UNIVERSITY OF FLORIDA
Claude D. Pepper Older Americans Independence Center

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CENTER DESCRIPTION

The mission of the University of Florida Older Americans Independence Center (OAIC) is twofold: 1) to optimize older persons' physical performance and mobility through interdisciplinary approaches; and 2) to train new investigators in aging and disability research while developing their leadership qualities. Our goal is to enhance late-life health and independence, with a special focus on mobility. To accomplish our mission, our strategy is to attract studies and inventive investigators from diverse behavioral, clinical, basic, and technological science disciplines with a common research focus: "mobility and prevention of disability." Traversing the entire spectrum of biomedical investigation, including molecular biology, animal studies, clinical research, behavioral sciences, epidemiology, and engineering, our research effort addresses the OAIC's general goal: to increase scientific knowledge that leads to better ways to maintain or restore independence of older people. Our research objectives are to: 1) assess, using translational research (among diverse disciplines), the biological, co-morbid, psychosocial, behavioral, and other factors that contribute to physical function decline, loss of mobility, and progression toward disability; and 2) develop and reliably test, in clinical and preclinical studies, interventions that target mobility to prevent, delay, or recover the age-related declines in physical function. Our educational objective is to train future leaders in clinical translational research on aging. To meet these objectives the proposed OAIC trains Junior Scholars and supports investigators, resources, services, external studies, development projects, and pilot/exploratory studies through seven integrated cores: *Leadership and Administrative Core; Research Education Core; Pilot/Exploratory Studies Core; Clinical Research Core; Metabolism and Translational Science Core; Biostatistics Core; Data Science and Applied Technology Core; and Circadian Rhythms Core.*A relevant strength of the proposed OAIC is the concerted action of the interdisciplinary cores, projects, and investigators who address one common research focus spanning the entire spectrum of biomedical investigation.

Research hypotheses:

- Multiple biological, co-morbid, psychosocial, cognitive, and behavioral factors contribute to agerelated physical function decline, loss of mobility, and progression to disability.
- Interventions that target individual or multiple biological, co-morbid, psychosocial, cognitive, and behavioral risk factors of physical function decline avert the loss of mobility and prevent disability.

Research objectives:

- Assess, by taking advantage of a bidirectional translation between basic and clinical research, the multiple factors that contribute to physical function decline, loss of mobility, and progression to disability.

- Develop and test pharmacological, nutritional, and behavioral interventions for preventing decline in physical function, loss of mobility, and progression to disability.

Educational objectives:

- Educate and train new investigators in research on aging and disability in older adults.
- Develop leadership qualities and roles in Junior Scholars supported by the OAIC.
- Develop skills for translating findings between basic and clinical research.

Operational objectives:

- To provide outstanding investigators and state-of-the-art resources, environment, and services to support the above-mentioned research and educational objectives.

CORES

Leadership and Administrative Core (LAC)

Leader 1: Marco Pahor, MD mpahor@ufl.edu
Leader 2: Karyn Esser, PhD kaesser@ufl.edu

The Leadership and Administrative Core (LAC) is responsible for strategic planning, organization, administrative operations, and evaluation of the Older Americans Independence Center (OAIC) research and training program. A special effort is devoted to ensure the cohesion of the Center and maintain an interdisciplinary and translational research focus on the common research theme, which is "mobility and prevention of disability." The Core Leader and three committees achieve the key LAC tasks. The Executive Committee, which is composed of the OAIC core leaders, administers, governs, provides scientific guidance, and sets productivity benchmarks for the OAIC. The External Advisory Board, which is composed of experts external to the institution, reviews all OAIC activities and provides overall scientific guidance to the OAIC. The Independent Review Panel, which is composed of ad hoc experts (at least one third external to the institution), reviews proposed support for development projects, and pilot/exploratory studies. Taken together, the LAC provides support for planning, organizational, evaluation, and administrative activities relating to the other cores and to the OAIC as a whole. The LAC monitors, stimulates, sustains, evaluates, and reports progress toward the overall goals of the OAIC.

Research Education Component (REC)

Leader 1: Christiaan Leeuwenburgh, PhD cleeuwen@ufl.edu
Leader 2: Roger Fillingim, PhD RFillingim@dental.ufl.edu

The REC promotes the development of independent investigators in interdisciplinary research on aging relevant to the independence of older Americans. One of our major goals is to identify the most promising Junior Scholars with research relevant to the OAIC theme at UF & VA and to provide them with mentorship, training activities, access to OAIC Core resources and funding and enable them to become independent investigators in interdisciplinary aging research. Furthermore, this core emphasizes the development of leadership, and research skills for translating basic findings into clinical research and clinical findings into basic research. The REC supports the research training of OAIC Junior Scholars that span the spectrum from beginning trainees who are not yet funded to advanced trainees who already have competed successfully for career development grants that provide substantial salary support.

Pilot and Exploratory Studies Core (PESC)

Leader 1: Yenisel Cruz-Almeida, Ph.D. cryeni@ufl.edu
Leader 2: Marco Pahor, MD mpahor@ufl.edu

The Pilot/Exploratory Studies Core serves to develop key information needed to select and design future, original and independently funded studies that can advance our insight into sarcopenia and prevention of disability in older Americans. Specifically, the core fosters the Pilot and Exploratory studies by ensuring the availability of optimal infrastructure, environment, funding, expertise, and instrumentation. Pilot and Exploratory studies foster Junior Scholars in their efforts to develop research careers in aging by providing opportunities for meaningful participation in well-designed research studies and by collecting the needed preliminary data for independent research applications. Furthermore, these studies will allow investigators already accomplished in aging

research to gather data that will extend and broaden their focus of research. Finally, these studies will also be a vehicle to encourage and facilitate experienced investigators traditionally working in other research fields to focus on aging.

Clinical Research Core (RC1)

Leader 1: Stephen Anton, PhD santon@ufl.edu
Leader 2: Marco Pahor, MD mpahor@ufl.edu

The Clinical Research Core (RC1) is a key resource for the UF OAIC in providing the infrastructure and investigators for conducting clinical research -- randomized controlled trials and observational studies. The clinical research core has four primary goals: 1) optimal selection and utilization of measures for clinical trials and observational studies 2) understanding the physiological and biomechanical mechanisms contributing to changes in walking speed, 3) in collaboration with the Biostatistics Core, conduct secondary analyses of randomized clinical trials and observational studies to provide preliminary data to support the rationale for future clinical trials, and 4) development of behavioral and pharmacological interventions to improve physical function and quality of life of older adults. The RC1 offers state-of the art infrastructure and experienced personnel to support the conduction of observational studies, and Phase 2 and 3 randomized controlled trials that involve behavioral and pharmacological interventions. Senior researchers with NIH and/or VA funding, who also have established track records as mentors for career development, lead each one of these goals.

Biostatistics Core (RC 3) (Biostats)

Leader 1: Peihua Qiu, PhD pqiu@ufl.edu

The Biostatistics Core is one of five research cores in the OAIC at UF. The mission of the UF OAIC is to assess risk factors of physical disability in older adults, to develop and test effective prevention and rehabilitation therapies, and to train new investigators in research on aging and disability. The Biostatistics Core is a key cog in the interaction among scientists from many disciplines to accomplish this mission. The core provides data coordination including: developing data collection forms, designing web-based capture systems, and managing the data (including quality control) for studies conducted within the OAIC. The core is also involved in all phases of these studies including initial study design and sample size calculations when preparing a grant proposal, randomization, and state-of-the-art statistical analyses once the data are collected. For study designs and data for which current methodology is lacking, the core has the expertise to develop new statistical methodology to perform appropriate analyses. The Biostatistics Core will also be involved in preparation of manuscripts for dissemination within the research community. The Core also conducts research using The UF & Shands Academic Health Center's new electronic medical record system (EPIC), which has gone live with new modules planned through the next few years. This includes the implementation of a clinical data warehouse (CDW). The CDW is the foundation for the development of a research data repository whereby researchers and junior scholars and faculty may have unfettered access to anonymized data for clinic research.

Circadian Rhythms Core (RC5)

Leader 1: Karyn Esser, PhD kaesser@ufl.edu

The new Circadian Rhythms research core within the UF OAIC provides the specialized resources and expertise to support scientists that want to incorporate circadian and sleep concepts into their aging research program. This includes new investigators, early-stage investigators and current investigators in aging. The core supports research through; 1) in vivo rodent circadian phenotyping across age; 2) resources to implement time restricted feeding with unique automated cages; 3) methods to test the robustness and resilience of the circadian system across ages; 4) non-invasive analysis of rodent sleep parameters; 5) statistical support for analysis of circadian data from rodents and humans. 6) ongoing development of an in vitro assay to analyze human circadian clock function using primary cells from subjects of different ages and health status. 7) work with the Data Science Core (RC4), the Biostatistics core to leverage UF machine learning strengths to define a blood marker assay as a biomarker of human circadian health.

Data Science and Applied Technology Core (RC 4) (Data Science)

Leader 1: Todd Manini, PhD tmanini@ufl.edu

Leader 2: Sanjay Ranka, PhD ranka@cise.ufl.edu

The Data Science and Applied Technology (DSAT) Core (RC4) provides an interactive data and technology ecosystem for preserving mobility and preventing disability. Big data initiatives, applied technologies, and new methodological approaches for data science have exploded in many various environments, and the world is moving toward a connected system of computing and sensing components. Additionally, mobile health (mHealth, smartphones and smartwatches) technologies are changing the landscape for how patients and research participants communicate about their health in real time. DSAT investigators provide OAIC leadership to assure that researchers in Geriatrics in general, mobility and disability are prepared for the rapid advances in these expanding technologies. The RC4 provides many unique attributes, such as developing software for interactive mobile technology (e.g., wearable sensors that are programmable in real time); validating new sensing technology; warehousing data; repurposing data; and applying machine learning techniques to domain problems. DSAT provides a central hub of expertise in computer science, biomedical engineering, biomedical informatics, data science, applied technology, epidemiology, and content expertise in the assessment of mobility. There is a growing demand for data science and applied technology for meeting the challenge of preserving mobility and preventing disability. The DSAT Core adds a highly innovative aspect to this challenge that will lead it into the future of connected systems of computing, sensing and biomedical informatics.

Metabolism and Translational Science (RC2) (Metabolism and Translational Science)

Leader 1: Christiaan Leeuwenburgh, PhD cleeuwen@ufl.edu

The Metabolism and Translational Science Core (RC2), in collaboration with other UF OAIC cores, supports biochemical analyses for preclinical, human interventional, or observational clinical studies. By measuring a selected set of biomarkers, we can determine how targeted interventions influence the rate of aging, as well as loss of mobility and independence. This core thereby provides the support for the Research Education Core (REC) Scholars and pilot study investigators. Aging and disease feature progressive deterioration of various physiological and metabolic processes. This is associated with altered functions or contents of protein, RNA, and DNA, which provide biomarkers to monitor aging. Multiple pathways and domains have been associated with aging, such as genomic instability (including telomere attrition, mutations, and deletions); epigenetic alterations; loss of proteostasis (including dysfunctional autophagy); deregulated nutrient sensing; mitochondrial (Mt) dysfunction; inflammation and cellular senescence; stem cell

exhaustion, disrupted circadian clock rhythms; and dysfunctional nicotinamide adenine dinucleotide (NAD+) homeostasis. The specific analyses of protein, RNA, and DNA biomarkers that this core will provide are related to major biological and metabolic pathways known to regulate aging and focus on: (i) Mt function; (ii) inflammation and senescence; (iii) autophagy; (iv) circadian clock biology; and (v) NAD+ homeostasis. We use innovative analytical tools and standard high-throughput analysis to determine the fundamental biological mechanisms of aging. The Metabolism and Translational Science Core (RC2) supports the overarching hypothesis that knowledge of specific protein, RNA, and DNA biomarkers, as well as measurements of metabolism of isolated mitochondria and white blood cells (WBCs), are critical for understanding the trajectory of healthy aging and the underlying biological causes of mobility loss. The core also supports extraction of proteins, RNA, and DNA, analysis of biomarkers, isolation of cells (WBCs) and organelles (mitochondria), and assessments of Mt function. The RC2 provides investigators across UF OAIC cores and REC scholars with established methodologies, scientific data, infrastructure, highly qualified personnel, and consultative and collaborative expertise and pursues the following aims: Aim 1: To support protein, RNA, and DNA isolation and analysis of specific biomarkers of aging. Aim 2: To support analysis of Mt respiration, Mt enzyme activities, and NAD coenzymes. Aim 3: To facilitate and provide consultation on analyses and sample storage, and collaborate synergistically with the other OAIC cores to pursue the common OAIC theme of promotion of mobility and independence.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications
Lakeshia Cousin, PhD, APRN, AGPCNP-BC Assistant Professor / College of Nursing A Pilot Feasibility Study of a Gratitude Journaling Intervention to enhance Well-being and Exercise Readiness in Older African American Female Breast Cancer Survivors	2022-2024 / 1 (total) 0 (1st/Sr)
Feng Yue, PhD Assistant Professor / Department of Animal Sciences Mechanisms of sepsis-induced myopathy in aging: insights from a new modified surgical sepsis model by single cell analysis • NIDDKD 1R01DK136722-01	2022-2024 / 3 (total) 0 (1st/Sr)
Clayton Swanson, PhD, MS Assistant Professor / Department of Aging & Geriatric Research Development of a Home-based Self-delivered Prehabilitation Intervention to Proactively Reduce Fall Risk in Older Adults	2022-2024 / 0 (total) 0 (1st/Sr)

Past Scholars

Rui Xiao, PhD, Department of Aging & Geriatric Research (2015-2017)
Hyochol "Brian" Ahn, PhD, ARNP, ANP-BC, College of Nursing, Department of Family, Community and Health System Science (2015-2017)
Scott Brakenridge, MD, College of Medicine, Department of Surgery (2015-2017)
Andrew Bryant, MD, College of Medicine, Department of Internal Medicine Pulmonary, Critical Care and Sleep Medicine (2015-2016)
Sara Burke, PhD, College of Medicine, Department of Neuroscience (2015-2017)
Huaihou Chen, PhD, Department of Biostatistics (2015-2017)
Sooyeon Lee, PhD, College of Medicine, Department of Surgery (2015-2016)
Joshua Brown, PhD, MS, Department of Pharmaceutical Outcomes & Policy (2017-2019)
Robert Mankowski, PhD, Department of Aging & Geriatric Research (2017-2019)
Yu-Jung “Jenny” Wei, PhD, MS, Department of Pharmaceutical Outcomes and Policy (2017-2019)
Joseph McQuail, PhD, Department of Neuroscience (2018-2019)
Terence Ryan, PhD, Department of Applied Physiology & Kinesiology (2018-2020)
Sung Min Han, PhD , College of Medicine Department of Aging and Geriatric Research (2019-2021)
Carolina Maciel, MD, Department of Neurology, Division of Neurocritical Care (2019-2021)
Scott Vouri, PharmD, MSCI, PhD, Department of Pharmaceutical Outcomes and Policy (2019-2021)
Matthew R. Burns, MD, PhD, Department of Neurology (2020-2022)

Sudeshna A. Chatterjee, BPTh, MS, PhD, Department of Aging & Geriatric Research (2020-2022)
Mamoun Al Mardini, PhD, Health Outcomes and Biomedical Informatics (2020-2022)
Samir K. Shah, MD, MPH, Department of Surgery (2020-2022)

PILOT/EXPLORATORY PROJECTS (7 Pilot Projects Listed)

1. **Project Title:** **Probing metabolomics of pancreatic cancer and skeletal muscle in elderly patients**

   Leader: **Ashwin S. Akki, MD, PhD**

   The overall goal of this research project is to increase the understanding of metabolic alterations in the skeletal muscle of elderly patients with cachexia and accelerated sarcopenia in pancreatic ductal adenocarcinoma (PDAC). Since skeletal muscle metabolism and strength are intricately linked to tumor metabolism, simultaneously probing PDAC metabolism is crucial. This knowledge will enable us to decipher the impact of a rapidly proliferating tumor on aggressive cachexia, accelerated sarcopenia and impaired mobility in elderly PDAC patients and help identify novel metabolic targets that could potentially be modulated to curb tumor growth, preserve skeletal muscle mass/strength, and prevent disability in the aging population. Consequently, the proposed project is highly relevant to the OAIC theme of "Mobility and Prevention of Disability". This proposal is extremely relevant to the interests of the "Clinical and Translational Research of Aging Review Committee (NIAT)" and/or the "Aging Systems and Geriatrics Study Section"

2. **Project Title:** **Pain Resilience and Inflammatory Marker Expression (PRIME)**

   Leader: **Emily J. Bartley, PhD**

   The overarching goal of this study is to elucidate the immunological and resilience mechanisms underlying self-reported and functional disability in older adults with cLBP. This project expands an existing community-based study (Adaptability and Resilience in Aging Adults [ARIAA]) whereby 60 adults (ages 60+ years) with cLBP completed clinical (psychological and pain measures), functional (tests of mobility), and somatosensory pain assessments. The study supplements the parent project through the inclusion of biomarker assays to assess pro- and anti-inflammatory function. These findings will provide novel and important information regarding the mechanisms underpinning pain and disability and will be a step toward the development of therapeutic modalities aimed at mobility preservation in older adults with cLBP.

3. **Project Title:** **Impact of Pain and Exercise on Mobility in Older Adults with Opioid Use Disorder**

   Leader: **Meredith S. Berry, PhD and Danielle E. Jake-Schoffman, PhD**

   This study aims to determine the effects of the exercise intervention versus control on (i) self-reported pain and pain catastrophizing, (ii) objective and self-reported mobility ratings (iii) biologically verified urinalysis results of illicit drug-use, and (iv) craving, withdrawal, and behavioral economic demand for opioids. The study directly aligns with the central OAIC themes of enhancing mobility, and reducing pain through an exercise intervention. This project has tremendous potential for public health impact with possibility for wide deployment for those in need. Our multidisciplinary team is uniquely suited to advance understanding of shared mechanisms underlying pain, mobility, craving and withdrawal, and to complete the proposed project with expertise in (i) OUD (ii) PA promotion (iii) pain (iv) exercise physiology (v) cardiology and (vi) biostatistics.

4. Project Title: **Prevention of Cancer-Induced Immobility and Dysfunction**
Leader: **Daria Neyroud, PhD and Andrew D'Lugos, PhD**

This study aims to 1. Quantify the extent to which cancer impacts mobility and skeletal muscle dysfuction; and 2. Determine the efficacy of exercise training for preventing cancerinduced disability and cachexia. The project is therefore highly aligned with the mission of the National Institute on Aging (NIA), in particular with goal C of the current NIA Strategic Direction for Research, “to develop effective interventions to maintain health, well-being, and function and prevent or reduce the burden of age-related diseases, disorders, and disabilities”.

5. Project Title: **Role of skeletal muscle Bmal1 on healthspan and survival**
Leader: **Miguel Gutierrez-Monreal, PhD (Karyn Esser, PhD)**

The goal of this pilot study is to provide feasibility and supporting data for a NIH grant application. This pilot is aimed to examine the effect of skeletal muscle molecular clock on systemic metabolism and inflammation during aging. We have recently identified there is a progressive age-related decline in circadian function in skeletal muscle. Disruptions in circadian rhythms have profound negative consequences on several pathways that comprise the hallmarks of aging including metabolism and inflammation.

