University of Florida
Claude D. Pepper Older Americans Independence Center

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I. CENTER DESCRIPTION

The mission of the University of Florida Older Americans Independence Center (OAIC) is to assess the risk factors of physical disability in older adults, develop and test effective prevention therapies, and train new investigators in research on aging and disability, while developing their leadership qualities. Our strategy is to attract studies and investigators from diverse behavioral, clinical, and basic science disciplines towards research on aging that is focused on a common research theme. The theme, "sarcopenia and prevention of disability", is pursued using an interdisciplinary approach that traverses the entire spectrum of biomedical investigation, including molecular biology, animal studies, clinical research, behavioral sciences, and epidemiology. This research theme addresses the general goal of the OAIC program, namely, to increase scientific knowledge that leads to better ways to maintain or restore independence of older persons. Our research objectives are to (1) assess multiple factors such as biological, co-morbid, psychosocial, and behavioral that contribute to sarcopenia, physical decline, and progression to disability and (2) develop and reliably test in clinical and pre-clinical studies interventions that target sarcopenia, in order to prevent, delay or recover the age-related physical decline and the progression to disability. To address these objectives the UF OAIC includes the following integrated cores, which support investigators, Junior Scholars, infrastructure, and services: the Leadership and Administrative Core, the Research Career Development Core, the Pilot/Exploratory Studies Core, the Clinical Research Core, the Metabolism and Translational Science Core, the Biostatistics and Data Management Core, and the Data Science Core. We train Junior Scholars and support external studies, research development projects, and pilot/exploratory studies. A major strength of the UF OAIC is the concerted action of the cores, projects and investigators that address one common research theme explored through the spectrum of biomedical investigation. Our leading research hypotheses are: 1) biological, co-morbid, psychosocial, and behavioral factors contribute to age-related sarcopenia, physical function decline, and progression to disability and 2) sarcopenia is a strong contributor to the decline in physical function and progression to disability.

<u>The research objectives:</u>

- To assess, by taking advantage of an inter-translation between basic and clinical research, the multiple factors that contribute to age-related sarcopenia, physical function decline, and progression to disability
- To develop and test pharmacological, nutritional and behavioral interventions for preventing decline in physical function and progression to disability

<u>The educational objectives:</u>

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

The operational objectives:

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

II. RESEARCH, RESOURCES AND ACTIVITIES

A. Cores

Leadership and Administrative Core (LAC)

Leader: Marco Pahor, M.D.
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The Leadership and Administrative Core (LAC) is responsible for strategic planning, organization, administrative operations and evaluation of the OAIC Research and Training program. A special effort is being devoted to ensure the coherence of the Center and maintaining an interdisciplinary focus on the common research theme, which is "Sarcopenia and prevention of disability". The LAC tasks are being achieved by the Core Leader and three committees: the Executive Committee, the Independent Review Advisory Panel and the External Advisory Committee. The specific functions of the Leadership Core are:

- To provide overall scientific leadership and direction for the OAIC research and training program.
- To render administrative and budgetary support for the program.
- To coordinate the functions of the OAIC cores and projects in order to facilitate communication and foster translation between basic and clinical research and ensure access of investigators to core resources.
- To assure the coordination of OAIC resources and functions with other research and training grants and institutional resources.
- To communicate with other OAICs and the NIA, and to foster collaborations with other OAICs.
- To facilitate compliance with guidelines and regulations regarding fiscal policy, human subjects, and animal care and use.
- To set productivity benchmarks and monitor progress of individual projects and progress of junior investigators (this aim is shared with the RCDC), and deal with inadequate progress.
- To promote quality, productivity and efficiency (timeliness) in all OAIC activities.
- To arrange the annual meeting of the OAIC External Advisory Committee.
- To maintain the OAIC web-based tracking and monitoring system to facilitate communication.
- To promote the use of uniform assessment batteries in OAIC supported clinical research studies to optimize the use of OAIC resources.
- To maintain the OAIC website and publish the OAIC newsletter.

