatically extends Drosophila lifespan (Parkhitko et al., Aging Cell, under revision). Recombinant Methioninase has been tested in various cancer models in vivo and was safely used in clinical trials in humans (Agrawal et al., 2012; Chaturvedi et al., 2018; Hoffman, 2015). Cancer patients receiving recombinant Methioninase intravenously had a steady decline in serum methionine levels directly proportional to levels of active enzyme with minimal or no toxicity (Tan et al., 1997). This creates a strong rationale for translating these findings to mammalian systems as anti-aging interventions or for the potential treatment of various age-related diseases.

Approach: We will use either young AD mice or wild-type C57BL/6J mice of different ages: young (4 mo) and old-age (24 mo). We will investigate how manipulations of methionine metabolism via dietary MetR (restricting methionine in mouse food) or enzymatic MetR (feeding mice with Methioninase) or manipulations of the tyrosine metabolism by feeding mice with an FDA-approved drug, nitisinone/orfadin, would affect the frailty index, wheel running, and epigenetic age. To confirm the efficiency of our manipulations and the effect of age, we will measure levels of metabolites from the methionine and tyrosine metabolism pathways in mouse plasma, liver, muscle, and brain. The Frailty Index (FI) is a non-invasive composite measure of health that can assess an effect of treatment on different aspects of healthspan and predict life expectancy and the efficacy of a lifespan-extending interventions up to a year in advance (Sukoff Rizzo et al., 2018), (Schultz, Kane et al., bioRxiv 2019). In addition to the FI, to estimate the potential effects of proposed interventions on lifespan, we will use mouse ‘epigenetic clocks’ to predict the effects of proposed intervention on biological age and lifespan extension. Through this Developmental Pilot, we expect to test how manipulations of methionine and tyrosine metabolism pathways affect the multitude of parameters relevant to aging in mice, with a special focus on the assessments of motor and fine motor function.

Core Collaborations/ grants: BMAC/ Preclinical Phenotyping Core.

Future Proposals: This pilot project will provide the necessary data for a National Institute of Aging R01 grant proposal. Long-term goals include evaluation of recombinant Methioninase and nitisinone/orfadin for lifespan extension in mice and for the effects on the FI in humans.

RESEARCH (0 Projects Listed)

PUBLICATIONS

2024

2023

1. **Non-esterified fatty acids and risk of peripheral artery disease in older adults: The cardiovascular health study.**
   Ahiawodzi P, Solaru KW, Chaves PHM, Ix JH, Kizer JR, Tracy RP, Newman A, Siscovick D, Djousse L, Mukamal KJ
   Atherosclerosis, 2023 Apr, 370: 25-32
   https://doi.org/10.1016/j.atherosclerosis.2023.01.020 | PMID: 36754661 | PMCID: PMC10079601
   Citations: 1 | AltScore: 17.08
2. **Influence of Recent Standing, Moving, or Sitting on Daytime Ambulatory Blood Pressure.**
   Barone Gibbs B, Muldoon MF, Conroy MB, Paley JL, Shimbo D, Perera S
   J Am Heart Assoc, 2023 Sep 5, 12(17): e029999
   https://doi.org/10.1161/JAHA.123.029999 | PMID: 37589152 | PMCID: PMC10547321
   Citations: NA | AltScore: 15.85
3. **The BACPAC Research Program Data Harmonization: Rationale for Data Elements and Standards.**
   Batorsky A, Bowden AE, Darwin J, Fields AJ, Greco CM, Harris RE, Hue TF, Kakyomya J, Mehling W, O'Neill C, Patterson CG, Piva SR, Sollmann N, Toups V, Wasan AD, Wasserman R, Williams DA, Vo NV, Psioda MA, McCumber M
   Pain Med, 2023 Jan 31, 24(Suppl 1): S95-S104
   pii: pnad008. https://doi.org/10.1093/pm/pnad008 | PMID: 36721327
   Citations: 1 | AltScore: NA
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Citations: 3 | AltScore: 9.45

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RECOGNITION AND AWARDS (2023-2024)

Aarohee Fulay, PhD, MPH (2023)

- RCCN Workshop Travel Award for Early Career Investigators on Healthy Aging Through Nutrition

Arjumand Ghazi, PhD (2023)

- Reproductive Geroscience K07 Award

Daniel Forman, MD (2023)

- Director, American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) Annual Meeting

Lilcelia (CeCe) Williams, PhD, MBA, BSRT(T) (2023)

- 2023 UPMC Rehabilitation Institute Pilot Grant for the School of Health and Rehabilitation Sciences
- abstract has been accepted for presentation at The Gerontological Society of America (GSA) 2023 Annual Scientific Meeting

Samaneh Farsijani, PhD, RD (2023)

- RCCN Workshop Travel Award for Early Career Investigators on Healthy Aging Through Nutrition

MINORITY RESEARCH

General Brief Description of Minority Activities:
Not defined.

Minority Trainee(s):

- Diana Alvarez-Davidek MD, Novice REC Member
  Age-related mitochondrial decline in lung function
- Gardenia Juarez, Pepper Novice Trainee
  Reducing Fear of Falling and Preventing Falls
- Gelsy Torres-Oviedo, PhD, Pepper REC Transitioned to Independence Trainee
  Increasing gait automaticity in older adults by exploiting locomotor adaptation
- Ikenna D. Ebuenyi, MBBS, PhD , Novice REC Member
  Rehabilitation in the Face of Progressive Decline: Practice and Perspectives
- Lilcelia Williams, PhD, MBA, BSRT(T), Novice REC Member
  She will explore beliefs, values, and perspectives about Mild Cognitive Impairment and associated health care services in black and African American older adults.

No minority grant information specified.