6. Project Title: **Sleep, pain and aging: potential underlying mechanisms**
Leader: **Soamy Montesino Goicolea, MD (Yenisel Cruz-Almeida, PhD)**

This study will quantify the levels of the GABA neurotransmitter after oral administration, regardless of the direct or indirect route that mediates its function in the brain. This constitutes the starting point in the development of cost-effective over-the-counter GABA treatments aiming at improving the currently costly and often co-morbid problems of sleep dysfunction and chronic pain in the aging population. The project addresses an existing knowledge gap and may potentially identify GABA.

7. Project Title: **Design of Printable Gelatin Microgel and Stem Cell-based Composite Bioink for Repairing Degenerated Intervertebral Discs**
Leader: **Yong Huang, PhD, Christiaan Leeuwenburgh, PhD, Brian Harfe, PhD, Kyle Allen, PhD**

The overarching goal of this pilot study is to design and evaluate a gelatin microgel and stem cellbased printable bioink as a delivery system for the repair and regeneration of age-related degenerative intervertebral discs (IVDs) for personal mobility and independence. Intervertebral disc degeneration (IDD) is an age-related condition that happens when one or more of the discs between the vertebrae of the spinal column deteriorate or even break down. As a natural occurrence that comes with aging, it may lead to lower back pain and even immobility due to weakness, numbness, and pain that radiates down the leg, resulting in disability. As a minimally invasive approach, the cell-therapy approach aims to address disc inflammation by inhibiting aberrant cytokine production as well as disc rehydration and height restoration by initiating matrix anabolism and repopulating native cells. While the cell-therapy approach needs a unified understanding of the disease mechanism of degeneration and useful interpretation of clinical evaluations, clinical trials also call for effective delivery systems of therapeutic cells, which is the subject of the study. Accordingly, two specific aims are proposed: Aim 1: Repair

of degenerative IVD using a gelatin microgel and mesenchymal stem cell-based printable composite bioink. Aim 2: Evaluation of the mechanical properties and formation of fibrocartilage-like intervertebral disc tissue of IVDs repaired using the proposed cell delivery system. This pilot study provides a novel gelatin microgel-based self-supported cell delivery system to repair degenerated IVDs for their better regeneration by integrating engineering and biology to create a costeffective and safe cell therapy for IVD regeneration. Such a printable stem-cell therapy will help improve the mobility and independence of seniors who are disabled due to IDD-induced weakness, numbness, and back pain that radiates down the leg. We further envision that the delivery system using the proposed printable self-supporting cellular bioink can be explored as a much-needed reliable and costefficient stem-cell therapy to facilitate in situ tissue repair and wound healing applications, to name a few.

DEVELOPMENT PROJECTS (2 Development Projects Listed)

1. **Project Title:** **Time restricted feeding to improve aging circadian clocks and healthspan in rodents**

   Leader: **Karyn Esser, PhD, Thomas Foster, PhD, Andrew Liu, PhD, Christiaan Leeuwenburgh, PhD**

   Core(s): Biostatistics Core (RC 3) (Biostats)
   Circadian Rhythms Core (RC5)
   Metabolism and Translational Science (RC2) (Metabolism and Translational Science)

   Aging is associated with changes in circadian rhythms including patterns of locomotor activity and sleep/wake states (114-120). Underlying circadian rhythms is a molecular clock mechanism that is found in virtually all cells throughout the body. Research has demonstrated that disruption of circadian timekeeping leads to increases in pathology, morbidity, and mortality (121-129). The purpose of this project is to implement a circadian-based intervention, time-restricted feeding, for its potential to enhance circadian function across organs and improve healthspan in aging mice. This preclinical study will complement the clinical DP-1 (described in RC1) with the ability to carefully control the times of feeding the mice, and to assess the health impact on organs such as brain, heart, and skeletal muscle.

2. **Project Title:** **Assessment of Fuel Utilization and Circadian Rhythms in Overweight, Older Adults Following Time Restricted Eating - Phase 2 (FAR Phase 2)**

   Leader: **Stephen Anton, PhD, Christiaan Leeuwenburgh, PhD, Todd Manini, PhD, Bhanuprasad Sandesara, MD**

   Core(s): Clinical Research Core (RC1)
   Biostatistics Core (RC 3) (Biostats)
   Data Science and Applied Technology Core (RC 4) (Data Science)
   Metabolism and Translational Science (RC2) (Metabolism and Translational Science)

   Both fuel metabolism and circadian rhythms have emerged as important targets to improve cellular and mitochondrial health and ultimately affect function in older adults. Thus, the purpose of this study is to develop minimally invasive measures that will allow us to accurately assess and detect changes in fuel metabolism and circadian rhythms in older adults following time-restricted eating. A growing body of evidence indicates the mitochondria have an important role in the etiologies of many chronic diseases as well as the onset of physical disability in older adults. Although it is recognized that the mitochondria have an important role in many functions relevant to healthy aging, the direct assessment of mitochondrial function in humans is complicated and typically involves a muscle biopsy. Muscle tissue obtained from a biopsy can be used to provide an index of mitochondrial function, but only at a single time point. Some individuals may be discouraged from participating in research studies involving biopsies due to the perceived pain and risk involved. Why there is a decrease in mitochondrial function with aging remains under debate, but emerging science indicates that there is a clear connection between mitochondrial biogenesis and function with fuel metabolism and circadian rhythms. Thus, the purpose of this development project is to develop relatively non-invasive measures that are sensitive to fuel metabolism and circadian health which can serve studies

conducted within the University of Florida's Pepper Center in the coming years. In the proposed project, we will investigate the extent to which our measures of fuel utilization and circadian health markers are time stable and also sensitive to change following an intervention of time restricted eating, which is expected to impact these variables. To our knowledge, no study has assessed fuel utilization patterns or circadian health markers in overweight older adults. Measurements of altered mitochondrial oxidation with a preference toward fat metabolism obtained from a blood sample would provide a sensitive biomarker that is relatively easy to obtain from participants for future interventions studies. The use of continuous glucose monitoring may also be used as surrogate measure of adherence to lifestyle interventions involving calorie restriction and/or intervention fasting, in future studies. In addition to fuel utilization, there is growing recognition that age-related disease conditions and functional decline are associated with disruption of circadian rhythms. These observations raise the possibility that targeting circadian rhythms through timing lifestyle cues, such as meal timing, could be health promoting and may also reduce age associated declines in mobility. The ability to assess markers of circadian and metabolic health in minimally invasive ways through temperature and glucose monitoring, will provide potential valuable measures for explanatory or outcome measures in future studies. In specific aim 1, we will develop a new measure to detect shifts in fuel utilization at the cellular level using Seahorse XF Technology to measure fuel utilization within white blood cells. We will also measure 24-hour fluctuations in plasma glucose levels using a continuous glucose monitor. In specific aim 2, we will develop a new measure to detect the expression of circadian clock genes, as well as non-invasive measures, from which circadian health parameters can be extracted. These measures include activity levels, body temperature, and heart rate, using Wearable Technology. The reliability and variability in measures of fuel utilization and circadian health markers will be assessed in relation to changes in some of our standard Clinical Research Core measures of physical function.

RESEARCH (0 Projects Listed)

PUBLICATIONS

2024

2023

1. **Comparing D3-Creatine Dilution and Dual-Energy X-ray Absorptiometry Muscle Mass Responses to Strength Training in Low-Functioning Older Adults.**
   Balachandran AT, Evans WJ, Cawthon PM, Wang Y, Shankaran M, Hellerstein MK, Qiu P, Manini T
   J Gerontol A Biol Sci Med Sci, 2023 Aug 27, 78(9): 1591-1596
   https://doi.org/10.1093/gerona/glad047 | PMID: 36752568
   Citations: 1 | AltScore: 10.05
2. **Male kidney-specific BMAL1 knockout mice are protected from Potassium-deficient, high salt diet-induced blood pressure increases.**
   Crislip GR, Costello HM, Juffre A, Cheng KY, Lynch IJ, Johnston JG, Drucker CB, Bratanatawira P, Agarwal A, Mendez VM, Thelwell RS, Douma LG, Wingo CS, Alli AA, Scindia YM, Gumz ML
   Am J Physiol Renal Physiol, 2023 Sep 14, 325(5): F656-F668
   https://doi.org/10.1152/ajprenal.00126.2023 | PMID: 37706232
   Citations: NA | AltScore: 9.5
3. **Genetic Testing for Cancer Risk and Perceived Importance of Genetic Information Among US Population by Race and Ethnicity: a Cross-sectional Study.**
   Hong YR, Yadav S, Wang R, Vadaparampil S, Bian J, George TJ, Braithwaite D
   J Racial Ethn Health Disparities, 2023 Jan 23 13-Jan
   https://doi.org/10.1007/s40615-023-01526-4 | PMID: 36689121 | PMCID: PMC9870197
   Citations: NA | AltScore: 1.5
4. **The Golden Bachelor: A rose or a thorn for geriatrics and gerontology?**
   Kaufmann CN, Kaufmann KM
   J Am Geriatr Soc, 2023 Oct 6
   https://doi.org/10.1111/jgs.18602 | PMID: 37801023
   Citations: NA | AltScore: NA
5. **Sex differences in body composition, voluntary wheel running activity, balance performance, and auditory function in CBA/CaJ mice across the lifespan.**
   Kim MJ, Carmichael PB, Bose U, Honkura Y, Suzuki J, Ding D, Erfe SL, Simms SS, Avaiya KA, Milani MN, Rymer EJ, Fragnito DT, Strom N, Salvi R, Someya S
   Hear Res, 2023 Feb, 428: 108684
   https://doi.org/10.1016/j.heares.2022.108684 | PMID: 36599258
   Citations: NA | AltScore: NA
6. **Pain severity, distribution, and duration are associated with spatiotemporal gait performance in community-dwelling older adults with chronic musculoskeletal pain.**
   Lipat AL, Peterson JA, Murillo BC, Clark DJ, Cruz-Almeida Y
   Gait Posture, 2023 Jun, 103: 178-183
   https://doi.org/10.1016/j.gaitpost.2023.05.011 | PMID: 37236053
   Citations: NA | AltScore: NA
7. **The role of mitochondria in the recovery of neurons after injury.**
   McElroy T, Zeidan RS, Rathor L, Han SM, Xiao R
   Neural Regen Res, 2023 Feb, 18(2): 317-318

https://doi.org/10.4103/1673-5374.343907 | PMID: 35900413 | PMCID: PMC9396508
Citations: 5 | AltScore: 0.5

8. **Relationship between Mitochondrial Quality Control Markers, Lower Extremity Tissue Composition, and Physical Performance in Physically Inactive Older Adults.**
Picca A, Triolo M, Wohlgemuth SE, Martenson MS, Mankowski RT, Anton SD, Marzetti E, Leeuwenburgh C, Hood DA
Cells, 2023 Jan 2, 12(1):
https://doi.org/10.3390/cells12010183 | PMID: 36611976 | PMCID: PMC9818256
Citations: 3 | AltScore: NA
9. **Conscious connected breathing with breath retention intervention in adults with chronic low back pain: protocol for a randomized controlled pilot study.**
Pratscher SD, Sibille KT, Fillingim RB
Pilot Feasibility Stud, 2023 Jan 24, 9(1): 15
https://doi.org/10.1186/s40814-023-01247-9 | PMID: 36694217 | PMCID: PMC9872326
Citations: NA | AltScore: 2
10. **Disease correction in mucopolysaccharidosis type IIIB mice by intraparenchymal or cisternal delivery of a capsid modified AAV8 codon-optimized NAGLU vector.**
Rouse CJ, Hawkins K, Kabbej N, Dalugdug J, Kunta A, Kim MJ, Someya S, Herbst Z, Gelb M, Dinelli I, Butterworth E, Falk DJ, Rosenkrantz E, Elmohd H, Khaledi H, Mowafy S, Ashby F, Heldermon CD
Hum Mol Genet, 2023 Jan 13, 32(3): 417-430
https://doi.org/10.1093/hmg/ddac209 | PMID: 35997776 | PMCID: PMC9851742
Citations: 2 | AltScore: 0.75
11. **Feasibility of a Smartwatch Platform to Assess Ecological Mobility: Real-Time Online Assessment and Mobility?Monitor.**
Smail EJ, Alpert JM, Mardini MT, Kaufmann CN, Bai C, Gill TM, Fillingim RB, Cenko E, Zapata R, Karnati Y, Marsiske M, Ranka S, Manini TM
J Gerontol A Biol Sci Med Sci, 2023 May 11, 78(5): 821-830
https://doi.org/10.1093/gerona/glad046 | PMID: 36744611 | PMCID: PMC10172974
Citations: 1 | AltScore: NA
12. **Media Consumption and COVID-19-Related Precautionary Behaviors During the Early Pandemic: Survey Study of Older Adults.**
Smail EJ, Livingston T, Wolach A, Cenko E, Kaufmann CN, Manini TM
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https://doi.org/10.2196/46230 | PMID: 37213166 | PMCID: PMC10242469
Citations: NA | AltScore: NA
13. **Exercise and Behavior: Adjuncts to Pro-Myogenic Compounds for Enhancing Mobility in Older Adults.**
Storer TW, Pahor M, Woodhouse LJ, Lachman ME, Fielding RA
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Citations: NA | AltScore: NA
14. **Defining the age-dependent and tissue-specific circadian transcriptome in male mice.**
Wolff CA, Gutierrez-Monreal MA, Meng L, Zhang X, Douma LG, Costello HM, Douglas CM, Ebrahimi E, Pham A, Oliveira AC, Fu C, Nguyen A, Alava BR, Hesketh SJ, Morris AR, Endale MM, Crislip GR, Cheng KY, Schroder EA, Delisle BP, Bryant AJ, Gumz ML, Huo Z, Liu AC, Esser KA
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https://doi.org/10.1016/j.celrep.2022.111982 | PMID: 36640301 | PMCID: PMC9929559
Citations: 13 | AltScore: 56.43

15. **Mechanosensitive GPCRs and ion channels in shear stress sensing.**
Xiao R, Liu J, Shawn Xu XZ
Curr Opin Cell Biol, 2023 Oct, 84: 102216
https://doi.org/10.1016/j.ceb.2023.102216 | PMID: 37595342 | PMCID: PMC10528224
Citations: NA | AltScore: NA
16. **Reducing tobacco-associated lung cancer risk: a study protocol for a randomized clinical trial of AB-free kava.**
Xing C, Malaty J, Malham MB, Nehme AMA, Freeman B, Huo Z, Firpi-Morrel R, Salloum RG
Trials, 2023 Jan 18, 24(1): 36
https://doi.org/10.1186/s13063-023-07081-x | PMID: 36653872 | PMCID: PMC9847434
Citations: NA | AltScore: 2

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MINORITY RESEARCH

General Brief Description of Minority Activities:

1. **Project Title:** **Cardiac Dysfunction in Older Sepsis Survivors**
   Leader(s): **MANKOWSKI, ROBERT TOMASZ**
   UNIVERSITY OF FLORIDA
   American Heart Association (AHA) 18CDA34080001 / (2018-2021)

   As a result of sepsis, approximately 30% of older Americans (age >65 years) have elevated levels of systemic inflammation at discharge from the intensive care unit (ICU) and die from cardiovascular (CV) events, including congestive heart failure, within 12 months. Although recently improved implementation of evidence-base high-risk new population for cardiac disease and death within 12 months post-sepsis. Cardiac dysfunction after discharge (i.e., impaired cardiac contractility) that may lead to cardiomyopathy and heart failure after sepsis, however, has not been characterized in this high-risk population. Novel measures of myocardial contractility the infrastructure of the NIH-funded project (P50GM111152202) at the University of Florida that is currently successfully enrolling and following sepsis patients for up to 12 months. For the proposed pilot study, we will perform biventricular myocardial contractility analyses and peripheral blood analyses for pro-inflammatory cy and help develop anti-inflammatory interventions to lower the CV risk in older sepsis survivors. (AHA Program: Career Development Award)

2. **Project Title:** **Role of PFKFB3 in peripheral artery disease**
   Leader(s): **RYAN, TERENCE**
   UNIVERSITY OF FLORIDA
   American Heart Association (AHA) 18CDA34110044 / (2018-2021)

   Peripheral artery disease (PAD) is a leading cause of atherosclerotic cardiovascular disease death which is estimated to affect more than 20% of individuals older than age 60 (~200 million people worldwide). PAD is defined as a blockage in the peripheral arteries which results in decreased blood flow to the lower legs. Patients v interventions aimed to improve blood flow to the leg, but mortality rates in PAD remain high (50% within 10 years of diagnosis). The low success rate of PAD therapies indicates that restoration of blood flow alone is not sufficient to rescue the limb, implying that factors other than limb perfusion regulate the limb's response to i systemic glycolytic flux display complete protection from ischemic muscle necrosis; (ii) among the genes responsible for elevated glycolytic flux, PFKFB3 is required for ischemic protection; and (iii) PFKFB3 protein expression is decreased in severe PAD patients. Based on these discoveries, we hypothesize that glycolytic met through metabolomics/proteomics experiments. This work will advance fundamental knowledge on ischemic cell metabolism, develop novel gene therapies, and offer mechanistic insight applicable to multiple diseases and tissues.