Research Career Development Core (RCDC)

Leader: Christiaan Leeuwenburgh, Ph.D.
Phone: 352-273-5735 Fax: 352-294-5836 Email: cleeuwen@ufl.edu

The RCDC 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 ideas 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 RCDC 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.

The current Junior Scholars are:

Brian Ahn, Ph.D., ARNP, ANP-BC hcahn@ufl.edu
Assistant Professor
College of Nursing
Department of Family, Community and Health System Science

Scott Brakenridge, M.D. Scott.Brakenridge@surgery.ufl.edu
Assistant Professor
College of Medicine
Department of Surgery

Andrew Bryant, M.D. andrew.bryant@medicine.ufl.edu
Assistant Professor
College of Medicine
Department of Medicine
Division of Pulmonary, Critical Care and Sleep Medicine

Sara Burke, Ph.D burkes@ufl.edu
Assistant Professor
College of Medicine
Department of Neuroscience

Huaihou Chen, Ph.D. huaihouchen@phhp.ufl.edu
Assistant Professor
College of Medicine and Public Health and Health Professions
Department of Biostatistics

Sooyeon Lee, Ph.D. Sooyeon.Lee@surgery.ufl.edu
Assistant Professor
College of Medicine
Department of Surgery

Rui Xiao, Ph.D. rxiao.ufl.edu
Assistant Professor
College of Medicine
Department of Aging and Geriatric Research

Clinical Research Core (RC 1)

Leader: Steve Anton, Ph.D.
Phone: 352-273-7514 Fax: 352-294-5836 Email: santon@.ufl.edu

Co-Leader: Marco Pahor, M.D.
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The Clinical Research Core (RC 1) 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 and Data Management 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 RC 1 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.

Metabolism and Translational Science Core (RC 2)

Core Leader: Christiaan Leeuwenburgh, Ph.D.
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The Metabolism and Translational Science Core provides the infrastructure, laboratory space, trained personnel, consultative and collaborative scientific expertise and a wide spectrum of established methodologies of biochemistry and molecular biology (Western blot and Quantitative-PCR, quantitative-Real-Time PCR, enzyme-linked immunosorbent assays, multiplex immunoassays), high resolution respirometry, and selected measures of metabolism (i.e., ATP measures and enzymes of metabolism) that will address a set of genetic and biological themes focused on causes for sarcopenia and disability. The Core utilizes this state-of-the-art technology to determine specific mechanisms of sarcopenia and the cause of reduced physical function present in elderly populations. The Core provides support for numerous independently funded studies, development projects, pilot studies and exploratory studies. Analyses of levels of biomarkers or cell signaling molecules will help to identify specific biological pathways of aging implicated in the development of sarcopenia. If the precise mechanisms underlying age-associated cellular deterioration can be identified, it will explain the loss of muscle mass and function with age and provide us with potential targets for intervention. In this context, we will also test if specific rehabilitation, physical activity and dietary interventions can attenuate biological pathways leading to sarcopenia and functional impairment. In addition, the Core supports preclinical phenotyping of various domains of function include: Cognition, Motor,Sensory/Hearing. Each of these measures is currently in use in our laboratories and are sophisticated procedures requiring expert oversight and the use of highly trained technicians. These assessment methodologies are conceptually similar to those used in humans and highly translatable.
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Biostatistics and Data Management Core (RC 3)

Leader: Samuel Wu, Ph.D.
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The Biostatistics and Data Management Core is one of four research cores in the OAIC at UF. The mission of the OAIC at UF 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 and Data Management 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 also is involved in all phases of these studies including initial study design and sample size calculations pre-proposal, randomization, and state-of-the-art statistical analyses once the data are completed. For study designs and data for which current methodology is lacking, the core has the expertise to develop new state of the art methodology to perform correct and appropriate analyses of data collected in the Center. The Biostatistics and Data Management 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.