3. **Project Title:** **Calf Muscle Mitochondrial Dysfunction and Impaired Autophagy in Peripheral Artery Disease**
   Leader(s): **LEEUWENBURGH, CHRISTIAAN**
   UNIVERSITY OF FLORIDA
   American Heart Association (AHA) 18SFRN33900136 / (2018-2022)

   Lower-extremity peripheral artery disease (PAD) results in ischemia-reperfusion-induced oxidative stress in calf skeletal muscle and reduced skeletal muscle metabolic activity, but the specific mitochondrial defects and their association with functional impairment and decline in people with PAD are not established. In this basic- transport chain (ETC) proteins have greater damage, resulting in poorer ETC function in PAD compared to those without PAD. In Aim 1B, we will investigate the D-loop region of mtDNA involved in regulating mtDNA replication, to determine if the increased mtDNA abundance in PAD is due to oxidative stress. Aim 1C will of >0.20 between their legs. We will determine whether: a) the leg with lower ABI (more ischemia) has greater mitochondrial abnormalities than the leg with higher ABI (less ischemia); b) mitochondrial abnormalities are associated with greater functional impairment and faster functional decline in PAD participants; and c) PAI associated with skeletal muscle pathophysiologic changes in PAD. Results are expected to identify new potential targets for interventions that may improve functional performance and prevent functional decline in PAD. (AHA Program: Strategically Focused Research Network)

4. **Project Title:** **Longitudinal Modeling and Sequential Monitoring of Image Data Streams**
   Leader(s): **QIU, PEIHUA**
   UNIVERSITY OF FLORIDA
   National Science Foundation 1914639 / (2019-2022)

   In imaging applications related to earth and environmental monitoring, manufacturing industries, medical studies and many others, collected image data are often in the form of data streams in the sense that new images are acquired sequentially over time. In such applications, one fundamental task is to monitor the image sequen distributed freely for convenient use by practitioners. A web portal will also be developed for individual researchers to try the proposed methods. The PI plans to integrate the research results into educational activities, including the development of new curriculum modules, the mentoring of Ph.D. students, and outreach to local h model for describing observed images in a given time interval is flexible, and its estimation procedure has the edge-preservation property while removing noise. It can accommodate both geometric misalignments among observed images and spatio-temporal data correlation in the observed image data. The proposed image monit

5. **Project Title:** **Mitochondrial Function in Postmortem Muscle**
   Leader(s): **SCHEFFLER, TRACY**
   UNIVERSITY OF FLORIDA
   United States Department of Agriculture 2017-67017-26468 / (2017-2021)

   Our goal is to understand how mitochondria influence postmortem metabolism and tenderization, in order to optimize meat quality and value. Living muscle relies primarily on mitochondria and aerobic metabolism for energy; ATP is necessary for muscle contraction and relaxation, and to fuel active transport and maintain ion g and result in pH declining to a final or ultimate pH (pHu) near 5.6. At this point, ATP is exhausted and no longer generated, and rigor is complete and additional ATP is not generated by metabolism. The rate and extent of metabolic processes postmortem significantly impact water holding capacity, color, and protease-mediated t properties influence mitochondria function and integrity. Our objectives are to evaluate changes in mitochondrial function in oxidative and glycolytic muscles during the first 24h postmortem determine mitochondrial function in oxidative and glycolytic muscles under pH and oxygen tension conditions that simulate postmortem r

6. **Project Title:** **Identifying Genes That Regulate Mitochondrial Positioning at the Synapse During Aging**
   Leader(s): **HAN, SUNG MIN**
   UNIVERSITY OF FLORIDA
   American Federation for Aging Research (AFAR) AGR00015406 / (2019-2021)

   A decline in the functions of the nervous system is a hallmark of aging, and can lead to many age-related changes in balance, mobility, hearing, vision, smell, and taste. The function of the nervous system depends on the maintenance of synapses-the special contact area where neurons communicate with other neurons. Many lines mediate mitochondrial positioning at synapses and how aging affects this regulation remain unclear. Our goal is to uncover the underlying mechanisms that regulate mitochondrial positioning and function at the synapse during the aging process. My proposed aims are based on my hypothesis that mitochondrial localization at the mitochondrial localization at the synapse, we have established an innovative visual genetic screen for assessing mitochondrial distribution in the AIY interneuron of Caenorhabditis elegans. We anticipate that these screens will identify novel molecules that regulate mitochondrial targeting or anchoring at the synapse. As evidence understanding the maintenance of synaptic function in aging and other neuronal diseases associated with abnormal mitochondrial positioning and function.

7. **Project Title:** **CEREBRAL NETWORKS OF LOCOMOTOR LEARNING AND RETENTION IN OLDER ADULTS**
   Leader(s): **CLARK, DAVID J**
   VETERANS HEALTH ADMINISTRATION
   VA I01RX003115 / (2019-2023)

   Aging often leads to substantial declines in walking function, especially for walking tasks that are more complex such as obstacle crossing. This is due in part to a lack of continued practice of complex walking (sedentary lifestyle) combined with age-related deficits of brain structure and the integrity of brain networks. Neurorehe is a need for research to develop strategies for enhancing motor learning of walking (?locomotor learning?) in order to improve the effectiveness of neurorehabilitation. The objective of this study is to use non-invasive brain stimulation to augment locomotor learning and to investigate brain networks that are responsible for locor proposed study is designed to address this gap. Our pilot data from older adults shows that prefrontal transcranial direct current stimulation (tDCS) administered during learning of a complex obstacle walking task contributes to multi-day retention of task performance. In the proposed study we will build upon this pilot work by c with individual differences in baseline and practice-induced changes in brain measures (working memory, gray matter volume, task- based prefrontal activity, and brain network segregation). Specific Aim 3: Investigate the extent to which tDCS modifies resting state network segregation. We anticipate that prefrontal tDCS will a

8. **Project Title:** **AEROBIC EXERCISE AND COGNITIVE TRAINING IN OLDER ADULTS**
   Leader(s): **NOCERA, JOE ROBERT**
   VETERANS HEALTH ADMINISTRATION
   VA IK2RX000744 / (2012-2018)

   DESCRIPTION This proposal, 'Aerobic Exercise and Cognitive Training in Older Adults', is resubmission for a Career Development Award- Level 2 with Dr. Joe R. Nocera as the Principal Investigator and a mentoring team of Drs. Bruce Crosson, Ron Shorr, Marco Pahor and Michael Marsiske. Dr. Nocera received his undergr Florida. Dr. Nocera then received a CDA-1 aimed at studying the effects aerobic exercise on executive language function in older adults. It was hypothesized, and demonstrated in the preliminary CDA-1 work, that the robust documented benefits of aerobic exercise on cognition could carry over to more specific executive langua purpose of designing interventions aimed at improving function and quality of life in older veterans. Specific training components in the proposal include; skills in cognitive neuroscience with specific training in cognitive aging, measurement, neuroanatomy, and basic imaging approaches. Additionally, the proposal is designed t generalizability of the cognitive training. Importantly, this study wil focus on older veterans at-risk for mobility disability. This area is of particular importance for he VA system, considering a large percentage of veterans are entering old age and therefore likely to suffer from age-related cognitive decline and mobility disability. arm will consists of a popular commercially-available brain fitness program that has demonstrated specific cognitive improvements and high adherence. Ultimately, this investigation will substantially advance the development of treatments for cognitive impairment because these goals explore an intervention that may potentially

9. **Project Title:** **PHARMACOLOGICAL MANAGEMENT OF PAIN IN ALZHEIMER'S DISEASE AND RELATED DEMENTIA**
   Leader(s): **WEI, YU-JUNG**
   UNIVERSITY OF FLORIDA
   NIH K01AG054764 / (2017-2022)

   Summary: My career goal is to become an independent geriatric pharmacoepidemiologist with expertise inpharmacotherapy quality measurement and outcomes evaluation in the fields of pain and aging. The clinicalfocus of my research has centered on the management of multi-morbidity in older adults and particularly, theinterp hasattempted to establish the effect of adequate pain control on preventing mental health (MH) disorders. Thegoal of my K01 proposed research is to provide preliminary data that improve our understanding of currentpain medication prescribing and potential discrepancies between practices and pain guidelines, and toformulate l validating MDS-based pain, depression, and behavioral symptoms against medical records at two nursinghomes (Aim 1). With the nationally representative Medicare-MDS data, we explore the quality ofpharmacological pain management and its determinants among ADRD and non-ADRD residents with non-cancer pain (Aim 2 3). This project is well tailored for me to apply the knowledge and skills that will beobtained from training activities with my Primary Mentor, Dr. Almut Winterstein (pharmacoepidemioloy, qualitymeasurement and outcome assessment) and Co-Mentors: Drs. Roger Fillingim (pain), Marco Pahor (aging),Babette Brumback (advi results from this line of research are expected to lead to better pharmacological painmanagement and improved pain and health outcomes in older adults with cognitive impairments.

10. **Project Title:** **INVESTIGATIONS OF BOTANICALS ON FOOD INTAKE, SATIETY, WEIGHT LOSS, AND OXIDATIVE**
    Leader(s): **ANTON, STEPHEN D**
    UNIVERSITY OF FLORIDA
    NIH K23AT004251 / (2009-2014)

    DESCRIPTION (provided by applicant): My training to date has provided me with a solid understanding of the behavioral, psychosocial, and environmental factors that contribute to eating behavior and weight management; however, my understanding of physiology and the biological mechanisms regulating eating behavior an research investigating alternative and adjunctive treatments involving botanicals for age-related metabolic conditions (obesity, type 2 diabetes). My immediate career goals are to 1) obtain a R01 grant to further examine the potential effects of different doses of the selected botanical compounds on food intake, body weight, and that botanical compounds have in affecting food intake, neuroendocrine signals, satiety, weight loss, and oxidative stress levels. Study 1 will investigate the effects of two promising botanicals (garcinia cambogia derived hydroxycitric acid, and glucomannan) on food intake, satiety, and weight loss using a double-blind, placebo (i.e., DNA and RNA oxidation). PUBLIC HEALTH RELEVANCE: Botanicals represent important sources of potential new adjunctive therapies for obese and insulin resistant individuals and may enhance the health benefits of weight loss interventions by reducing systemic oxidative stress levels.

11. **Project Title:** **PICS: A NEW HORIZON FOR SURGICAL CRITICAL CARE**
    Leader(s): **MOORE, FREDERICK A**
    UNIVERSITY OF FLORIDA
    NIH P50GM111152 / (2014-2019)

    DESCRIPTION (provided by applicant): Despite 30 years of intensive research, morbidity and mortality of sepsis in surgical intensive care unit (ICU) patients remain unacceptably high. Although recent advances in early ICU care have reduced in-hospital mortality, with the aging population a new epidemic of chronic critical least in part, by dysregulated myelopoiesis and expansion of myeloid-derived suppressor cells (MDSCs), aggravated by aging and largely driven by acute kidney injury (AKI), resulting in imbalance of angiogenic and anti-angiogenic factors. This Sepsis and Critical Illness Research Center (SCIRC) application comprises four p ICU patients and what are the long-term cognitive and functional consequences? #1b) Can novel biomarkers predict, early, which patients will develop CCI, and, later, which CCI patients will have morbid long-term outcomes (i.e., PICS)? #2) Is PICS inherently driven by dysregulation in myelopoiesis and inappropriate MDSC reduce inflammation, and alter the trajectory of CCI away from the PICS phenotype? We will study 400 surgical ICU patients who develop sepsis for at least one year, and use murine models of chronic polymicrobial sepsis for mechanistic studies and interventional methods. We recognize that no single therapeutic intervention understood and novel therapies developed.

12. **Project Title:** **ADAPTABILITY AND RESILIENCE IN AGING ADULTS (ARIAA)**
    Leader(s): **BARTLEY, EMILY J.**
    UNIVERSITY OF FLORIDA
    NIH R00AG052642 / (2016-2021)

    Growing evidence supports the presence of dysregulated pain modulation in older adults, an effect which may heighten age-associated risk for chronic pain. While persistent pain is common in older adults, chronic low back pain is the leading cause of disability in this population and results in significant impairments in psychos fostering adaptive physiological and affective responses to pain. Given this, capitalizing on positive resources is a promising target for enhancing pain adaptation, and is especially salient to older adults given the burden of high-impact pain in this group. Therefore, the overall goal for this mentored career development applicatic and assessment of psychosocial and biological (i.e., inflammatory, neuroendocrine) markers associated with pain and resilience; and 3) augment training in the design, implementation, and analysis of randomized clinical trials. The proposed study is delineated into two phases. Study 1 (K99 Phase) will examine associations amo effects on pain modulatory function and patterns of pain- evoked recovery in physiological and affective systems, and will establish whether a resilience-oriented intervention confers benefits in psychosocial and physical functioning in older adults with chronic low back pain. The proposed career development plan extends fron

13. **Project Title:** **ESTROGEN AND COGNITION OVER THE LIFESPAN**

d ICU care has resulted in decreased early hospital mortality in older adults, many survivors become chronically critically ill (CCI) with persistent inflammation and fail to recover. CCI patients are defined as patients who remain in the ICU for more than 14 days with organ failure, in contrast to those who experience rapid recovery (RA
by speckle-tracking echocardiography can detect clinically meaningful dysfunction undetectable by conventional echocardiography (i.e., ejection fraction). Therefore, we propose an observational pilot study to test our central hypothesis that the persistent systemic inflammation that occurs in CCI patients following sepsis is associated v
/tokine levels in a subset of older (>65 years) sepsis patients (CCI=40 and RAP=40) enrolled in the parent P50 study at discharge (RAP) or at day 14 in ICU (CCI) and 3 months after sepsis onset. This research project is in close alliance with the mission of the American Heart Association because of the high risk of cardiac events and de

vith PAD present clinically with symptoms ranging from mild discomfort to unbearable ischemic rest pain and gangrene. Recent clinical work has demonstrated that patients with similar limb blood flow can have markedly different symptoms, suggesting that the patients' response may be dependent on genetic mechanism(s) regulating th
schemia. This proposal seeks to address this knowledge gap by advancing the fundamental knowledge on ischemic cell metabolism in both skeletal muscle and endothelial cells, with a long-term goal of developing novel therapies to improve ischemic outcomes in PAD and other ischemic disease. This proposal focuses on the role of glyc
abolism, driven by PFKFB3 expression, regulates muscle cell survival and angiogenesis in ischemia. We will test this hypothesis using the following: Aim 1 will determine if loss of PFKFB3 expression increases ischemic pathology; Aim 2 will determine if overexpression of PFKFB3 is protective against ischemic injury; and Aim 3 will

-science research study of Northwestern Universitys Strategically Focused Research Network (SFRN), we will delineate the specific mitochondrial abnormalities in calf muscle of people with PAD. In Aim 1, we will analyze calf-muscle biopsy specimens stored at Northwestern from 75 well-characterized people with and without PAD.
investigate whether autophagy, the process that removes damaged mitochondria is incomplete in PAD. In Aim 2, we will analyze calf-muscle biopsies collected in the SFRNs population/epidemiology study (PI Greenland). This project will recruit 50 participants with PAD and 50 without PAD and follow them longitudinally with baselir
) participants have more adverse changes in their muscle at 2-year follow-up than non-PAD particpants. In Aim 3, we will analyze calf-muscle biopsies from the NICE trial (PI McDermott) to determine whether the NICE Trial interventions significantly increase activity of pathways involved in mitochondrial biogenesis and metabolic h

ce to see whether the underlying longitudinal process of the observed images changes significantly over time. This project aims to develop novel and effective statistical methods for answering this question. Because of the wide applications of image sequence monitoring, this project will have broader impacts on society through its appli
igh schools students for after-school activities to raise their interests in data modeling and scientific research, and contribute to the workforce development in Science, Technology, Engineering and Mathematics. This project aims to develop a flexible longitudinal modeling approach and an effective sequential monitoring scheme for ana
oring approach can account for dynamic longitudinal patterns of the observed image data streams. To this end, image pre-processing, including image denoising and image registration, will be performed properly before image monitoring. The proposed methods will consider both cases where the observation times are equally or unequall

radients. In fact, mitochondrial density varies in muscle cells and is a key factor influencing energy producing capacity. At slaughter, exsanguination eliminates the blood supply to muscle cells, and oxygen is no longer delivered to mitochondria for oxidative phosphorylation. Anaerobic glycolysis predominates in the postmortem period;
tenderization of meat. Because the oxygen supply to muscle is removed at harvest, the contribution of mitochondria to postmortem metabolism and meat quality has been largely disregarded. However, the role of mitochondria in cellular function and homeostasis is multifaceted and extends beyond ATP production. Our overall objective
nuscle assess mitochondrial respiration and postmortem metabolism in longissimus muscles with varying mitochondrial content.

s of?evidence suggest that the function and structure of synapses change with aging. At the synapse, mitochondria remain tightly packed to supply adequate energy and maintain calcium homeostasis. These mitochondrial functions are required to support synaptic function. Despite clear evidence supporting the important role of mitochon
synapse is actively regulated by currently unknown molecules in response to local demand for mitochondrial support and function. We will apply our expertise in cell biology and our novel imaging approaches to discover short- and long-term changes in mitochondrial behavior at synapses in a wide range of genetic backgrounds in resp
supporting the strength and feasibility of this approach, our unsaturated pilot screens have already identified several mutants with abnormal mitochondrial targeting to the synapse. Successful completion of the proposed research will substantially increase the knowledge base of how synaptic mitochondria respond to aging. We expect th

bilitation can contribute to recovery of lost walking function in older adults, but major and persistent improvements are elusive. A cornerstone of neurorehabilitation is motor learning, defined as an enduring change in the ability to perform a motor task due to practice or experience. Unfortunately, in most clinical settings, the time and c
notor learning in mobility-compromised older adults. We have shown that frontal brain regions, particularly prefrontal cortex, are crucial to control of complex walking tasks. Our neuroimaging and neuromodulation studies also show that prefrontal cortex structure and network connectivity are important for acquisition and consolidation
onducting a full scale trial that also investigates mechanisms related to brain structure, functional activity, and network connectivity. We will address the following specific aims: Specific Aim 1: Determine the extent to which prefrontal tDCS augments the effect of task practice for retention of performance on a complex obstacle walkin
ugment retention of locomotor learning, and that our data will provide the first evidence of specific brain mechanisms responsible for locomotor learning/retention in older adults with mobility deficits. This new knowledge will provide a clinically feasible intervention approach as well as reveal mechanistic targets for future intervention

raduate degree (B.A., 2001) from the University of California, Los Angeles. He completed his graduate degrees in Kinesiology from the University of Nevada, Las Vegas (M.S., 2004) and the University of Georgia (Ph.D., 2007). Following completion of his terminal degree, Dr. Nocera earned a post- doctoral fellowship under a National
ge functions. Concurrently, the CDA-1 was designed to increase Dr. Nocera's understands of cognitive neuroscience thus bridges the gap between cognitive functions and Dr. Nocera's previous education emphasis of physical function in older adults. The general purpose of the career development in this CDA-2 application is to further a
develop Dr. Nocera's skills in clinical/translational research necessary for high-quality clinical trials research. The purpose ofthe CDA-2 study will build on the CDA-1, which demonstrating an improvement in cognitive function via aerobic exercise, by adding a cognitive training component that will be done immediately following the
To address our research question 60 older veterans (age 65-89) will be randomized to one of two 12-week intervention groups: 1) Cognitive Training alone (CT) or 2) Aerobic Exercise + Cognitive Training (AE+CT). The aerobic exercise arm of the study will follow the same format shown to improve a broad range of executive functio
have pervasive effects on patient quality of life from a cognitive as well as a physical standpoint. Concurrently, this proposal will provide Dr. Nocera with the skill necessary to grow into a successful, independent VA Research.

lay of mental and physical disease and its treatment. One example of combination of health problems iselderly patients who live with Alzheimer's disease and related dementia (ADRD) and also suffer from chronicpain. To date, data on quality of pain medication prescribing and the sequelae of poor pain control in patientswith ADRD ar
ypotheses for future research regarding the role of pain control in reducing MH problems in ADRD.We propose a longitudinal design using 4 years (2011-2014) of Medicare 5% sample whose billing records arelinked to nursing home resident assessment data (Minimum Data Set, MDS, 3.0). Because it is unclearwhether MDS 3.0 can a
). The quality will be examined based on five common clinical standards--pain medicationselection, pain medication scheduling, pharmacological prevention of drug adverse event, contraindicatedmedication use, and overall pain control. We then explore the extent to which pain control is associated with adecreased risk for select MH d
anced methods for longitudinal data), and Laurence Solberg (clinical geriatric care andassessment). For further guidance, I enlist the expertise of Dr. Siegfried Schmidt in the field of pain medicineand Dr. Steven DeKosky in ADRD. This K01 award will provide protected time for me to receive trainingneeded to prepare an R01 grant app

d body weight remains to be improved. Therefore, I seek to increase my knowledge of the physiological aspects of age- related metabolic conditions, and the potential role botanical extracts may have in affecting physiology, eating behavior, body weight, and oxidative stress levels. This knowledge, coupled with my previous training, wi
oxidative stress levels and 2) increase my understanding of the effects that botanicals have on physiological processes related to food intake. My long-term career goal is to become an independent investigator focused on developing safe and effective alternative or adjunctive interventions involving natural compounds for the treatment o
controlled design. Based on the findings from study 1, the botanical with the most significant effects on food intake will be used in a 24-week, placebo controlled calorie restricted weight loss trial. In addition to body weight, this trial will examine the effects of the selected compound on: 1) food intake, 2) self-reported satiety, 3) postpra

illness (CCI) has emerged and its progression into what we call the persistent inflammation, immunosuppression and catabolism syndrome (PICS) has unacceptable morbid long-term consequences. Our overarching hypothesis is that PICS is now a predominant clinical trajectory in the surgical ICU patients after sepsis, and is the greatest
rojects and five cores drawn from two colleges (Medicine and Public Health and Health Professions) and eight University of Florida Health departments (Surgery, Medicine, Anesthesiology, Biostatistics, Molecular Genetics and Microbiology, Aging and Geriatric Research, and Physical Therapy) and will address the following questions
expansion, promoting persistent inflammation, immunosuppression and catabolism?; #3) Does AKI, through dysregulation of anti-angiogenic and angiogenic cytokines, drive the expansion of MDSCs, inflammation, and anti-angiogenesis?; and #4) Does CCI contribute significantly to muscle atrophy, especially in mechanically ventilat
will prevent PICS, but the SCIRC's overall goal is to understand the prevalence and pathogenesis of this new syndrome at a mechanistic level. Only through multi-disciplinary translational research by basic and clinical scientists with diverse expertise in critical care medicine, physical therapy, immunology, molecular biology, and under

ocial and physical functioning. Given reports of suboptimal treatment of pain in older adults, improvements in pain management in this cohort are of critical importance. Resilience is characterized as a dynamic process resulting in positive adjustment and adaptation after exposure to adversity. The benefits of resilience in health-related
on (K99/R00) is to fill this knowledge gap and characterize resilience mechanisms associated with adaptive pain modulatory capacity in older adults with chronic low back pain. Primary training goals for the current application are to: 1) develop a comprehensive knowledge base in biopsychosocial processes of aging and enhance training
ong measures of resilience, biological markers of inflammation and neuroendocrine activity, and pain modulatory capacity in older adults with chronic low back pain. Increased knowledge and understanding of the resilience pathways that promote adaptability to pain will allow for the development of a targeted resilience intervention dur
the PI's prior work on affective regulation and mechanisms of vulnerability in chronic pain, and will forge a path towards understanding and investigating psychological therapies of resilience that improve pain and disability in older adults.

P). Due to persistent inflammation, we believe that older CCI patients represent an extremely
vith impaired myocardial contractility over 3 months after sepsis onset. We will capitalize on
aths among older adults after sepsis. A future long-term study may help predict heart failure

ıe limbs response to decreased blood flow. The current treatments for PAD include surgical
:olytic metabolism in the ischemic limb based on the following discoveries: (i) mice with elevated
l identify novel metabolic targets/pathways regulating ischemic pathology in human PAD samples

Aim 1A will test the hypothesis that mitochondrial (mt)DNA regions that encode the electron
ıe and 2-year follow-up biopsies. Of those with PAD, 30 will have an Ankle-Brachial Index (ABI)
ealth, compared to placebo. This projects overall goal is to identify specific mitochondrial defects

:ations in different disciplines and areas. Open source R packages will be developed and
lyzing image data streams, and study their statistical properties. The proposed longitudinal
y spaced.

breakdown of glycogen generates lactate and H+, which accumulate in postmortem muscle
is to define how postmortem conditions and inherent muscle metabolic and contractile

dria at synapses, and the effect aging has on synaptic function, the molecular mechanism(s) that
onse to aging and acute mitochondrial stressors. To reveal new mechanisms that mediate
is research to have widespread implications in the neurobiology of aging, particularly in

ost demands of delivering a sufficiently intensive motor learning intervention is not feasible. There
ı of new motor skills. However, a major gap exists regarding learning of walking tasks. The
g task. Specific Aim 2: Determine the extent to which retention of performance is associated
s to enhance locomotor learning and rehabilitation.

l Institute of Health T32 training grant within the Department of Neurology at the University of
nd more substantially develop Dr. Nocera's understanding of cognitive neuroscience for the
aerobic exercise. It is hypothesized that the aerobic exercise will potentiate and increase the
ns in older adults in previous research as well as our CDA-1 pilot work. The cognitive training

e scarce. Studies investigating these associations are limited by small sample size, and none
ccurately detect patients with pain and MH disorders, we first conduct a feasibility studyof
isorders, including depression, behavioral symptoms, anxiety, and sleepdisorders in ADRD (Aim
dication to examine pain medication practices and their impact on healthoutcomes in ADRD. The

ll provide an ideal foundation from which I can build a unique and independent line of
f obesity and other metabolic conditions. The proposed line of research will explore the role
ındial neuroendocrine signals (i.e., CCK, GLP-1, insulin, and leptin), and 4) oxidative stress levels

, near-term clinical challenge in surgical ICUs. We further hypothesize that PICS is caused, at
s in four projects: #1a) What is the incidence and early risk factors for CCI in septic surgical
ed patients' diaphragms and extremities, and will resistance exercise improve muscle strength,
rstanding of muscle, kidney, and aging physiology, can CCI progression into PICS be

ınctioning are manifold, and recent evidence suggests that resilience plays an important role in
in the assessment and treatment of older adults; 2) increase knowledge in the understanding
ring Study 2 (R00 Phase). This phase will provide the opportunity for examining intervention

Leader(s): **FOSTER, THOMAS C ; KUMAR, ASHOK ;**
UNIVERSITY OF FLORIDA
NIH R01AG037984 / (2010-2023)

AbstractSex differences are evident in vulnerability to age-related cognitive decline and diseases of aging. Estradiol(E2) is protective against neurodegenerative diseases, including Alzheimer?s disease, implicating sexhormone effects on sex differences in vulnerability. However, obstacles to sex steroid treatments includeclosin receptor(NMDAR)-mediated synaptic transmission examined several days after treatment. Aim 1 will test thehypothesis that E2 treatment, several days prior to testing, specifically influences NMDAR-dependentepisodic memory, such that it can rescue an age-related decline in episodic memory examined on the watermaze and E2 treatment will promote antioxidant enzyme activity, reduce oxidative stress, andminimize redox-mediated decrease in CaMKII activity and NMDAR function. Further, following closing of thetherapeutic window (i.e. for animals in which E2 does not rescue cognition and NMDAR function), E2treatment will not promote an particularly in gene body regions (introns), and specific to CpG,relative to non-CpG methylation sites. The proposed studies will employ a powerful combination of behavioraltests that are sensitive to NMDAR function, patch-clamp recording of NMDAR synaptic responses, measuresof oxidative stress and enzyme activity, tra

14. Project Title: **SENESCENCE AND GROWTH DIFFERENTIATION FACTORS AS MODIFIERS OF AGING**
Leader(s): **LEBRASSEUR, NATHAN K**
MAYO CLINIC
NIH R01AG055529 / (2018-2023)

PROJECT SUMMARY/ABSTRACTAging is the primary risk factor for the majority of chronic diseases. Studies in mice have implicated specificgrowth and differentiation factors (GDFs) and proteins secreted by senescent cells as potential modifiers ofaging. The objective of this proposal is to establish the rationale and provi health outcomes and can be altered by physicalactivity. Samples from the Lifestyle Interventions and Independence for Elders (LIFE) Study; the largest andlongest randomized trial of a physical activity intervention in older adults, will be used to test this hypothesis,and samples from the Health, Aging, and Body Composition (CCL11, ICAM1, AA and PAI2 are associated withbaseline measures of physical (i.e., gait speed, Short Physical Performance Battery (SPPB) score),cardiopulmonary (i.e., blood pressure, forced expiratory volume), and cognitive (i.e., processing speed,memory) function, inflammation, and prevalence of multimorbidity (based the number of chronic conditions (asin Aim 1), at 1 and 2 years in LIFE and at 2 and 4 years in HABC will be determined. Finally, Specific Aim 3 willaddress whether a structured physical activity intervention impacts longitudinal changes in GDF8, GDF11,CCL11, ICAM1, AA, and PAI2, compared to a health education contr may be viable targets for innovative therapiesto extend human healthspan.

15. Project Title: **INTERMITTENT PNEUMATIC COMPRESSION FOR DISABILITY REVERSAL IN PAD: THE INTERCEDE TRIAL**
Leader(s): **MCDERMOTT, MARY MCGRAE**
NORTHWESTERN UNIVERSITY AT CHICAGO
NIH R01AG057693 / (2018-2023)

PROJECT SUMMARY Our work and that of others has established that people with lower extremity peripheral artery disease(PAD) have greater functional impairment and faster rates of functional decline than people without PAD.However, few therapies improve functioning or prevent functional decline in people with PAD. suggests that IPC improves lower extremity blood flow and walking endurance in people with PADand that benefits persist for up to 12 months after intervention completion. However, evidence is limited bysmall sample sizes, high loss to follow-up, lack of blinding, and lack of sham controls. Clinical practiceguidelines do not (2 x 2 factorial design) of 230 PAD participants randomized to one of four groups:Group A: IPC + exercise; Group B: IPC + ?no exercise? control; Group C: sham control + exercise; and GroupD: sham control + ?no exercise? control. The IPC and sham interventions will be delivered for six months. Inour primary specific aim delineate mechanisms by which IPC affects walking performance, by measuringchanges in MRI-measured calf muscle perfusion, physical activity (measured with ActiGraph), and calf musclebiopsy measures of angiogenesis, muscle regeneration, mitochondrial biogenesis, mitochondrial activity, andautophagy. Based on precli intervention will have a major impact onpreventing mobility loss and improving quality of life in the large and growing number of people with PAD.

16. Project Title: **MECHANISMS OF OXYTOCINS ANALGESIA IN OLDER ADULTS**
Leader(s): **CRUZ-ALMEIDA, YENISEL ; EBNER, NATALIE C ;**
UNIVERSITY OF FLORIDA
NIH R01AG059809 / (2018-2023)

ABSTRACTOsteoarthritis (OA) represents a significant cause of disability worldwide in individuals aged 65 and older, arapidly growing segment of our population. The knee is the most commonly affected joint with pain being theprimary symptom, negatively impacting physical, cognitive, and emotional functioning. Sympto mechanisticmodel of OT's analgesic effects leveraging pilot data supporting efficacy and safety of self-administeredintranasal OT over 4-weeks in older individuals. Relative to placebo (P), daily administration of intranasal OTdiminished self-reported pain intensity, reduced experimental pain sensitivity, and increased self-repo effect ofintranasal OT administration on clinical and experimental pain sensitivity in older adults with symptomatic kneeOA and 2) characterize inflammatory mechanisms contributing to the inter-individual variability in analgesicresponses to OT. Older adults with symptomatic knee OA will self-administer intranasal OT or P management in older adults with littlepotential for addiction. Embedded in a biopsychosocial framework, our proposal will help pave the way for futureinvestigations using a mechanism-based treatment optimization strategy for individuals suffering from chronicpain.

17. Project Title: **ACTIVE ROLES OF GLIAL CELLS IN OLFACTION AND AGE-RELATED OLFACTORY DECLINE**
Leader(s): **XIAO, RUI**
UNIVERSITY OF FLORIDA
NIH R01AG063766 / (2019-2024)

Project SummaryAge-dependent olfactory decline (presbyosmia) is widely present in many species, including humans. At leastfifteen million Americans over 55 years old suffer from presbyosmia. By affecting the well-being, quality of life,and overall health, presbyosmia presents a significant challenge to public health. Patient physiology andhealth, the cellular and molecular mechanisms underlying presbyosmia are poorly understood (knowledgegap).As a major cell type in the nervous system, glial cells are typically considered as passive modulators duringneural development and synaptic transmission. Whether glial cells play active roles in sensory process across species.This proposal will bring together in vivo calcium imaging, optogenetics, molecular genetics, and behavioralanalysis to investigate and discover the molecular mechanisms through which the olfactory glial cells playactive roles in odorant detection and age-dependent olfactory decline. Since both olfaction

18. Project Title: **BIOBEHAVIORAL BASIS OF KNEE OSTEOARTHRITIS PAIN**
Leader(s): **CRUZ-ALMEIDA, YENISEL**
UNIVERSITY OF FLORIDA
NIH R01AG067757 / (2020-2025)

Discovery and validation of strong candidate biomarkers and clinical endpoints for pain is urgently needed that can be used to facilitate the development of non-opioid pain therapeutics from discovery through Phase II clinical trials. Emerging research using a combination of biomarkers deliver individualized predictions about biological changes using a biobehavioral perspective which is needed for predicting future health and to be able to use as clinical endpoints for interventions. The proposed study will prospectively address biobehavioral factors (i.e., cognitive, psychological, social and cultural) affecting the experience and interpretation of knee using a comprehensive biobehavioral multi- methods approach, we will be the first to prospectively determine the trajectory and interactions among pain, biological biomarkers and multiple domains of function within race/ethnic groups in OA pain. Findings will contribute towards increased understanding of pain and its biobe

19. Project Title: **THE EFFECT OF INTERMITTENT HEMIDIAPHRAGM STIMULATION DURING SURGERY ON MITOCHONDRIAL FUNCTION, SINGLE FIBER CONTRACTILE FORCE AND CATABOLIC PATHWAYS IN HUMANS**
Leader(s): **SMITH, BARBARA K ; BEAVER, THOMAS M ;**
UNIVERSITY OF FLORIDA
NIH R01AR072328 / (2017-2021)

Although mechanical ventilation (MV) is life-sustaining in patients with respiratory failure, it comes with a cost.MV dramatically reduces diaphragm contractility, induces ventilator-induced diaphragm dysfunction (VIDD) andsometimes leads to weaning failure. VIDD includes reduced mitochondrial respiration and increased prevents/attenuatesVIDD in the active hemidiaphragm.Mitochondrial function is central to energy metabolism and skeletal muscle function in a chronically activemuscle, such as the diaphragm. Although abnormal mitochondrial function is thought to precipitate VIDD inanimal models, limited data are available concerning mit a within-subjects experimental design,muscle samples from a stimulated hemidiaphragms will be compared with samples from the unstimulatedhemidiaphragm. We will investigate mitochondrial dysfunction and oxidative stress during prolonged CTS/MV,and the potential of ES to attenuate or prevent VIDD (Aim 1). Next, we mechanisms contributing to human VIDD. Our long-term goal is to test variousintermittent hemidiaphragm ES protocols on a larger population to determine its ability to prevent or attenuateVIDD. Data from this R01 application will advance our understanding of mechanisms giving rise to humanVIDD, and may inspire new th

20. Project Title: **REVIVE - RESVERATROL TO ENHANCE VITALITY AND VIGOR IN ELDERS**
Leader(s): **ANTON, STEPHEN D**
UNIVERSITY OF FLORIDA
NIH R01AT007564 / (2013-2019)

A large and growing number of older adults experience progressive declines in physical function, culminating in age-related physical disability with no clear connection to a single disease. Although the etiology of age-related physical disability is complex and multi-factorial, emerging evidence implicates the mitochondria as p and specific Sirtuins (i.e., SIRT3) in skeletal muscle, both of which are regulators of mitochondria biogenesis. The natural compound resveratrol appears to oppose the reductions in mitochondrial function associated with aging by affecting the expression of key genes, such as PGC-1a;, which support oxidative phosphorylation of resveratrol supplementation on mitochondrial function in older adults, or whether the hypothesized changes in mitochondrial function translate to improvements in physical functioning. Thus, the proposed randomized, parallel study will determine, in older men and women (> 70 years), whether 90 days of resveratrol supplen resveratrol (n=20), or 1500 mg/day of resveratrol (n=20) for a 90-day period. We will collect muscle specimens from the vastus lateralis and blood at baseline and 90 days for biochemical analyses, as well as monitor blood chemistries and adverse events at monthly clinic visits. If our hypotheses are supported, this study will be

21. Project Title: **THE BENEFITS AND HARMS OF LUNG CANCER SCREENING IN FLORIDA**
Leader(s): **BIAN, JIANG ; GUO, YI ;**
UNIVERSITY OF FLORIDA
NIH R01CA246418 / (2020-2023)

Lung cancer is the leading cause of cancer related death in both men and women in the United States. Currently, approximately 70% of lung cancer patients are diagnosed at advanced stages, and the 5-year survival rate of advanced stage lung cancer is very low, at only 16%. Investigators have been searching for effective screen years making history or former smokes who have quitted within the past 15 years. Since the release of the landmark NLST results, many medical associations published guidelines to recommend LDCT-based screening for individuals at high risk for lung cancer and the Centers for Medicare and Medicaid Services (CMS) also and policy makers started questioning whether the complication rate and false positives in real-world settings would be even higher than the rates reported in the NLST, which was conducted in a setting with well-established facilities and proficiency in cancer care. Therefore, we propose to understand the contemporary use of l related clinical information from clinical notes such as radiology reports; 2) to determine the appropriate and inappropriate use of LDCT among high-risk and low-risk individuals in Florida and to examine the test results of LDCT, the rates of invasive diagnostic procedures, postprocedural complications, and incidental findings patients and physicians better understand the harm- benefit tradeoff of lung cancer screening and transform such knowledge into practice to prevent avoidable postprocedural complications.

22. Project Title: **COCHLEAR DETOXIFICATION SYSTEM**
Leader(s): **SOMEYA, SHINICHI**
UNIVERSITY OF FLORIDA
NIH R01DC014437 / (2015-2020)

DESCRIPTION (provided by applicant): Living organisms are continuously exposed to and must defend against naturally occurring toxins and non- nutrient foreign chemicals (1-3). Cells possess a wide range of detoxification enzymes capable of removing thousands of toxic and foreign compounds. The glutathione transferase have become attractive drug targets. Epidemiological studies found a significant association between age-related hearing loss and GSTT1 and GSTM1 null polymorphisms was found in a Finnish population (5) and a Hispanic population (6). McElwee et al (7) conducted a cross-species comparative analysis to compare gene exp display increased expression of Gsta4, Gstm1, Gstm5, and Gstt1 genes in the cochlea. Collectively, these results suggest that GST detoxification enzymes may play an important role in ototoxicity. Cisplatin, a platinum-containing compound, is one of the most widely used chemotherapeutic agents (8-10). Evidence indicates tha associated with increased cisplatin resistance. Our preliminary study also found that cisplatin treatment up-regulates GSTA and GSTM genes in mouse cochlear organotypic cultures. Yet, how the cochlear detoxification system fights such ototoxic drugs at the molecular level remain poorly understood. The overall goal of our re

23. Project Title: **AUTOPHAGY IN LIVER INJURY**
Leader(s): **KIM, JAE-SUNG**
WASHINGTON UNIVERSITY
NIH R01DK079879 / (2007-2020)

DESCRIPTION (provided by applicant): Mitochondrial dysfunction is the major mechanism precipitating I/R injury which commonly occurs during liver surgery, trauma, hemorrhagic shock and liver transplantation. Sirtuin 1 (SIRT1) is an NAD+-dependent deacetylase that induces longevity, stress resistance and tumor suppre Accordingly, we propose that restoration or enhancement of hepatic SIRT1 will promote mitophagy and consequently ameliorate mitochondrial failure and liver dysfunction after reperfusion. To test our hypothesis, we will use hepatocytes isolated from SIRT1 wild type (WT) and knockout (KO) mice for characterization of cel establish novel therapeutic approaches for improving I/R-mediated liver failure.