Data Science Core (RC 6)

Core Leaders: Todd Manini, Ph.D. and Sanjay Ranka, Ph.D.
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The overall goal of the Data Science Core is to store, retrieve, clean, organize and summarize complex data from a variety of origins for monitoring and enhancing the health of older adults. The core provides infrastructure, trained personnel, consultative and collaborative expertise to repurpose data from electronic health records (EHR) and to derive key features from high-resolution biomechanical and physiological signals to meet the goals of the UF OAIC. Lastly, the core conducts exploratory analyses with existing epidemiological data to support grant development (e.g. preliminary data and cohort identification) and offers trainees unique publication opportunities. The core collaborates with the UF Health IT system to capture data from the EHR to identify cohorts of geriatric patients for ongoing interventions being conducted in RC1. The EHR is also used to discover factors during hospitalization that are connected to post-hospital functional recovery. These data are organized in a manner that can either be tested using traditional statistical methodologies or mining techniques provided by the expertise in the core. The ultimate goal of the core is to extract as much information as possible from the data to build high performing prediction models. Our research can be hypothesis driven as well as data driven. Our techniques have the potential of deriving non-obvious patterns to better model the underlying data and use it to improve health care of older adults.

Pilots/Exploratory Studies Core (PESC)

Core Leader: Marco Pahor, M.D.
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Co-Leader: Christy Carter, Ph.D.
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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.

B. RESEARCH

The UF OAIC has demonstrated outstanding productivity in supporting and contributing to externally funded grants through its integrated Core infrastructure, pilot funding and mentoring. The UF OAIC supports and contributes to a total of 62 active grants. The UF OAIC has also supported 100 grants that have been completed.

C. DEVELOPMENT/PILOT/EXPLORATORY PROJECTS

The current research development projects are:

Project Title: Development of Clinical Methods to Evaluate Neural Function in Aging (MIND)
Project Leader: Stephen Anton, Ph.D.

A primary focus of the University of Florida (UF) Claude D. Pepper Older Americans Independence Center (OAIC) is to build a comprehensive understanding of the causes and consequences of declining physical function and disability development among older adults. To date investigators have largely focused on sarcopenia, the age-related decline in skeletal muscle mass and strength, as the primary contributor to physical decline. However, recent findings indicate that changes in the central or peripheral nervous systems may play a larger role than previously thought in the development of functional limitations. While these fields hold extensive promise for identifying novel contributors to age-related functional decline, currently the investigators of the Clinical Research Core (RC1) lack the methodological expertise to accurately assess novel aspects of nervous system function. Therefore, the overarching aim of this project is to develop the ability of RC1 to assess novel neural contributors to mobility and overall physical function. Importantly, the development of these techniques will provide the RC1 with the tools to evaluate the potential involvement of the central and peripheral nervous systems in age-related functional decline and disablement. The primary aim of this project is to develop techniques for quantifying peripheral motor unit number and size as well as spinal cord integrity.

The past research development projects are:

Project Title: MALDI Imaging for co-Localizing Oxidative Damage and Lipids in Skeletal Muscle
Project Leader: Christy Carter, Ph.D.

The loss of muscle mass occurring with aging is accompanied by concomitant increases in whole body adiposity and excessive storage of lipids around and into the myocte. Indeed, lipotoxic consequences occur in non-adipose tissues and evolve given that the amount of ectopic fat deposited surpasses the oxidative capacity of the tissue, therefore, feeding fatty acids into toxic metabolic pathways such as de novo ceramide production and diacyglycerol deposition. We have used rodent models of aging to demonstrate that decline in physical performance is associated with increased inflammation, oxidative stress, and subsequent apoptosis in skeletal muscle. We plan to refine our ability to determine if there are in fact age-related changes in lipid deposition that co-localize with changes in inflammation and apoptosis using an innovative approach: Matrix Assisted Laser Desorption Ionization Mass Spectrometry and tandem mass spectrometry or MALDI-MS and MS/MS. The MALDI technique provides for direct ex vivo sample analysis from tissue sections using mass spectrometry and in conjunction with tandem MS, the ability to identify unknown ion signals as well as provide a semi-quantitative measure. This technique also permits repeated assessment of the same tissue sample, allowing for development of more exploratory hypothesis without repeating the same experiment. Our preliminary MALDI experiments demonstrate that in skeletal muscle of 27 month old F344/BN rats treated with an angiotensin enzyme inhibitor enalapril, there is a reduction in known lipid targets (TAG and DAG) which overlap with an increase in the antioxidant anserine, however it is unclear how these compounds are distributed in muscle across the lifespan. We will use MALDI MS and MS/MS methodologies for maximizing our ability to measure lipid content in skeletal muscle across age (6, 26 and 36 months) in male Fischer344/Brown Norway rats and to co-localize anserine with various lipid moieties. To validate this method, we will also use traditional mass spectrometric approaches to characterize the composition of muscle tissue extracts to. Developing these techniques will provide us with new ex-vivo methodologies to image lipid deposition into skeletal muscle and the relationship to declining performance.

Project Title: Skeletal Muscle Apoptosis and Physical Performance/Oxidative RNA/DNA Damage and Repair in Aged Human Muscle
Project Leader: Christiaan Leeuwenburgh, Ph.D.

The objectives of the study are (1) to assess the extent of muscle apoptosis in old low- and high functioning subjects and to verify the presence of an association between muscle apoptosis, sarcopenia and physical disability. (2) to correlate levels of RNA and DNA oxidation with muscle mass and strength, and (3) to quantify gene expression of DNA repairing enzymes in old low- and high- functioning subjects.

Project Title: Clinical tolerance of the microbiopsy and the Bergstrom muscle biopsy technique
Project Leader: Christiaan Leeuwenburgh/Thomas Buford, Ph.D.s

The analyses offered and performed by the Older American Independence Center (OAIC) Biomarkers and Metabolism Core are closely linked to apoptosis, oxidative stress, inflammation and measures of mitochondrial function in tissues such as blood, urine and skeletal muscle. Mitochondrial dysfunction is central to the aging process and the pathogenesis of diseases. A primary objective of this Core is to assess mitochondrial function in skeletal muscle from elderly subjects, and to correlate these measures with the subject's physical performance. To obtain skeletal muscle samples from human participants, the Core has traditionally utilized the large bore Bergström needle technique. This technique ensures large tissue yields, but bears the risk for discomfort and pain, especially in elderly subjects. To avoid these adverse events, it becomes essential to identify, develop, test and optimize minimally invasive techniques of tissue acquisition, particularly for large clinical trials with the elderly. The main focus of this Development project is, therefore, to compare a skeletal muscle microbiopsy technique with the traditional Bergström technique. In contrast to the traditional technique, the microbiopsy relies on a small 16-gauge disposable needle. The consequentially reduced invasiveness holds great potential for its applicability in large clinical trials. The aims of this study are threefold. We will compare the minimally invasive microbiopsy and the traditional Bergström technique with regard to 1) perceived pain by research subjects; 2) their evaluation by the operating physicians; and 3) the tissue yield and quality for mitochondrial function measurements. We hypothesize that the microbiopsy technique will lead to less pain in the subjects, will be the preferred method by the physician, and still provide the minimal sample amount needed to assess mitochondrial function in skeletal muscle. The proposed project will take advantage of an ongoing study, the Developmental Project (OAIC RC5 RD1), and thereby substantially maximize cost-effectiveness. The subjects of this ongoing Developmental Project are young healthy adults and healthy elderly research participants. To achieve the proposed aims, we will perform muscle biopsies of the vastus lateralis on each leg. One leg will be biopsied using the traditional Bergström technique and the other will be biopsied using the microbiopsy technique. Patients and physicians will fill in questionnaires related to the procedures. Mitochondrial function will be assessed and quantified in each of the biopsy specimens to determine the quantity of mitochondria and to compare their quality. If this new procedure for the OAIC shows to be more efficacious, this will allow us to quickly test skeletal muscle mitochondrial bioenergetics and their correlation with clinical interventions (e.g., life style, exercise, pharmacological, nutritional) using a technique that is less invasive for participants.