24. Project Title: **Evaluation of an Adaptive Intervention for Weight Loss Maintenance**
Leader(s): **ROSS, KATHRYN MARIE**
UNIVERSITY OF FLORIDA
NIH R01DK119244 / (2019-2024)

Obesity remains a substantial public health challenge in the United States. Behavioral weight management programs have demonstrated effectiveness for weight loss, but long-term maintenance of these weight losses after the end of treatment tends to be poor. Evidence has demonstrated that individuals who can maintain their attendance at intervention sessions). Attendance has been closely tied to weight outcomes, but rates tend to be poor and decline over time. The once-per-month, static treatment schedules of existing programs may contribute to these suboptimal outcomes; a participant experiencing a small lapse in weight-related behaviors may adherence to program goals, and long-term weight maintenance outcomes. We propose to evaluate an innovative method of providing phone-based extended-care adaptive to participant needs. We have built a smartphone application that can be used by participants to track weight, dietary intake, and physical activity (key self-m propose to conduct a randomized controlled trial evaluating the impact of ADAPTIVE (delivered only when indicated by our algorithm or when initiated by participants via an in-app support request) versus STATIC (the monthly, pre-scheduled format used in existing extended-care programs) treatment provision on weight reg research will fill a critical gap in the weight management literature by building a foundational evidence base of proximal predictors of weight-related behaviors for future adaptive intervention development.

25. Project Title: **HEMATOPOIETIC STEM CELL DYSFUNCTION IN THE ELDERLY AFTER SEVERE INJURY**
Leader(s): **EFRON, PHILIP A**
UNIVERSITY OF FLORIDA
NIH R01GM113945 / (2015-2020)

g of the therapeutic window observed as decreased effectiveness of E2 treatment with advanced age.The goal of the proposed research is to provide an understanding of the mechanisms for E2 effects onmemory and the closing of the therapeutic window. Closing of the therapeutic window is marked by a decreasein E2-responseive transc
novel object recognition tasks. Aim 2 will test the hypothesis that E2 effects on memory andNMDAR function are mediated by reversal of NMDAR hypofunction, mediated by redox regulation ofphosphatase/kinase activity, similar to that previously described in aging males. Thus, it is predicted that priorto closing of the therapeutic wi
tioxidant enzyme activity or reduce oxidative stress, and the NMDAR responseand CaMKII activity will be decreased due to an oxidized redox state. Aim 3 will test the hypothesis that age-related changes in transcriptional responsiveness to E2 are due, at least in part, to epigenetic regulationthrough DNA methylation. It is predicted that
scription, and DNA methylation.

de robust clinical evidence for GDF8,GDF11, and senescence-related proteins cotaxin (CCL11), intracellular adhesion molecule 1 (ICAM1), activinA (AA), and plasminogen activator inhibitor 2 (PAI2), as indicators of biological age and age-related conditionsin humans. The central hypothesis is that circulating concentrations of GDFs
HABC) Study will be used to validate studyfindings. A novel multiplexed liquid chromatography-tandem mass spectrometry assay will be leveraged toaccurately quantify GDFs, and an advanced multiplexing platform will be used to measure senescence-relatedproteins in LIFE and HABC biospecimens. In Specific Aim 1, a multidiscipl
on the ICD-9 codes for 20 chronicconditions). In Specific Aim 2, the degree to which baseline concentrations of GDFs and senescence-relatedproteins predict longitudinal changes in a) gait speed and SPPB score, b) major mobility disability (i.e., theinability to walk 400m), c) combined cardiovascular events (e.g., myocardial infarction,
ol intervention, and the degree to whichchange in the concentrations of these proteins parallel change in the health outcomes described in Aim 2. Thesuccessful completion of the proposed research will fill an important translational gap in our understanding ofhow GDFs and senescence-related proteins predict and, therefore, potentially

Intermittent pneumatic compression (IPC) is a non-invasive intervention, consisting of an air pumpinside inflatable cuffs that are wrapped around the feet, ankles, and calves and worn for two hours daily. Every20 second, the cuffs rapidly inflate, followed by rapid deflation. During deflation, arterial blood return into thearteriovenous pr
mention IPC as a therapeutic option in PAD. A definitive randomized trial is needed. Walking exercise is first-line therapy for PAD. However, many PAD patients are unable or unwilling toexercise. Therefore, in people with PAD, we will determine whether IPC augments the benefits of exercise onwalking endurance and whether IPC
s, we will determine whether IPC combined with exercise improves the 6-minute walkat 6-month follow-up compared to exercise alone and whether IPC alone improves the 6-minute walk at 6-month follow-up, compared to sham control. In secondary aims, we will determine whether benefits of IPCpersist by re-measuring study outcom
nical evidence that IPC increases nitric oxide abundance and promotesvasodilation in skeletal muscle distant from the lower extremities, we will determine whether IPC improvessystemic endothelial function, by measuring changes in brachial artery flow-mediated dilation. If the IPC intervention with and without exercise improves funct

matic knee OAhas been traditionally attributed to peripheral mechanisms, but measures of joint damage only modestly accountfor the presence or severity of OA-related pain. The neuropeptide oxytocin (OT) has been recognized as amediator of endogenous analgesia in animal and human studies. However, little is known about theneuro
rtedphysical and emotional functioning. Further, participants treated with OT, compared to P, showed decreases inbrain metabolite concentrations associated with inflammation. Thus, our overarching goal is to evaluate theeffects of intranasal OT on pain and function in aging and to determine the extent to which central and peripheralin
ver 4 weeksusing a double-blinded, parallel study design. With strong support from the University of Florida and the McKnightBrain Institute, our interdisciplinary project, using a comprehensive multi-methods approach, will be the first todetermine the potential benefit of OT as a novel analgesic therapy for knee OA pain in aging. OT

s with presbyosmiaoften show a decreased interest in food, can withdraw socially, and exhibit higher rates of depression.Furthermore, many age-related neurological diseases, including Parkinson's disease and Alzheimer's disease,are commonly associated with olfactory dysfunction. In fact, olfactory loss often precedes various motorics
transductionand brain aging is not well understood. C. elegans is a well-established model organism for neuroscience andaging research due to its simple nervous system, short lifespan, and powerful genetic tools. Very importantly,genetic studies from multiple model organisms have shown that the evolutionarily conserved genetic prog
and aging areregulated by the evolutionarily conserved genes and signaling pathways, our innovative studies on C. elegansglial cells in olfaction and age-associated olfactory decline will provide mechanistic insights into similarprocesses in other species.

future brain and body health. Our own findings suggest that behavioral chronic pain characteristics are associated with multiple biological biomarkers where a greater pain burden is associated with accelerated detrimental biological processes. However, prospective research is urgently needed to determine pain?s impact on the heterogene
pain and physical function across racial/ethnic groups over time. We will prospectively assess pain along with multiple biomarkers as predictors of cognitive, psychological and physical functional progression among middle-aged and older non- Hispanic Blacks and non-Hispanic Whites with knee pain and controls over a four-year study
avioral basis, with the potential to reduce race/ethnic group disparities and improve pain-related health and functional outcomes.

xidativestress, muscle fiber damage and decreased diaphragm force production. In animal models, intermittentdiaphragm contraction during MV support attenuates VIDD. However, there are only limited data addressingthis problem in humans. Here, we propose to directly test the hypothesis that intermittent electrical stimulation(ES) o
ochondrial contributions to VIDD in humans. Of evengreater importance, there are no interventions available to attenuate these defects in humans. Here, we willtest the impact of an innovative experimental treatment, intermittent electrical stimulation (ES) of thehemidiaphragm during prolonged surgeries with MV, on mitochondrial fun
will investigate the effects of ES onsingle fiber contractile properties and Titin integrity (Aim 2). Finally, we will study the effect of ES on proteolyticpathways (caspase, calpain and ubiquitin-proteasome) and ribosomal RNA markers of decreased proteinsynthesis implicated in VIDD (Aim 3).This research will provide evidence concern
erapeutic strategies to maintain human diaphragm function during MV support.

laying a key role in the initial onset and progression of functional decline in many older adults. Additionally, our pilot data strongly suggest functional declines are associated with reductions in mitochondrial respiration, as well as decreases in oxidative mitochondrial enzyme activities and enzyme content. These changes were linked to a
and mitochondrial biogenesis. In another recently completed pilot study, we found resveratrol, at a dose of 1000 mg/day, significantly enhanced resting muscle oxidative metabolism (measured using near infrared spectroscopy), as well as cognitive and physical function, in older adults (age > 65 years). Despite promising findings from o
entation is associated with (i) increases in muscle mitochondrial function (State 3 & 4 respiration), (ii) increases in levels of PGC-1a, AMP-activated protein kinase (AMPK), and Sirtuins (i.e. SIRT1 and SIRT3), and (iii) improvements in functional performance, as well as metabolic risk factors. To achieve these aims, 60 moderate to le
the first to show that resveratrol improves mitochondrial function in muscle, and that these changes are associated with increased levels of physical function in moderate to low functioning older adults - the population who is at greatest risk of functional decline and physical disability.

ning modalities for the early detection of lung cancer so that patients can receive curative treatments at an early stage. When the National Lung Screening Trial (NLST) demonstrated the effectiveness of using low-dose computed tomography (LDCT) scan for lung cancer screening (LCS), researchers and physicians hope to save lives fro
ecided to cover the LCS for Medicare beneficiaries who are at high risk for lung cancer. While many efforts have been made to accelerate the dissemination the beneficial LCS, the concerns over the high false positive rates (96.4% of the positive results), invasive diagnostic procedures, postprocedural complications and health care costs
ung cancer screening and associated health care outcomes and costs using data from a real-world setting. Our study has three goals: 1) to develop an innovative computable phenotype algorithm to identify high-risk and low-risk individuals for LCS from both structured and unstructured (i.e., clinical notes) electronic health record (EHR)
in real-world settings; and 3) to develop and validate a microsimulation model of the clinical courses of LCS incorporating the real-world data in LCS to estimate the long-term benefits and the cost-effectiveness of LCS. Our proposed study has the potential to reduce lung cancer incidence and mortality by informing policymakers and p

(GST) detoxification system converts a non-polar toxic compound into a more water-soluble and less toxic form by conjugating the toxic compound to reduced glutathione by a variety of GST enzymes. GSTs are a superfamily of enzymes that are divided into several classes on the basis of their primary structure (1-3). Because of their
pression changes in long-lived worms, flies, and mice, and found that GST and other cellular detoxification gene categories were significantly up- regulated in long-lived members of the three species, suggesting the GST detoxification system plays a major role in longevity or protection against aging in multiple species. Consistent with t
t one-third of all cisplatin-treated patients develop hearing loss. Such hearing impairment is dose-dependent, irreversible, and associated with loss of hair cells. Wheeler et al (11) performed meta-analyses of over 3 million single-nucleotide polymorphisms (SNPs) for cisplatin-induced cytotoxicity in 608 lymphoblastoid cell lines from se
search proposal is to provide new basic knowledge of the molecular basis for the cochlear detoxification system and its role in the elimination of foreign chemicals throughout the lifespan.

ssion. The role of SIRT1 in ischemia/reperfusion-mediated liver injury is unknown. The goal of this study is to investigate the role of SIRT1 in I/Rinjury to liver and to develop therapeutic strategies to improve liver function after I/R. Our principal hypothesis is that calpain-dependent SIRT1 loss causes a sequential chain of defective mi
lular mechanisms causing SIRT1 depletion, defective mitophagy, and onset of the MPT and cell death after I/R. In addition, we will use anesthetized WT and KO SIRT1 mice to confirm and extend our in vitro findings to an in vivo model of hepatic I/R. Finally, we will extend and translate our findings from mice into human liver biopsi

hanges in eating and activity can successfully maintain their weight loss; thus, attempts to improve weight loss maintenance have often involved provision of continued support through monthly ?extended-care? intervention sessions. While these interventions have demonstrated significant improvements in weight loss maintenance, effe
ot receive support for several weeks, by which point they may be experiencing a larger lapse or weight regain. This can lead to feelings of frustration, shame, or embarrassment and disengagement from intervention. In contrast, tailoring intervention delivery such that sessions are provided when individuals are at ?high risk? for weight r
onitoring behaviors in traditional behavioral weight management programs) and can further query participants throughout the week regarding self-report factors (e.g., ratings of hunger and the importance of staying on track with weight management goals) that indicate high risk for weight regain. We have also developed a predictive alg
ain at 24 Months in 258 adults who successfully lose = 5% of initial weight during a gold-standard 16-week behavioral weight management program. Results of this study have clear treatment implications for the timing/frequency of sessions within extended-care weight maintenance programs, and this study will result in an innovative, l

ription and an inability of E2 treatment to enhance N-methyl-D-aspartate
ndow (i.e. in animals in which E2 treatment improves cognition and increasesNMDAR function),
decreased responsiveness of E2-sensitive genes will beassociated with DNA hypermethylation,

and senescence-related proteinsare associated with, and predictive of, clinically important
inary team will first determine theextent to which baseline concentrations of GDF8, GDF11,
heart failure, stroke); d)adjudicated falls and injurious falls, e) cognitive function (as Aim 1), and f)
mediate aging related disabilityand disease in older women and men. Ultimately, these proteins

essure gradient generates shear stress and stimulates nitric oxide production. Preliminaryevidence
alone improves walking endurance compared to sham control. We willconduct a randomized trial
es at twelve-month follow-up, six months after the IPC intervention iscompleted. We will also
tional performance and preventsfunctional decline in PAD, this non-invasive and well tolerated

biological mechanisms underlying OT's pain-relieving properties. This proposal is based on a
flammatory mechanisms contribute to these analgesic responses. We aim to 1) determine the
is currentlyused in obstetrics and may be an inexpensive, effective method for pain

ymptoms in these deadly neurological diseases. Despite the importance of olfaction to human
ramsand signaling pathways play pivotal roles in regulating sensory transduction and aging

city of these biological processes within an individual to elucidate the underlying patterns of
/ period. With strong support from the University of Florida, our interdisciplinary project,

f the human hemidiaphragm during prolonged cardiac surgeries with MV support
ction, single fiber contractileproperties and catabolic muscle pathways in human diaphragm. Using
ning the ability to improve mitochondrial function in the stimulatedhemidiaphragm, and identify

large decline in peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a)
ne recent clinical trial involving obese, middle-age men, no study to date has examined the effects
w functioning participants will be randomized to receive a placebo (n=20), 1000 mg/day of

m lung cancer by screening high-risk population who aged 55 to 77 years and have a 30 pack
may hinder the utilization of lung cancer screening. This concern was magnified as researchers
data and to develop advanced natural language processing (NLP) methods to extract LCS
ractitioners on the appropriateness of contemporary use of LCS. This knowledge will help both

cytoprotective role and involvement in the development of resistance to anti-cancer agents, GSTs
hese reports, our preliminary studies found that long-living calorie-restricted C57BL/6 mice
ven HapMap panels. The study found that increased GSTM1 and GSTT1 expression was

itophagy, mitochondrial permeability transition (MPT) onset and hepatocyte death after I/R.
es. These studies provide critical mechanistic insights into lethal I/R injury to the lver, and will

cts have been modest. A key challenge is continued participant engagement (often assessed as
egain offers potential to disrupt this cycle and significantly improve program engagement,
gorithm that uses this data to identify when individuals are at ?high risk? of weight regain. We
ow-cost, and easily scalable intervention for weight loss maintenance. Further, the proposed

DESCRIPTION (provided by applicant): People of advanced age (greater than 55 years old) have significantly increased morbidity and mortality after trauma. Since the elderly population is expanding, research into this disease process is increasingly relevant, especially with the escalating economic and health care burdens on
aged after severe injury and subsequent infections. Specifically, neutrophils are replaced after inflammation through a process known as 'emergency myelopoiesis.' This occurs after severe injury when bone marrow granulocyte stores are rapidly released, and increased stem cell proliferation and differentiation along myeloid pat
associated with aging modifies the emergency myelopoietic response to traumatic injury, resulting in inappropriate differentiation and maturation of myeloid cells, leaving the host susceptible to subsequent infection. We further propose that this failure of emergency myelopoiesis is due to age-associated, chronic activation of N
properly expand and differentiate along myeloid pathways in the elderly response to trauma, and, if the resultant dysfunctional neutrophil population seen in the elderly after trauma results from these suboptimal ST-HSCs; (2) determine if the defects in aged ST-HSC function after severe injury, as compared to their juvenile coo
in aging is due, at least in part, to defects in myelopoiesis that lead to genotypically, phenotypically and functionally deranged PMNs that fail to control infection. The third specific aim will translate our 'bench side' animal work to humans and this innovative approach could identify areas for intervention in cell types that are sti

26. Project Title: **THE ROLE AND MECHANISMS OF LIPID AND LIPOPROTEIN DYSREGULATION IN SEPSIS**
Leader(s): **GUIRGIS, FAHEEM W**
UNIVERSITY OF FLORIDA
NIH R01GM133815 / (2020-2025)

Sepsis is a dysregulated response to infection that has both fatal and non-fatal morbid consequences. Unfortunately, initial survival does not provide relief from morbidity for most sepsis survivors. Initial clinical trajectories include rapid recovery, early in-hospital death, and progression to chronic critical illness (ICU stay = 14
sepsis via several mechanisms (antioxidant/anti-inflammatory function, bacterial toxin clearance, steroid synthesis), but the exact mechanisms by which HDL and LDL protects against sepsis are not known. Lipid and lipoprotein dysregulation occurs in early sepsis, leading to failure to protect against sepsis. We have shown that
sepsis, and the severity of the drop is predictive of death; and 5) low baseline LDL levels are associated with increased long-term community-acquired sepsis risk. Highly biologically active lipid metabolites are also present in the circulation during sepsis that may propagate and promote inflammation resolution and contribute t
illness and sepsis recidivism). To test our hypothesis, we will capitalize on an established and experienced sepsis research team and the opportunity provided by an existing bank of samples from a diverse cohort of 80 community-acquired (CA) and 85 hospital-acquired (HA) sepsis patients from two-centers. This approach has
also propose two-site prospective enrollment of a small cohort of sepsis readmission patients to study this novel and important outcome. This project satisfies the NIGMS mission of researching biological mechanisms that underlay the foundation for advances in treatment of diseases such as sepsis.