Project Title: Non-invasive approaches to study skeletal muscle O2 delivery and utilization
Project Leader: Susan Nayfield, M.D./Todd Manini, Ph.D.

A primary focus of the Clinical Research Core (CRC) is to build a biological understanding of causes and consequences of losses in physical function and disability among older adults. Ongoing research by the CRC frequently uses muscle biopsies to accomplish this goal, adding burden and discomfort to participants that directly influences recruitment and adherence in all studies. The overarching aim of this project is to provide the resources to implement and clinically evaluate non-invasive imaging techniques to investigate blood flow, tissue perfusion and mitochondrial function that are major factors that lie in the pathway to aging of skeletal muscle mass and loss in physical function. Such assessments are critical in understanding the etiology of sarcopenia in humans and are well suited for the scope of the OAIC's mission. The goal will be to implement an efficient nuclear magnetic resonance (NMR) protocol to fully assess blood flow, tissue perfusion and mitochondrial function in a single visit that will minimize expensive MRI and staff time as well as participant burden. Specifically, we will assess peripheral blood flow using Phase Contrast Imaging (PCI), muscle

perfusion via Arterial Spin Labeling (ASL), and O2 metabolism via 31P Spectroscopy. To accomplish the implementation phase of the study we will consult with the world's experts who have agreed to assist our efforts. We will also support an educator who can implement the technology on the specific MRI equipment being used by the CRC. Our efforts will lead to further collaborations across the University of Florida by providing new tools to access cardiovascular function and energy metabolism making the CRC a resource for researchers at large. We will finalize our goals by conducting a reliability and validity study that will provide evidence of proficiency in conducting the evaluations. First, we will compare healthy older adults to patients with peripheral arterial disease to establish that we can detect differences in muscle physiology in differing clinical conditions using the newly developed techniques. We will then established test-retest reliability of these techniques in healthy older and PAD patients. The completion of project will provide the CRC a thorough evaluation of O2 delivery and utilization in a single package thus reducing participant burden while maximizing cost effectiveness.

Project Title: Models to Reduce Adiposity and Oxidative Stress
Project Leader: Phillip Scarpace, Ph.D.

This development project is evaluating interventional models that modulate adiposity in aged rats for assessing effects on physical function, inflammation, oxidative stress, apoptosis, and sarcopenia. This study will set the basis and methodologies for preclinical testing of other weight lowering interventions on relevant age-related outcomes. The central hypothesis of this development project is that increased adiposity with age contributes to two age-related outcomes: 1) a decline in physical performance; and 2) changes in muscle quality as measured by increased oxidative stress, inflammation, and subsequent apoptosis in skeletal muscle. We have established several relevant interventional strategies to reduce or increase adiposity in the Fischer 344/Brown Norway (F344xBN) rat, a well-established animal model of aging. F344xBN rats demonstrate declining physical performance, occurring in the context of a steady increase in body weight and adiposity into early senescence followed by a decline, similar to what occurs in humans (1). We will employ one paradigm that elevates adiposity (fat-feeding) and should further reduce physical performance in aged rats, and two interventions that reduce adiposity (mild 8% caloric restriction and POMC gene therapy) and should restore physical performance. Subsequently, we will assess muscle quality, in the context of each of these interventions. We are addressing the following specific aims: 1) Does high-fat feeding exacerbate the already elevated oxidative stress/inflammatory status with age and accelerate the decline in physical performance? 2) Aged rats are obese and, similar to obese humans are profoundly leptin resistant. Therefore, does activation of the central melanocortin pathway (through POMC gene therapy) circumvent leptin resistance and evoke weight loss in aged-obese rats, ameliorate the elevated oxidative stress/inflammatory status with age and lead to improved physical performance? 3) Does short-term, mild (8%) CR prevent the decline in physical performance with age? Thus, these studies will compare the effects of either adiposity inducing or reducing interventions in a model of age-related physical decline, and link these outcomes to dysregulation of muscle quality. The first phase of the developmental project was completed in the first year, in which the responses of aged rats to high-fat (HF) feeding were examined. Results indicated aged rats ate more food, gained more fat and weight compared with young. In addition, high-fat feeding decreased the tendency for wheel running, suggesting the propensity for inactivity with age and high-fat feeding may contribute to the accelerated the rate of diet-induced obesity. These results demonstrate that aged rats are more susceptible to the detrimental effects of a high fat diet. The second phase of study was completed in second year examining gene delivery of anorexic agents to prevent and reverse obesity and the decline in physical activity with age. We discovered that leptin synergized with wheel running (WR) to greatly reduced obestiy and improved metabolich parameters. The mechanism appears to involve a restoration in the age and obesity impared decline in leptin signaling. In the third year, we discoved that small amounts of WR, that were without effect in young rats, decreased body weight and increased physical performance in aged rats. Intervention in aged rats with POMC gene delivery revealed that overexpression in the ventral tagmental area or hypothalamus was effective at detering high-fat feeding mediated weight gain. Data collected from this Developmental project supported the