27. Project Title: **IMPROVE PAD PERFORMANCE WITH METFORMIN. THE PERMET TRIAL**
Leader(s): **MCDERMOTT, MARY MCGRAE**
NORTHWESTERN UNIVERSITY AT CHICAGO
NIH R01HL131771 / (2016-2021)

PROJECT SUMMARY Improve PAD PERformance with METformin: The PERMET Trial. Our work and that of others has established that people with lower extremity peripheral artery disease(PAD) have greater functional impairment, faster functional decline, and increased rates of mobility losscompared to people without
propertiesof metformin in pre-clinical models that may benefit people with PAD include: calf skeletal muscle increases inperoxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a) (a major regulator ofmitochondrial biogenesis), calf skeletal muscle increases in mitochondrial protein expression and activit
skeletalmuscle perfusion. No randomized clinical trials have studied whether metformin improves lowerextremity functioning in PAD. A definitive trial is needed. We propose a placebo controlled double-blind randomized clinical trial to establish whether metformin(2,000 mgs daily) improves and/or prevents decline in walkin
performance, and quality of life. Calf muscle outcomes consist ofchanges in PGC-1a abundance, mitochondrial quantity, mitochondrial enzyme activity, capillary density,reactive oxygen species (ROS)-induced tissue damage, and autophagy. If metformin improves functional performance and prevents functional decline in PAI

28. Project Title: **TRANSCRIPTIONAL REGULATION OF KCNH2**
Leader(s): **DELISLE, BRIAN P**
UNIVERSITY OF KENTUCKY
NIH R01HL141343 / (2019-2023)

SummaryCircadian rhythms help to match the optimal function of the cardiovascular system to the daily changes in theenvironment. Normal cardiovascular rhythms provide a physiological advantage to people. Unfortunately,normal circadian signaling can also unmask a time-of-day pattern in adverse events like heart attack, st
that helps toentrain endogenous rhythms to the environment. SCN rhythms are synchronized to the environment via light,and its signaling helps to coordinate the molecular rhythms in cells throughout the body. What is new abouthis application is we determine how repeated changes in light cycle will impact molecular circadia
molecular clocksignaling in the mouse heart and its regulation on ion channel function.Aim 1. To identify new mechanisms with which the cardiac molecular clock regulates different ion channels.Aim 2. To determine how repeated changes in light impact molecular clock signaling in the heart and ionchannel regulation.This pr

29. Project Title: **IMPAIRED MITOCHONDRIAL ENERGETICS IS A DRIVER OF HEMODIALYSIS ACCESS RELATED HAND DYSFUNCTION**
Leader(s): **SCALI, SALVATORE T.**
UNIVERSITY OF FLORIDA
NIH R01HL148597 / (2019-2024)

PROJECT SUMMARYCurrently, in the United States, there are ~425,000 patients receiving hemodialysis (HD) and it is estimated that30-60% of this population have some element of hand dysfunction after hemoaccess surgery. The underlyingpathophysiologic mechanisms responsible for this devastating problem are poorly u
AVF surgery causes significanthemodynamic changes in the extremity which presents an adaptive challenge to the skeletal muscle andneuromotor end-plate. Supported by our previous work, as well as preliminary data on RD associated skeletalmuscle mitochondrial phenotypic changes, we propose that RD driven mitochondri
undergoing AVF surgery todeveloping skeletal muscle and neuromuscular junction perturbations causing clinically significant handdysfunction. RD mediated mitochondrial impairments are further exacerbated by local hemodynamic changesfollowing AVF creation through maladaptive OS metabolic responses that drives the d
mitochondrial-targetedantioxidant therapies delivered prior to- and following AVF surgery in mice. Using a novel RD murine AVF model,we will determine whether global (N-acetylcysteine) or mitochondrial-targeted (AAV delivery of mitochondrialtargeted catalase) antioxidant therapy have therapeutic potential for AVF-ind
outcomes modulating the spectrum ofhand function will be determined.

30. Project Title: **MOLECULAR MECHANISMS REGULATING PERIPHERAL ARTERIAL DISEASE PATHOBIOLOGY IN CHRONIC KIDNEY DISEASE**
Leader(s): **RYAN, TERENCE E**
UNIVERSITY OF FLORIDA
NIH R01HL149704 / (2019-2024)

Peripheral artery disease (PAD) is caused by atherosclerosis in the lower extremities which leads to a spectrum of life-altering symptomatology, including claudication, ischemic rest pain, and gangrene requiring limb amputation. Complicating the etiology of PAD, patients typically present with comorbid conditions or risk facto
diabetes). We have uncovered a novel molecular pathway that may link CKD and PAD pathobiology. We find that many uremic metabolites, which accumulate in CKD, cause chronic activation of the aryl hydrocarbon receptor (AHR) which leads to disruption of the mitochondrial electron transport system that exacerbates isch
pathobiology. This hypothesis will be tested using muscle- and vascular-specific inducible knockout of the AHR as well as adeno- associated virus-mediated expression of the a constitutively active AHR in pre-clinical models of CKD/PAD. Finally, our recent human data indicate elevated AHR signaling in PAD patients with C

31. Project Title: **CIRCADIAN CLOCK REGULATION OF MYOCARDIAL ION CHANNEL EXPRESSION AND FUNCTION**
Leader(s): **ESSER, KARYN A ; DELISLE, BRIAN P ;**
UNIVERSITY OF FLORIDA
NIH R01HL153042 / (2020-2024)

The overall objectives of this proposal are to 1) define the genomic and transcriptomic mechanisms by which the cardiomyocyte clock regulates ion channels that contribute to cardiac excitability; and 2) disrupt the cardiomyocyte clock to link changes in circadian-ordered gene expression with electrophysiological properties of
link time of day with a large-scale transcriptional program to support cellular homeostasis To date, our labs have used an inducible cardiomyocyte specific mouse model to knock out the core clock gene, Bmal1 (iCSBmal1). These studies showed that disruption of the myocardial clock is sufficient to decrease ventricular K+ amp
approaches with our mouse model system to define the circadian clock dependent control of temporal gene expression in both atrial and ventricular tissues. To address abnormal circadian clock function, our lab has used different models of circadian disruption, such as chronic phase advance or time restricted feeding to test link
myocardial clock function with outcomes that include modified ion channel expression, cardiac excitability and arrhythmia vulnerability. The aims of this proposal are designed to test the following hypotheses: 1) The molecular clocks in both atrial and ventricular cardiomyocytes are necessary to direct daily chromatin accessib

32. Project Title: **EMOTIONAL ENGAGEMENT DRI**
Leader(s): **DING, MINGZHOU ; KEIL, ANDRE**
UNIVERSITY OF FLORIDA
NIH R01MH112558 / (2017-2022)

Project?Summary/?'Emotional?dysfunction?is?at?the?core?of?many?psychiatric?disorders,?in?particular?fear,?anxiety,?post-?traumatic,?and?mood?disorders.?Describing?the?neural?mechanisms?associated?with?emotional?processing?is?therefore?a?critical?issue?in?mental?health?care.?Previous?attempts?to?define?the?neu
functional? brain? imaging,? which? is? high? in? spatial? precision.? This?approach,?called?steady-?state?potential?frequency-?tagging,?achieves?stimulus?specificity,?temporal,?and?spatial?resolution?across?the?whole?brain.?It?is?unique?in?that'it?allows?researchers?to?identify?distinct?brain?networks?selectively?activa
large-?scale? brain?dynamics? mediating? the? emotional? response? to? an? element? that? is? embedded? in? a? complex? visual? array.? (2)?We? determine? how? conflicting? appetitive? and? aversive? information,? visual? and? auditory,? affects? these? brain?dynamics.? (3)? Finally,? we? translate? this? novel? method?
avenues? for? objectively? evaluating? pre-?? to? post-?treatment? changes? in? appetitive/aversive?neural? reactivity.? It? also? enables? measuring? neural? circuit? function? to? enable? quantitative? measurements? of?specific?psychopathology?and?for?identifying?treatment?targets?in?a?personalized?medicine?framework

33. Project Title: **BIOBEHAVIORAL MECHANISMS UNDERLYING SYMPTOMS AND HEALING OUTCOMES IN OLDER INDIVIDUALS WITH CVLU**
Leader(s): **STECHMILLER, JOYCE K. ; LYON, DEBRA E ;**
UNIVERSITY OF FLORIDA
NIH R01NR016986 / (2018-2023)

ABSTRACT Our long-term goal is to elucidate the complex biobehavioral mechanisms responsible for symptoms andhealing outcomes for older adults? with venous leg ulcers (VLUs) for the development of targeted therapies thataddress both the patient-oriented outcomes and healing outcomes in this growing group of affecte
both wound-relatedsymptoms and symptoms of pain, depression, anxiety, fatigue and cognitive dysfunction, collectively labeled as?psychoneurologic symptoms (PNS).? Guided by the National Institutes of Health Symptom Science Model(NIH-SSM) framework, the central hypothesis of this application is that there are interrel
wound-related); and,(2) Test associations and models over time for: (a) Patient-host factors and systemic inflammation with woundmicroenvironment; (b) Patient-host factors and wound microenvironment with systemic inflammation; (c)Patient-host factors, systemic inflammation, and wound microenvironment with wound he
across eight weeks time. We willfully characterize patient-host characteristics (age, comorbidities, sex, race/ethnicity, BMI, nutritional status,lifestyle habits, and wound treatment [pressure therapy, debridement, antibiotics]); systemic inflammatoryactivation (C-reactive protein and cytokines); wound microenvironment factors
from a holistic perspective and toprovide a basis for preventing or reversing the adverse health outcomes of CVLUs, a condition thatdifferentially affects older and minority individuals.

34. Project Title: **OPTIMIZING AAV VECTORS FOR CENTRAL NERVOUS SYSTEM TRANSDUCTION**
Leader(s): **HELDERMON, COY D**
UNIVERSITY OF FLORIDA
NIH R01NS102624 / (2017-2022)

Project SummaryMucopolysaccharidosis (MPS) IIIB is a neurodegenerative lysosomal storage disease (LSD) caused by deficientdegradation of heparan sulfate. Clinically this manifests as cognitive decline, developmental regression, impairedmobility and ultimately premature death. There are currently no effective therapies. I
been published for AAV9. However,for translation to human trials, it is essential to identify a highly effective AAV capsid serotype which will deliverto cells in the requisite brain regions. More generally, for any treatment of human neurologic disease in whichthe central nervous system (CNS) is of substantially larger volume
genetic bar code that identifies each vector and a second barcode that is incorporated during PCR amplification of each brain region isolated. The bar code system allowsdetermination of distribution and the expression levels of each serotype in anatomical areas of interest. We willuse this novel two-step barcoded AAV vector s
provide the best delivery by region, are altered by presence of the disease,and are similar between primate and mouse models. The results will inform clinical trial vector selection acrossthe spectrum of central neurologic disorders, including MPS III. Subsequently, our MPS IIIB gene construct willbe packaged into the optimal
two-step bar-coded AAV vector system to allow simultaneous delivery and assessment of 40 serotypes with capsid variants in each animal via injections into the brain or surrounding fluid. Brain distribution for each serotype will be assessed by quantitative next generation RNA sequencing of the various brain regions. The top
enzyme assays to determine preclinical benefit in the mouse model.Overall, these studies will determine the effects of species, delivery site and disease state on brain delivery froma multitude of AAV serotypes. Through this study, we will identify the most promising vector(s) for clinical trialdevelopment in MPS IIIB and othe

35. Project Title: **HEAT SHOCK PROTEINS AND DISUSE MUSCLE ATROPHY**
Leader(s): **JUDGE, ANDREW ROBERT**
UNIVERSITY OF FLORIDA
NIH R03AR056418 / (2009-2013)

DESCRIPTION (provided by applicant): Project summary/Abstract Skeletal muscle disuse atrophy is a widespread physiological phenomenon associated with immobilization, bed rest, denervation, and space flight, or any general reduction in weight bearing activity. However, our understanding of the signaling molecules that r
rapidly, induced by a variety of cellular stresses. This induction has been shown to provide a variety of cytoprotective functions. During muscle disuse a member of the heat shock family, Hsp70, is consistently down-regulated and overexpression of Hsp70 during disuse abolishes the increase in NF-:B and Foxo3a transactivatio
Aims 1 and 2 if an increase in Hsp70 expression is sufficient to inhibit NF-:B-induced or Foxo3a-induced muscle fiber atrophy, and in Aim 3 if knock down of Hsp70 is sufficient to cause muscle fiber atrophy. To address these specific aims we will inject WT IKK2 plus Hsp70 expression plasmids (Aim 1), WT Foxo3a plus Hs
The findings from these experiments will lead to a greater understanding of Hsp70 in the regulation of NF-:B and Foxo3a signaling during skeletal muscle atrophy. PUBLIC HEALTH RELEVANCE: Project Narrative Skeletal muscle wasting due to disuse is associated with immobilization, bed rest, denervation, and space flig
wasting.

36. Project Title: **WEARABLE TECHNOLOGY INFRASTRUCTURE TO ENHANCE CAPACITY FOR REAL-TIME, ONLINE ASSESSMENT AND MOBILITY (ROAMM) OF INTERVENING HEALTH EVENTS IN OLDER ADULTS**
Leader(s): **MANINI, TODD ; RANKA, SANJAY ;**
UNIVERSITY OF FLORIDA
NIH R21AG059207 / (2019-2021)

ABSTRACTOlder Americans experience approximately 29 million falls and 13 million hospitalizations per year. Theseintervening health events (IHE - episodic falls, injuries, illnesses, and hospitalizations) are strong precipitants ofdisability in older adults. Because of their episodic nature, IHEs are extremely difficult to study.
continuousconnectivity, bidirectional interactivity and remote programming. ROAMM will create a detailed narrative aboutmobility (activity patterns, walking speed, life space), patient reported outcomes/symptoms (pain, poor mood,fatigue, disability), cognition (working memory, processing speed, and executive functioning)
framework consisting ofthe watch application and accompanying server. We will also assess test-retest reliability, convergent validityand participant usability/acceptability. Each year, an Independent Advisory Panel and External AdvisoryCommittee will evaluate milestone-driving activities and our Go/No-Go checkpoints for t
collected by ROAMM areindependent predictors of incident IHE's; 2) IHE's will negatively impact the course of ROAMM measures; and3) Additional value will be gained for explaining the change variability and recovery trajectories. An exploratoryaim will evaluate safety while using ROAMM features and identify predictor
become the go-to place forremote data capture. These activities will create a sustainable infrastructure to ensure research on older adultsis keeping pace with the state-of-the-art ?smart and connected? health with wearable technology.

37. Project Title: **SYSTEMATIC ANALYSIS OF CLINICAL STUDY GENERALIZABILITY ASSESSMENT METHODS WITH INFORMATICS**
Leader(s): **HE, ZHE ; BIAN, JIANG ;**
FLORIDA STATE UNIVERSITY
NIH R21AG061431 / (2019-2021)

our society. Despite decades of promising preclinical and clinical investigations in trauma, our understanding of this entity and why its effects are exacerbated in the elderly remains incomplete, with few therapies demonstrating success in any patient population. Recently, several aspects of innate immunity have been determined to be of
thways results. Proper differentiation of myeloid cells from stem cells is dependent on activation of nuclear factor kappaB (**NF**, a protein complex that partially controls DNA transcription after stressful stimuli. Anappropriate emergency myelopoietic response to inflammation is essential to host survival but appears to be inadequate in the
FB-dependent inflammatory pathways, and a failure of hematopoietic stems cells (LSK populations) after trauma to create functional myeloid populations in a NFB-dependent manner. Using a novel murine polytrauma (PT) model of murine hemorrhagic shock and injury that better recapitulates the human condition, we will: (1) determi
nterparts, are caused by a chronic low-grade NF B-dependent inflammatory state and a subsequent failure to appropriately activate NFB-dependent pathways after trauma; and, (3) determine if the HSC senescence associated with elderly humans after severe trauma is also due to a failure to appropriately activate NFB-dependent pathway
ll exhibit plasticity.

days with organ dysfunction). Late complications include sepsis readmission and late death, both of which have rates of approximately 40% at 90 days and 6 months, respectively. Circulating lipids play an important role in sepsis and cholesterol levels of both high density lipoproteins (HDL-C) and low density lipoproteins (LDL-C) are
:. 1) HDL becomes dysfunctional (pro-oxidant and pro-inflammatory) in early sepsis (Dys-HDL); 2) elevated Dys-HDL levels positively correlate with and predict organ failure severity and are associated with poor outcomes including 28-day mortality; 3) HDL from older septic patients exhibits impaired cholesterol efflux capacity (requ
o cholesterol dysfunction. Our data strongly suggest that lipid and lipoprotein dysregulation occurs in sepsis and leads to altered function, oxidation, and reduced levels that may influence clinical outcomes. We hypothesize that specific functional, lipidomic, and genomic changes in lipid and lipoprotein metabolism occur in early sepsis a
several advantages: 1) cost-savings from use of existing samples with isolated mRNA, 2) a recent cohort of sepsis patients (2016-2018) consistently treated with institutional evidence-based management bundles, 3) availability of serial samples over time (enrollment, 48h, 28d, and 90d), sepsis readmission samples, and mRNA for the C.