funding of one VA Merit application in 2009, and NIH grant in 2012 and an American Heart application in 2011. Study is complete.

Project Title: Longitudinal Examination of Physical Performance
Project Leader: Michael Daniels, Ph.D.

This developmental project uses a data set from an RO1 grant, "ACE Inhibition (ACEi) and Physical Performance in Aged Rats" (NIH R01 AG024526-02, PI Dr. Christy Carter) to develop statistical methodologies that will have application to the study of longitudinal assessment of physical performance in aged rats and humans. Specifically, we are refining our understanding of the relationship between pathophysiological changes and declining physical performance and ultimately can design better interventions to attenuate/reverse these changes. Therefore, we will develop new methodology for assessing modeling trajectories from different longitudinal processes (declining physical performance, muscle pathophysiology, and longevity).

The current pilot/exploratory projects are:

CLINICAL

Project Title: Statistical learning methods for incorporating multimodal imaging biomarkers to advance aging researchProject Leader: Huaihou Chen

In contrast to the increasing emergence of multimodal imaging data in geriatric studies, the development of cutting edge statistical methods for analyzing those data has lagged behind the needs of geriatric researchers. Due to the high dimensionality and temporal-spatial dependence of imaging data, conventional statistical methods are not sufficient for analysis. The lack of cutting edge statistical analytic tools has impeded the application of imaging biomarkers to clinical studies. We address several major limitations of existing work: 1) Linear models are inadequate in modeling aging-related nonlinear changes in motor and cognitive outcomes and imaging biomarkers. 2) Marginal correlation between two brain regions of interest (ROIs) is indirect and weak in the sense that all the components in a system are correlated to some degree [56]. 3) Due to the challenge of high-dimensionality, only a small subset of the ROIs is considered in a model, which could miss important ROIs. 4) Prediction of future outcomes is different from building association between observed outcomes and predictors. A biomarker with weak association may improve the prediction accuracy, while a strong association does not necessarily imply better prediction performance in discriminating subjects.

Project Title: Hypoxia Inducible Factor Regulation of Secondary Pulmonary Hypertension
Project Leader: Andrew Bryant, M.D. (This project is both clinical and preclinical)