PAD. However, few therapies are available that improve functioning or preventfunctional decline in people with PAD. Metformin is an inexpensive, widely available, well tolerated biguanide medication and the mostcommonly prescribed drug for Type 2 diabetes mellitus worldwide. Recent pre-clinical and preliminary humanevidence
y,increases in capillary density in ischemic tissue, reductions in oxidative stress, increased autophagy (repair ofcellular damage), and improved endothelial function. These therapeutic properties target pathophysiologicconditions present in PAD. Therefore, we hypothesize that metformin will improve lower extremity functioningin peopl
g performance in people with PAD. Participantswill be 212 people with PAD who do not have diabetes mellitus, since metformin is a first-line therapy for Type2 diabetes. Our primary outcome is change in six-minute walk at 6-month follow-up. Secondary outcomes are6-month changes in treadmill walking performance, brachial artery
), this widelyavailable, inexpensive, and well tolerated medication will have a major impact on preventing mobility loss andimproving quality of life in the large and growing number of people with PAD.

roke,and sudden death in patients with underlying cardiovascular disease.Emerging data now show that abnormal or unhealthy daily rhythms can create a negative impact on normalhealth too. For example shiftwork, which repeatedly causes shifts in endogenous circadian rhythms, is anindependent risk factor for cardiovascular disease.I
un signaling inthe heart.Most cells have a molecular clock signaling mechanism that cycles with a periodicity of ~24 hours. We foundgenetic disruptions in the molecular clock mechanism of heart cells (cardiomyocytes) primarily causesabnormal changes in cardiac electrophysiology by disrupting the regulation of ion channel function.T
ject creates new knowledge at the interface between chronobiology and cardiac electrophysiology.

nderstood. The renaldysfunction (RD) milieu causes a variety of physiologic derangements in HD patients including increasedoxidative stress (OS) and chronic inflammation that have been implicated as major contributors to acceleratedatherosclerosis and elevated mortality. Profound changes in OS contribute to skeletal muscle and ne
al dysfunction alters skeletalmuscle and neuromuscular junction responses to AVF induced ischemia leading to clinically apparent handdysfunction. Further, these pathways can be modified either prior to AVF creation or at first evidence of handdysfunction to reverse/prevent the functional impairment. Our hypothesis is that the RD mil
iversity of clinicallyapparent hand dysfunction. Aim 1 will establish how RD impacts mitochondrial and cellular energetics that areexacerbated by AVF-induced limb ischemia. Using a series of in vitro experiments, we will uncover thebiochemical mechanisms by which RD impacts mitochondrial energetics leading to impaired oxidativ
uced muscle dysfunction. Aim 3will evaluate the association between mitochondrial health and AVF-induced hand dysfunction in humanpatients. Mitochondrial health will be examined in-situ using permeabilized myofibers prepared from RD patientsbefore and after AVF surgery: mitochondrial phenotypic changes will be evaluated an

rs that accelerate disease evolution and substantially worsen pathology contributing to increased mortality risk. Among these, chronic kidney disease (CKD) accelerates the development of atherosclerosis, decreases functional capacity, and increases risk of amputation or death, however the underlying biologic mechanism(s) are poorly
emic muscle injury and impairs angiogenesis. Preliminary experiments demonstrate that genetic knockdown of the AHR is protective against uremic toxicity, whereas expression of a constitutively active AHR causes mitochondrial dysfunction. Thus, we propose to test the novel hypothesis that the chronic activation of the AHR pathwa
:KD. We propose to extend these findings to establish a clinical link between muscle health/function, mitochondrial energetics, and AHR signaling in human PAD patients. Success in these studies will provide mechanistic insight into the impact of CKD on PAD pathobiology, and would provide a novel target for therapeutic developmei

atrial and ventricular cardiomyocytes. The outcomes will address significant gaps in our understanding for how the myocardial circadian clock regulates the expression of key cardiac ion channels and how abnormal cardiac clock function contributes to arrhythmia vulnerability. The mechanism regulating circadian timing, the molecular
l Na+ channel gene expression, disrupt current levels, disrupt cardiac excitability, and increase arrhythmia susceptibility. These studies establish a critical role for the cardiomyocyte clock, independent of the central clock, in regulating the expression of different families of ion channel genes that impact the ionic balance needed for norm
s between circadian disruption and arrhythmia vulnerability in mouse models. We have found that disrupting either light or feeding time cues is sufficient to induce pathological changes in cardiac rhythms in normal mice and to accelerate sudden cardiac death in a genetic mouse model of arrhythmia susceptibility. These studies support
ility and transcriptional output including expression of key ion channel and ion channel regulatory genes. 2) Chronic disruption of the cardiomyocyte clock using altered time of feeding is sufficient to cause dysregulation of the cardiac clock resulting in an imbalance in cardiac ion channel expression and currents leading to altered excita

VEN BY COMPLEX VISUAL STIMULI: NEURAL DYNAMICS REVEALED BY MULTIMODAL IMAGING

AS ;

rophysiology?of?human?emotions?in?the?cognitive? neuroscience? laboratory? have? been? hampered? by? the? unavailability? of? conceptual? and?methodological? frameworks? for? studying? complex? emotional? responses? in? context? and? with? conflicting?information?present.?The?proposed?research?establishes?a?novel?tec
ted?by?different?elements?of?a?complex?visual?scene?even?when?the?elements?are?spatially?overlapping? and? accompanied? by? stimulation? in? other? sensory? modalities.? We? combine? this? innovative?approach?with?a?novel?conceptual?framework?that?considers?changes?in?visual?perception?an?active?part?of?an?observ
' to? socially? anxious? observers,? testing? mechanistic?hypotheses? regarding? the? interactive? effects? of? trait? anxiety? and? chronic? stress? on? short-?term? reactivity? to?emotional? challenge.? The? long-?term? clinical? implications? of? the? proposed? research? are? manifold:? For?diagnostic?assessment?and?for?monitoring
.?

d individuals.VLUs, which account for 70?90% of ulcers found in the lower leg, affect 2 million persons annually, includingnearly 4% of people over age 65 years. To date, the basic biology underlying the development and persistenceof VLUs and the influence of aging and multiple disease conditions on wound healing are generally nc
lated molecularmechanisms by which the immune activation that contributes to the development and persistence of CVLUalso leads to the development, persistence and severity of PNS. The specific aims of the proposed study areto: (1) Characterize the strength of the associations at baseline among patient-host factors, systemicinflamm
aling; (d) Patient-hostfactors, systemic inflammation, and wound microenvironment with symptoms (PNS and wound-related) and (e)Patient-host factors, systemic inflammation, wound microenvironment and wound healing with symptoms (PNSand wound-related). To achieve the specific aims, we will longitudinally examine 200 older
(local inflammation [Matrixmetalloproteinase (MMP) enzymes C-reactive protein, cytokines], biofilm, and micro RNAs); symptoms (PNS[cognitive dysfunction, pain, fatigue, and depressive/anxiety symptoms] and wound-related); and woundcharacteristics and healing trajectory at the five timepoints. This knowledge is critical to provi

ue to the neurodegenerativenature of this disease, optimal CNS transduction is necessary for human trials. Several groups havedemonstrated improvement of the mouse model using different adeno-associated viral (AAV) vectors. We haverecently demonstrated that AAV8 has better brain gene delivery in MPS IIIB than wild type mice.
and is phylogenetically distant compared toour current mouse models, we will need to identify an optimal vector and delivery method for CNS approaches.To this end, we have developed a novel two-step bar code AAV vector system that allows assessment of multipleAAV vector serotypes within the same animal, greatly reducing the
ystem to simultaneously identify brain delivery of 40 AAVserotypes and capsid variants in wild type and MPS IIIB mice as well as in non-human primates - the closest tohuman model available to us. We will identify whether injections into the body of the brain or the less invasiveinjection into the fluid around the brain method provides
vector to assess treatment effect in MPS IIIB mice. We hypothesize that CNStransduction and distribution will differ by serotype and species and that some serotypes will transduce differentlybetween wild type and Sanfilippo Syndrome mice. Our specific aims are therefore:1. We will determine the brain delivery of AAV serotypes in n
three vectors for brain delivery by this method will be used individually to identify the cell types treated and pattern of gene expression in mice and NHP.2. Assess the effect of the AAV serotype with the best distribution in the thought processing and motor coordination regions of the brain carrying the MPS IIIB gene to treat the MPS II
r neurodegenerative disorders. If this project is successful, we will be in aposition to quickly move towards such clinical trials.

egulate muscle mass during disuse are ill defined. Therefore the long-range goal of our research program is to understand the regulation of signaling pathways that cause muscle atrophy during disuse. Eventually improved understanding will lead to the identification of targets for specific interventions. Heat shock proteins (Hsps) are a f
n, and completely prevents skeletal muscle atrophy. This is important since NF-:B and Foxo3a are required for disuse muscle atrophy. However, it is currently unknown whether Hsp70 overexpression is sufficient to specifically inhibit NF-:B-induced or Foxo3a-induced muscle atrophy. It is also unknown whether knock down of Hsp70
p70 expression plasmids (Aim 2), or a plasmid producing shRNAs specific for Hsp70 (Aim 3) into the skeletal muscle of rats and measure NF-:B or Foxo3a activity, the mRNA expression of specific atrophy genes and muscle fiber cross sectional area. If an increase in Hsp70 expression inhibits NF-:B activity and/or Foxo3a activity we
t, or any general reduction in weight bearing activity. In the proposed work we will genetically overexpress or knock down a protein that is believed to regulate muscle size and is known to be down-regulated during muscle wasting caused by disuse. This will allow us to directly determine the involvement of this protein in the regulatio

Continuous,long-term monitoring with remote capabilities using wearable technology is an ideal solution for capturinginformation surrounding an IHE and in particular, preceding it. This R21/R33 project aims to develop asustainable research infrastructure built on the foundation of a smart watch application and server calledROAMM
and reports ofhealth events (falls and hospitalizations). The infrastructure is composed of a diverse group of investigatorswith expertise in mobile technology/data science and applied/medical sciences who will serve in the followingcores: Wearable Technology, Phenotyping, Clinical Outcomes, Data Science Management & Quality, an
ransitioning to the R33phase. Work proposed in the R33 phase will showcase the ROAMM infrastructure by conducting aprospective, longitudinal study (range 1.25-2.5 yrs) in 200 community-dwelling persons aged 70+ yrs. Thisphase will test a field deployable version of ROAMM in real world settings to address the following hypoth
s of ROAMM adherence using bothkey-informant interviews and examine demographic and health histories to create boundaries for usingROAMM and other systems like it for long-term, continuous monitoring in research and practice. We willsustain ROAMM by targeting grant opportunities for the wearable technology surge for rema

vital importance to the young adult immune response, and this response is suboptimal in the elderly as compared to younger patients. Specifically, we hypothesize that the myelodysplasia ne if certain hematopoietic stem cells (HSCs), specifically short term-HSCs (ST-HSCs), fail to rs in bone marrow HSCs. This work proposes that increased susceptibility to infection after trauma

ynamically regulated in sepsis. HDL and LDL are both thought to play protective roles in ired for toxin clearance and steroidogenesis); 4) HDL and LDL levels drop precipitously during nd relate to relevant clinical trajectories (rapid recovery, early death, and chronic critical cohort, 4) age/gender matched control samples, 5) available clinical and outcomes data. We

suggest that metformin has previously unrecognized therapeutic properties. Therapeutic e with PAD, by facilitating favorable changes in calf skeletal muscle and by increasing calf flow-mediated dilation, calf skeletal musclebiopsy measures, patient-reported walking

n mammals the suprachiasmatic nucleus (SCN) in the brain is the primary circadian pacemaker he goal of this application is to determine how repeated shifts in the light cycle impact

romuscularjunction dysfunction associated with muscle atrophy and frailty in this population. ieu disruptsmitochondrial and cellular energetics resulting in elevated OS predisposing patients ephosphorylation and increased OS. Aim 2 will determine the efficacy of global or d their association withchanges in serial hemodynamic, neurophysiological and biomechanical

nderstood and vastly understudied compared with other comorbidities (i.e. smoking and y results in ischemic muscle injury and impaired angiogenesis, thereby linking CKD and PAD t aimed to treat a patient population that currently has few available options.

clock, exists in virtually all cell types in the body. A critical function of the molecular clock is to al excitability. One goal of this project is to utilize large scale genomic and transcriptomic our premise that disruption of day- night rhythms through environmental factors leads to altered bility and increased arrhythmia vulnerability.

hnique?for?combining?electrophysiological?recordings,? high? in? temporal? precision,? with? r?s? emotional? response,? to? address? the? following? Aims:? (1)? We? characterize? the? ?treatment?efficacy,?a?quantitative?brain-?based?marker?of?emotional?engagement? opens?

t wellunderstood. Individuals living with chronic VLU (CVLU) have a high symptom burden of ation, and wound microenvironment with wound area and symptoms (PNS and adults (age >60)who are receiving state of the art, standardized wound treatment biweekly de a foundationfor developing targeted interventions to address this critical health problem

A similar findingof altered brain delivery in Sly Syndrome compared to wild type mice has umber of animals needed for statisticalcomparisons of brain delivery. This system has a a better vector distribution. We will identify which wild-type AAV serotypes or capsid mutants n-human primates (NHP) and in wild type and MPS IIIB affected mice. We will use a novel IB mouse. We will use day/night activity, hearing, coordination, lifespan, lysosomal storage and

mily of proteins that are constitutively expressed in cells, but whose expression is further, and is sufficient to cause skeletal muscle atrophy. The objective of the current proposal is to determine in will determine the mechanisms of this by determining the proteins in each pathway that Hsp70 binds. of skeletal muscle mass, and could identify the protein as a novel therapeutic target for muscle

(Real-time Online Assessment and Mobility Monitor). It will offer long-term and Recruitment, Retention & Compliance. In the R21 phase, we will create the ROAMM ses:1) Pre-event patterns of low mobility, disability, fatigue, pain and depressive mood te patientinteraction, adopting licensing fees, and aligning our services with larger entities to

Clinical studies are often conducted under idealized and rigorously controlled conditions to improve their internal validity and success rates, but compromise their external validity (i.e., generalizability to the target populations). These idealized conditions are sometimes exaggerated and reflected as overly restrictive eligibility cr
assess the generalizability of a clinical study, so that stakeholders including pharmaceutical companies, policymakers, providers, and patients would be able to understand and anticipate the possible effects of the interventions in the real world. In the past two decades, a large number of studies have assessed generalizability, but
two-fold: (1) the lack of evidence to demonstrate their validity, which also leads to the lack of consensus on the best practice for generalizability assessments; and (2) the lack of readily available, well-vetted statistical and informatics tools. Motivated to fill this gap, we propose to first systematically review the extant methods fo
documentations and tutorials. The success of this R21 project will (1) fill a knowledge gap on the validity and utility of the different generalizability assessment methods; (2) provide an easy-to-use toolbox etGATE for assessing study generalizability much-needed by the clinical research community; (3) help the clinical researc

38. Project Title: **ADVANCING INTERDISCIPLINARY SCIENCE OF AGING THROUGH IDENTIFICATION OF IATROGENIC COMPLICATIONS: THE UF EHR CLINICAL DATA INFRASTRUCTURE FOR ENHANCED PATIENT SAFETY AMONG THE ELDERLY (UI**

Leader(s): **INGIBJARGARDOTTIR BJARNADOTTIR, RAGNHILDUR ; LUCERO, ROBERT J ;**

UNIVERSITY OF FLORIDA

NIH R21AG062884 / (2019-2021)

Iatrogenic conditions are a continuing public health concern, causing death among an estimated two hundred and fifty thousand older adults annually in United States (US) hospitals. Hospital-acquired falls and hospital- induced delirium are among the most common and costly iatrogenic conditions, and their occurrences are linl
methods. The development of a research data infrastructure that supports the use of text and structured data is critical for a learning health system aimed at improving care and patient outcomes. In this project, we propose to expand the research infrastructure for electronic data-driven knowledge generation through the developm
registered nurses' (RNs) progress notes for prediction of hospital-acquired falls. We will employ a combination of supervised and unsupervised text-mining methods to identify text attributes associated with patient falls. We will then leverage a predictive model of patient fall risk factors developed in previous work to generate a
into the existing UF Health Clinical Data Warehouse (CDW) infrastructure and test to assess functionality, durability and scalability. In addition, we propose to develop the human resource infrastructure to support data-driven interdisciplinary aging research. This will be achieved by training graduate students in interdisciplinar
every day.

39. Project Title: **NICOTINAMIDE RIBOSIDE AS AN ENHANCER OF EXERCISE THERAPY IN HYPERTENSIVE OLDER ADULTS: THE NEET TRIAL**

Leader(s): **MANKOWSKI, ROBERT**

UNIVERSITY OF FLORIDA

NIH R21AG064282 / (2019-2021)

ABSTRACTMore than 80% of older adults have hypertension, with higher prevalence of high systolic blood pressure (SBP)putting them at high risk for cardiovascular (CV) disease and death. Because drug therapy that lowers SBP isassociated with side effects such as hypotension, syncope, and kidney dysfunction, there is a g
adeninedinucleotide (NAD+), a cofactor for the deacetylase sirtuin1 (SIRT1), may contribute to age-related vasculardysfunction via oxidative stress and reduced nitric oxide (NO). Exercise-induced overexpression of NAD+-dependent SIRT1 improves the bioavailability of NO. Preclinical evidence suggests that poor vascular-l
SBP-lowering effect in hypertensive older adults. Initial human clinical trials demonstrated that nicotinamide ribosidesupplementation (1,000 mg/day) was safe and showed a higher potential to reduce SBP and arterial stiffnessin participants with elevated SBP. As we have preclinical evidence that combining NAD+ replenishm
center-basedwalking exercise, or (2) the same exercise program combined with placebo, or (3) 1,000 mg/day ofnicotinamide riboside alone. All participants will undergo daytime continuous SBP and arterial-stiffnessmeasurements by pulse-wave velocity at baseline and at 6 weeks. Elevated SBP will then be determined asdaytii
Phase III clinical trial in hypertensive older adults. The ultimate goal of this line of research is to findadjuvant strategies to improve the exercise's SBP-lowering effects in older adults.

40. Project Title: **DYSREGULATION OF SARCOMERE STABILIZING PROTEINS CAUSE MUSCLE ATROPHY AND WEAKNESS DURING CANCER CACHEXIA**

Leader(s): **JUDGE, ANDREW ROBERT**

UNIVERSITY OF FLORIDA

NIH R21CA194118 / (2015-2018)

DESCRIPTION (provided by applicant): Cachexia is characterized by progressive skeletal muscle and body weight loss and affects up to 80% of cancer patients. This loss of muscle mass contributes to significant muscle weakness and diminished physical function and is associated with reduced tolerance to chemotherapy and i
stimulus, and there is speculation that these disruptions may initiate catabolic processes which lead to the muscle atrophy and weakness. Unpublished and preliminary data from our lab has identified that Kyphoscoliosis peptidase (Ky), which is essential to the structural integrity of the sarcomeric Z-disk, and Myocilin (Myoc), v
downregulation of Ky and Myoc are causative to the loss of muscle structure leading to muscle wasting and weakness during the progression of cancer cachexia. Unpublished bioinformatics analyses of the -1kb to +1kb proximal promoters of genes significantly downregulated in skeletal muscle of C26 tumor-bearing mice reve
activity in skeletal muscle of tumor-bearing hosts is causative in the downregulation of Ky and Myoc, and initiates disruptions in muscle fiber integrity and muscle wasting. Thus, our two specific aims are: Specific Aim 1: To test the hypothesis that the downregulation of Kyphoscoliosis peptidase (Ky) and Myocilin (Myoc) pla
muscle wasting and weakness, opening up new avenues for therapeutic interventions.

41. Project Title: **MOLECULAR BIOLOGY IN BURNS AND TRAUMA**

Leader(s): **MOLDAWER, LYLE L**

UNIVERSITY OF FLORIDA

NIH T32GM008721 / (1999-2024)

This Ruth Kirschstein NRSA training Program proposes to take primarily surgeons and other critical caremedicine physicians during the second or third year of their general residency programs, and expose them totwo, three and even four years of mentored research in inflammation biology with highly productive basic science
research experience. Select trainees will have the opportunity to complete a Ph.D. program in the GraduateSchool in three to four years. Other trainees can participate in graduate certificate programs which are formalcollections of courses that together form a coherent program of study offered through an academic unit. Thistrai
vascular injury,delayed wound healing and the burn wound. The faculty will be drawn from funded basic and clinical scientistsin the Surgery, Medicine, Pathology, Aging and Geriatric Research and Molecular Genetics and MicrobiologyDepartments, who will serve as research mentors to the trainees. Clinical mentors from the
Jacksonville). Successfulapplicants with the Executive Committee will identify a research and clinical mentor who will help formulate aformal training program and periodic review of the trainee?s progress. Furthermore, trainees are expected toparticipate in basic science seminars in the Institute on Aging, Emerging Pathogens
successfully compete fortransitional funding in inflammation research and become leaders in academic surgery.

42. Project Title: **THE ENRGISE STUDY**

Leader(s): **PAHOR, MARCO ; AMBROSIUS, WALTER T ;**

UNIVERSITY OF FLORIDA

NIH U01AG050499 / (2015-2019)

DESCRIPTION (provided by applicant): Growing evidence from our group and others shows that low-grade chronic inflammation, characterized by elevations in plasma C-reactive protein, tumor necrosis factor alpha, and particularly Interleukin-6 (IL-6), is an independent risk factor o disability, impaired mobility, and lower w
interventions for preventing major mobility disability by improving or preserving walking ability. We have maximized the public health impact of our proposed interventions by selecting interventions that are safe, tolerable, acceptable, and affordable for vulnerable older persons. Based on an extensive literature review, we proj
impairment, as measured by slow gait speed and self-reported mobility difficulty, and who have elevated levels of IL-6, the marker most consistently associated with mobility limitations. Preliminary data regarding feasibility need to be gathered before such a tria can be effectively designed and implemented. We propose to con
needed for the ENRGISE pilot and main trials, including the biorepository, and we will develop the materials needed for implementing the trials, including the protocol, manual of operations, data and safety monitoring plan, forms, quality control and quality assurance plan, and recruitment and retention materials.