Idiopathic pulmonary fibrosis is often complicated by the development of pulmonary hypertension (PH), resulting in increased morbidity and mortality. Since the hypoxia-inducible factor (HIF) signaling pathway is important for development of pulmonary hypertension in chronic hypoxia, we investigated whether HIF signaling in vascular endothelium regulates development of PH secondary to pulmonary fibrosis. We generated a transgenic model in which HIF1-α and HIF2-α are deleted in vascular endothelial cells using the VECad promoter to drive Cre recombinase. Following a 33 day protocol of intraperitoneal bleomycin to induce lung fibrosis with secondary PH, we found that endothelial HIF1/2 deficient mice were protected against development of PH, right ventricle remodeling, and pulmonary artery muscularization without any change in the degree of pulmonary fibrosis. In addition, endothelial HIF1/2 deficient mice were protected from chronic hypoxia-induced PH. Studies on isolated pulmonary microvascular endothelial cells (PMVECs) exposed to hypoxia revealed that HIF1/2 deficient PMVECs had greater potassium channel expression, increased transendothelial electrical resistance, and decreased calcium flux compared to controls. HIF1/2 deficiency prevented a hypoxia induced increase in connective tissue growth factor (CGTF), while calcium

supplementation restored the hypoxia-driven CTGF increase in endothelial HIF targeted PMVECs. HIF1/2 and CTGF were more prominently expressed in human PMVECs isolated from IPF lung compared to control, as well as in the vascular endothelium of patients with PH secondary to IPF. These studies demonstrate that vascular endothelial HIF signaling regulates development of secondary PH and suggest that the HIF-CTGF axis is a therapeutic target in these conditions.

Sepsis in the intensive care unit (ICU) is a significant problem which carries significant morbidity, mortality and costsProject Title: The acute development and persistence of frailty, comorbidity and disability in critically ill patients after intra-abdominal sepsis: "Induced Frailty".
Project Leader: Scott Brakenridge, M.D.
Sepsis in the intensive care unit (ICU) is a significant problem which carries significant morbidity, mortality and costs, especially in the elderly. ***Intra-abdominal sepsis***, caused by disease processes such as appendicitis, diverticulitis, bowel obstruction and post-operative abscess, adds significant additional risk and morbidity due to need for infection source control, which most often requires invasive procedures. Advancements in early detection, sepsis resuscitation and critical care management have significantly decreased rates of multiple organ failure and in-hospital mortality. However, it now appears that the burden of sepsis has shifted from early deaths to a prolonged course of **chronic critical illness** (defined as ≥14 days ICU course with persistent organ dysfunction) and poor long-term outcomes.9,10Although not strictly age-dependent, this clinical phenotype appears to occur most commonly in older individuals that survive intra-abdominal sepsis, where functional, "robust" and "pre-frail" individuals in the preseptic state subsequently develop a new, post-sepsis baseline state of cognitive, physiologic and functional morbidities consistent with the frailty syndrome of the elderly. We have coined this proposed phenotype of an acute, persistent, sepsis-associated decline in health status as "***Induced Frailty"***. We hypothesize that this clinical phenotype is secondary to well described mechanisms of persistent immunologic and catabolic dysfunction that occur after sepsis. In order to further elucidate and describe this phenotype, we propose to enroll 50 surgical ICU patients with intra-abdominal sepsis into a prospective, longitudinal study over 18 months (six months enrollment, one year follow up). Subjects will be monitored and treated via strict evidence based protocols in the ICU. Pre-sepsis health status will be determined via patient/proxy surveys and electronic medical record extraction. The complete in-hospital clinical course will be recorded at set intervals until, death, ICU discharge or ICU day 14, whichever comes first. Frailty, cognitive, and functional assessments will be performed at three, six, and 12 months after enrollment.

Project Title: Knee Pain and Transcranial Direct Current Stimulation in Older Asian Americans
Project Leader: Hyochol Ahn, Ph.D., ARNP, ANP-BC
Pain is a complex phenomenon under the control of endogenous, descending modulatory systems with the brain playing an important role. In chronic pain, abnormal reorganization of pain-related brain networks is known to occur. This reorganization has the potential to alter motor function due to the overlap of pain and motor networks in the brain. This may be relevant in conditions such as osteoarthritis where pain is the primary complaint of individuals and is associated with decreased function including decreased walking performance. Given the shared networks involved in pain and motor processing, the present study will compare older adults with a chronic pain condition with older adults without chronic pain. We will perform a neuroimaging battery, a quantitative sensory assessment battery along with simple and complex walking tasks performance measures.