43. Project Title: **UF PASS: REGULATION OF EXERCISE TRANSDUCERS**

Leader(s): **ESSER, KARYN A**

UNIVERSITY OF FLORIDA

NIH U01AG055137 / (2016-2022)

Abstract Exercise is a powerful and pleiotropic physiological stimulus that helps prevent many chronicdiseases and is used as a therapeutic for disease. While the beneficial effects of exercise are extensivelyacknowledged there is still very little understood about the molecular transducers of the systems-wide effects.The goal of
support screening of novel transducers to quickly move the field forward.In Phase 1, UF PASS proposes to collect biospecimens for the Chemical Analysis sites following endurance(run-training) or resistance exercise protocols on male and female Fischer 344xBrown Norway rats (F344-BN)at three different ages. To better cap
transducersthat function throughout the system to improve the well-established stress tolerance. The goal of these studieswill be to employ high throughput screening technologies to test up to 1500 myokines. We will then usesecondary screening techniques to test 100 candidates from which we will select up to 3 candidates for
at 3-4, 16-18, and 27-29 mo.Specific Aim 3: Phase 2 Studies. The goal in Aim 3 is to test myokines as the exercise transducers forimproved stress tolerance.

44. Project Title: **MULTIMODAL IMAGING OF BRAIN ACTIVITY TO INVESTIGATE WALKING AND MOBILITY DECLINE IN OLDER ADULTS**

Leader(s): **MANINI, TODD ; CLARK, DAVID J. ; SEIDLER, RACHAEL D ;**

UNIVERSITY OF FLORIDA

NIH U01AG061389 / (2018-2023)

Project Description: Mobility impairments in older adults decrease quality of life and are associated with highsocietal and economic burden. NIH RFA-AG-18-019 solicits applications ??to investigate the central neuralcontrol of mobility in older adults?using innovative and cutting-edge methods.? Current approaches to studyth
Wewill achieve this by using innovative mobile brain imaging with high-density electroencephalography (EEG).This approach relies upon innovative hardware and software to deliver three-dimensional localization of activecortical and subcortical brain regions with high spatial and temporal resolution during walking. The resu
walking explainsmobility decline. In both cross sectional and longitudinal designs, we will determine whether poorer walkingperformance and steeper trajectories of decline are associated with the Compensation Related Utilization oNeural Circuits Hypothesis (CRUNCH). CRUNCH is a well-supported model of brain activity
tasks of increasingcomplexity. When the ceiling is reached, performance suffers. The RFA also calls for proposals to?Operationalize and harmonize imaging protocols and techniques for quantifying dynamic gait and motorfunctions?. In accordance with this call, our second aim is to characterize and harmonize high-density EE
amajority of the objectives in NIH RFA-AG-18-019 and will identify the neural correlates of walking in olderadults, leading to unprecedented insight into mobility declines and dysfunction.

45. Project Title: **MOTRPAC CONSORTIUM COORDINATING CENTER**

Leader(s): **PAHOR, MARCO ; MILLER, MICHAEL E. ; REJESKI, WALTER JOHN ; TRACY, RUSSELL P ;**

UNIVERSITY OF FLORIDA

NIH U24AR071113 / (2016-2022)

SummaryPhysical inactivity is a major public health challenge underlying a broad range of health problems at all ages.While physical activity (PA) has shown to produce relevant health benefits, the underlying molecularmechanisms are poorly known. The coordinated effort of clinical and animal studies supported bybioinform
pivotal role in ensuring the cohesion of the MoTrPAC by enhancing communication and integration across allstudy components, including the Clinical Sites, the Preclinical Animal Study Sites, the Bioinformatics Center,the Chemical Analysis Sites, and the various study committees. The CCC will develop strategies and strateg
goals andmaximize the progress and productivity of the MoTrPAC, the CCC will promote team science, team leadership,and innovative leadership approaches across all study components. Strategic planning that follows theprinciples of the dynamic theory of strategy will be fostered to evaluate alternative approaches, maintain
the DataManagement, Analysis, and Quality Control Center (PI Dr. Miller), the Biospecimens Repository (PI Dr. Tracy),and the Exercise Intervention Core (PI Dr. Rejeski). The CCC will employ innovative project management toolsand web-based tracking of exercise adherence and diet, and will capitalize on the outstanding t
multidisciplinary teams.The CCC will ensure and promote the continued success of the MoTrPAC in advancing knowledge about themolecular changes that occur in response to PA, and relating these changes to the health benefits of PA.

46. Project Title: **1/2 + PROMOTE WEIGHT LOSS IN OBESE PAD PATIENTS TO PREVENT MOBILITY LOSS: THE PROVE TRIAL**

Leader(s): **MCDERMOTT, MARY MCGRAE**

NORTHWESTERN UNIVERSITY AT CHICAGO

NIH UG3HL141729 / (2019-2020)

PROJECT SUMMARY for the PROVE Trial More than 65% of people with lower extremity peripheral artery disease (PAD) are overweight or obese.People with PAD who are overweight or obese have greater functional impairment and faster functional declinethan normal weight people with PAD. Walking exercise is first li
will improve walking ability more than EX alone. However, effects of intentional weight loss in overweight/obese people with PAD are unknown and maynot be beneficial if weight loss exacerbates PAD-related sarcopenia. Behavior change that achieves sustainedWL is challenging in older obese people with chronic disease. T
achieved mean weight loss of 5.6 pounds andimproved the 6-minute walk by 64.1 meters in eight PAD participants with BMI> 28 kg/m2. Preclinical evidence shows that obesity is associated with impaired limb perfusion. Human evidenceshows that obesity is associated with reduced skeletal muscle mitochondrial biogenesis a
University, andthe U. of Minnesota. Our primary outcome is change in six-minute walk distance at 12-month follow-up.Secondary outcomes are change in 6-minute walk distance at 6-month follow-up and change in exerciseadherence, physical activity, patient-reported walking ability (measured by the Walking ImpairmentQue
arecorrect, the PROVE Trial will have a major public health impact by preventing functional decline and mobilityloss in the large and growing number of people with PAD who are overweight or obese.

riteria. Certain population subgroups are often excluded with unjustified criteria and are subsequently underrepresented. Older adults have been especially underrepresented in cancer studies. The underrepresentation of these population subgroups reduces the treatment effects and increases the likelihood of adverse outcomes in diverse pe
mostly were after the fact, ad hoc, not systematic, and focused on specific diseases and sets of trials without a formalized approach. So far, there is a significant knowledge gap between the available methods for generalizability assessment and their adoption in research practice. Most generalizability assessments have been conducted as
or generalizability assessments, and then use a data-driven strategy to reproduce, evaluate, and compare these methods with our unique data resource, the OneFlorida Data, one of the 13 PCORI-funded Clinical Data Research Networks that contains linked EHRs, claims, and cancer registry data for ~15 million Floridians. We will develo
hers choose the most appropriate generalizability assessment methods with readily available implementations; and (4) build a body of evidence to support the development of an eligibility criteria design tool for optimizing study generalizability at the study design phase.

-ECLIPSE)

ked to each other. Advances in computing technology and availability of electronic data presents opportunities to more accurately identify identifying patients at risk of suffering a hospital-acquired fall or hospital-induced delirium. Clinical data is now being captured electronically for about 80% of the US population. Approximately 75-
ent of the University of Florida (UF) EHR Data Infrastructure for Patient Safety among the Elderly (UF-ECLIPSE). The long-term goal of our research program is to enhance the safety of hospitalized older adults by reducing iatrogenic conditions through an effective learning health system. We plan to carry out the following aims: Spe
composite model of text and structured data to predict the odds of a patient falling. Specific Aim 2 (R33 Phase): Determine and evaluate the structural and human resources of an expanded research-data infrastructure to support sustained interdisciplinary aging studies. We will develop and pilot test text-mining pipelines to generate a pr
y data science for aging research. The UF-ECLIPSE research team will be among the first to implement and test an integrated data repository that utilizes nurse-generated structured and text data to support a learning health system. This study will create important new research data infrastructure, and will be a model for health care organ

reat need foreffective lifestyle SBP-lowering interventions for the older population that can replace drug therapy. Whileaerobic exercise is a recommended lifestyle intervention for controlling SBP and preventing CV diseasenaturally, in older adults it has been shown to be less effective in vascular-tissue remodeling because ofarterial sti
unctionimprovement in response to exercise in older mice is caused by insufficient NAD+ levels to stimulate SIRT1activity. Importantly, replenishment of NAD+ levels induced vascular remodeling, improved vascularfunction, and reduced SBP in mice. An objective of this study, therefore, is to test a combination of aerobicexercise and
ent withexercise is an ideal strategy for improving vascular function, our central hypothesis is that the intervention ofaerobic-exercise training combined with nicotinamide riboside supplementation will reduce SBP inhypertensive older adults more effectively than will exercise alone. We will enroll 45 participants 65 years andolder into
ne average above 130 mmHg, measured by the 24-hour blood-pressure device. To our knowledge, thisstudy will be the first attempt to enhance exercise therapy with nicotinamide riboside in hypertensive olderadults. We believe that nicotinamide riboside is ?the missing piece of the puzzle? in improving vascularremodeling and SBP ma

ncreased complications from surgical/radiotherapeutic treatments. Consequently, cachexia decreases both quality of life and survival time in cancer patients and cachexia itself is responsible for up to 30% of all cancer-related deaths. Interestingly muscles from preclinical models of cancer cachexia as well as cachectic human cancer pati
which is important to the sarcolemmal dystrophin associated protein complex (DAPC), are highly downregulated at the mRNA and protein level at time points which precede and parallel muscle atrophy and weakness during tumor progression. Moreover, preliminary data show that overexpression of Ky in the muscles of tumor bearing n
aled a conserved consensus binding motif for myocyte enhancing factor-2 (MEF2) among the top most commonly shared motifs. Moreover, both the Ky and Myoc gene promoters contain conserved MEF2 binding motifs. This observation, coupled with the findings that MEF2 protein c (MEF2c) is decreased at the mRNA and protein lev
y causative roles in the cancer-induced loss of muscle fiber integrity and the initiation of muscle wasting. Specific Aim 2: To test the hypothesis that loss of MEF2c transcriptional activity is causative in the cancer- induced downregulation of Ky and Myoc and initiates muscle wasting. The results of these studies will provide new insight

mentors focused on inflammation-related topics. Four training positions are requested. The overall researchprogram will focus on mastery of molecular biology, functional genomics and gene regulation, as it appliesbroadly to inflammation research. Although the bulk of the training program will be in the laboratory of anexperienced res
ning program takes advantage of the unique strengths of the College of Medicine in the expanding field offunctional genomics and molecular biology, as well as the existing collaborations between basic scientists andclinicians committed to the training of future clinical academicians. The interface between molecular biology andinflamm
Surgery, Medicineand Pathology Departments will interact with the trainees and the research faculty to assure that the traineesare being exposed to clinically-important issues in inflammation research. Overall direction of the program willrest with the Program Director and an Executive Committee. Candidates for the fellowship are rec
Institute and GeneticsInstitute, and in their own basic science departments, as well as laboratory research meetings. They will also beexpected to attend clinical seminars, including Surgery and Critical Care Medicine Grand Rounds and theDepartment of Surgery Academic Research Conference. Based on our past experiences, it is antici

/alking speed. Low-grade chronic inflammation is a modifiable risk factor. However, it is unknown whether interventions that reduce the levels of inflammatory markers per se improve mobility, or avert decline in mobility in older persons. To address this gap in evidence we propose the randomized clinical trial ENRGISE (ENabling Re
pose to test the efficacy vs. placebo of the angiotensin receptor blocker losartan and omega-3 polyunsaturated fatty acids in the form of fish oil, alone and in combination. Both angiotensin receptor blockers and omega-3 polyunsaturated fatty acids have shown to reduce IL-6 in clinical trials and preliminary data suggest that they may imp
duct a feasibility phase that includes performing meta-analyses of existing trials and cohorts, and conducting a pilot trial to assess the effects of the interventions on several inflammatory markers and walking speed. This will allow us to refine the design, recruitment yields, target population, adherence, retention, tolerability, sample-size,

this University of Florida Molecular Transducers of Physical Activity Preclinical Animal StudySites application (UF PASS) is to conduct experiments in animals that will provide tissues/blood (i.e.biospecimens) to the Chemical Analysis Sites for identification of molecular transducers induced by definedmodels of physical activity from
ture the dynamics of the exercise/adaptation responses we propose to:1) Collect biospecimens at 5 selected timepoints following an acute bout of exercise on na?ve and trained rats;2) Collect biospecimens following short duration training (after 5 bouts) and 3) Collect biospecimens followinglong-term (8 weeks) training.For Phase 2, ou
in vivotesting. The results of the experiments in Aim 3 will provide molecular evidence identifying a set of transducers,released from muscle, that are necessary for exercise induced systemic health. The goals of the UF PASS willbe pursued by the following Specific Aims:Specific Aim 1: Center Coordination Phase.Specific Aim 2: Pha

e neural control of walking are limited by either the inability to measure people during walking (functionalmagnetic resonance imaging, fMRI) or the inability to measure activity below the cortex (functional near-infrared spectroscopy, fNIRS). We assert that a full and accurate understanding of the neural control of walkingin older adult
It isunprecedented insight into the neural control of walking. Here, our overarching objective is to determine thecentral neural control of mobility in older adults by collecting EEG during walking and correlating these findingswith a comprehensive set of diverse mobility outcomes (clinic-based walking, complex walking and community
patterns that areseen when older individuals perform tasks of increasing complexity. CRUNCH describes the over-recruitmentof frontoparietal brain networks that older adults exhibit in comparison to young adults, even at low levels oftask complexity. CRUNCH also describes the limited reserve resources available in the older brain. T
Gduring walking with fNIRS (during actual and imaged walking) and fMRI (during imagined walking). This willallow us to identify the most robust CRUNCH-related hallmarks of brain activity across neuroimagingmodalities, which will strengthen our conclusions and allow for widespread application of our findings. Ourthird aim is to

atics and chemical analyses will achieve the Molecular Transducers of Physical Activity Consortium(MoTrPAC) goals of assessing the molecular changes that occur in response to PA. The ConsortiumCoordinating Center (CCC) for the MoTrPAC will provide support for the organization, administration, planning,standardization, docum
icplanning processes by integrating activities of the MoTrPAC investigators with the input provided by the DataSafety Monitoring Board, the External Scientific Advisors, outside experts, and the NIH. The CCC will facilitateinteractions and communications with junior and senior investigators outside the consortium to maximize theuse
thecutting-edge scientific focus, leverage state-of-the-art coordination technologies, anticipate challenges, andmaximize future opportunities to ensure the success of the consortium. The CCC will comprise four integratedcomponents led by four highly qualified PIs who have a long-lasting track record of successfully working insynergy.
rack record andexpertise of its investigators in: (a) working together; (b) successfully coordinating, managing, and leadinglarge long-term multicenter clinical trials involving PA and other interventions; (c) implementing rigor andtransparency in research, (d) acquiring, managing, storing and analyzing biological samples; (e) conducting

ne therapy to improve functional performancein PAD. However, our observational longitudinal data show that overweight and obese PAD participants whocombined weight loss with walking exercise had less functional decline than those who walked for exercise butdid not lose weight. Therefore, we hypothesize that among people with
herefore, among people with PAD and BMI>28kg/m2, we will test the hypothesis that WL+EX achieves greater improvement in functional performance thanEX alone. Our innovative weight loss intervention uses a group mediated cognitive behavioral framework,connective mobile technology, remote monitoring by a coach, and a calo
d activity. Theseobesity related changes exacerbate the pathophysiology of PAD. Therefore, we hypothesize that weight losswill improve walking ability in part by improving calf perfusion, and increasing calf mitochondrial activity. We will randomize 212 participants with PAD and BMI > 28 kg/m2 to one of two groups for 12 months
estionnaire), and quality of life (measured by the SF12 Physical Component Score) at 12-month follow-up.Tertiary outcomes include MRI measured calf perfusion, MRI-measured calf muscle quantity and fatabundance, and diet quality. We will perform calf muscle biopsies in 50 participants to measure mitochondrialbiogenesis and activ

pulations when the interventions were moved into clinical practice. It is imperative to rigorously an ad hoc auditing effort by a third party after the fact. We believe the key barriers are an open-source generalizability assessment software toolbox and its accompanying

80% of clinical data is text data which cannot be analyzed using traditional statistical cific Aim 1 (R21 Phase): Identify and test the feasibility of text-mining pipelines to process ediction model of hospital-induced delirium. We will then integrate the developed pipelines izations to increase safe effective care for the millions of older adult Americans hospitalized

ffness, resulting in less efficient SBP control. Reduced bioavailability of nicotinamide l nicotinamide riboside, a compound that replenishes NAD+ levels, to optimize exercise's either: (1) 1,000 mg/day of nicotinamide riboside plus 3 days/week of supervised, nagement in older adults. Preliminary evidence from this pilot study may support a full-scale

nts show disruptions in sarcomere and myofiber membrane integrity despite the lack of an injury nice inhibits muscle fiber atrophy. These observations support our first hypothesis that the el in tumor bearing mice, supports our second hypothesis that loss of MEF2c transcriptional into transcriptional mechanisms involving protein downregulation which initiate cancer-induced

earch mentor, trainees will be expected to participate in didactic experiences that complementtheir nation research will be targeted to trauma, sepsis syndromes, ischemia/reperfusion injury, ruitednationally and from the University of Florida College of Medicine (Gainesville, pated thatsuccessful graduates of this training program will possess sufficient research skills to

duction of low-Grade Inflammation in SEniors) to test the ability of anti-inflammatory rove physical function. We plan to recruit older persons who are at risk for, or with, mobility and cost for the main ENRGISE trial. We will assemble the multicenter research infrastructure

tissues that cannot be obtained from humans as well as to conductmechanistic studies that can r hypothesis is that factors released from muscle (i.e. myokines) are the molecular se I Studies. To perform endurance and resistance exercise using male and femaleF344BN rats

s requires real time measurement of active regions throughout the brain during actual walking. mobility measures). Our first aim is to evaluate the extent to which brain activity during actual hesefactors cause older adults to quickly reach a ceiling in brain resources when performing study the mechanisms related to CRUNCH during walking. Thus, our project will address

entation, monitoring and reporting activities relating to the MoTrPAC. The CCC will playa of the MoTrPAC resources toward achieving the overall research goals. To accomplish these . The four CCC components comprise the Administrative Coordinating Center (PI Dr. Pahor), animal exercise studies; (f) sharing resources; (g) publishing results; and (h) leading

PAD who are overweight or obese, aweight loss intervention combined with exercise (WL+EX) rie restricted DASH-derivedOMNIHeart diet. In a seven week pilot study, our intervention s:WL+ EX vs. EX alone. Participants will be randomized from Northwestern University, Tulane ity, capillary density, inflammation, and senescent cell abundance. If our hypotheses