Project Title: Pain and mobility function in older adults
Project Leader: Yenisel Cruz-Almeida, Ph.D.
There are 17.3 million Asians in the United States, and Asian American was the fastest growing ethnic group in the United States between 2000 and 2010. Ethnic group disparities in pain and disability in the United States are often reported in the literature, but few studies have examined differences in pain and disability

between Asian Americans and other ethnic groups. While it is generally believed that Asian Americans' pain experiences do not differ from those of whites, our current findings suggest Asian Americans display increased pain and disability compared to non-Hispanic whites. Osteoarthritis (OA) of the knee affects 16% of the population above 45 years old, and leads to a chronic pain state that decreases physical performance and mobility. Because pharmacologic modalities for pain may increase the risk of adverse effects, researchers are becoming interested in therapeutic approaches to pain that target the central nervous system and do not depend on pharmacologic agents. In particular, clinical studies of Transcranial Direct Current Stimulation (tDCS) have shown promising preliminary results for other types of chronic pain; however, these studies are limited in number and have not focused on older adults or ethnic minorities. In addition, a small number of studies reported that outcomes following pain treatment may differ by ethnic group. Therefore, the overall goal of this proposed study is to examine ethnic differences in pain and mobility disability among older Asian Americans and non-Hispanic whites with knee OA, and to evaluate the efficacy of tDCS on pain and disability in this population. We also propose to explore ethnic group differences in biological and psychosocial factors and their contribution to pain sensitivity, and to investigate whether tDCS effects differ by ethnic group. This will be one of the first studies to characterize ethnic group differences and underlying mechanisms of pain and mobility disability in Asian Americans and non-Hispanic whites with knee OA, and to test the efficacy of the innovative pain treatment tDCS in older adults with knee OA. Moreover, this study will evaluate the role of ethnicity in determining pain sensitivity and pain treatment outcomes in individuals with OA.

Project Title: A Pilot Study to Evaluate the Role of Brain Integrity on Post-Hospital Sarcopenia
Project Leader: Adam Woods, Ph.D., Todd Manini, Ph.D.

Hospitalization is a strong and independent risk factor for Sarcopenia. Older adults who are hospitalized in the previous year experience greater losses of lean mass and muscle strength than their non-hospitalized peers. Most of the research has focused on understanding muscle atrophy as the cause of weakness. However, post-hospitalization muscle weakness is not solely due to muscle atrophy— it explains less than 10% of the variance. We propose that the sequela of hospitalization (e.g. deconditioning, disease severity, etc) reduces the integrity of brain motor pattern that is used to produce forceful muscle contractions. Evidence from the literature suggests that central nervous system impairments explain approximately 60% of the variance in the loss in muscle strength observed following hospitalization. However, while these findings have helped to move the field forward, the measures lack spatial resolution (i.e. where is the impairment). Accordingly, there remains a major gap in understanding whether deterioration of specific brain motor tracts contribute to posthospitalization induced sarcopenia. We intend to conduct a one-year prospective cohort study to examine the integrity of the cortical-spinal white matter tract in post-hospitalized older adults. However, we lack some essential elements in which to conduct this future study. Therefore, this pilot study will refine the following: patient eligibility, feasibility of collecting outcomes in patients, variances for statistical power, influence of covariates, timeline, patient attrition rates, data analysis strategies and magnetic resonance imaging protocol for mapping the cortical-spinal tract. We will accomplish these operational aims efficiently and cost-effectively by leveraging funding with a newly awarded R01 by Dr. Catherine Price, which seeks to identify pre-surgical neuroimaging biomarkers following total knee arthroplasty (TKA) (R01NR014181). Specifically, we request pilot funds to add measures of sarcopenia (muscle strength, mass and gait) and purchase additional MRI scan time to assess the integrity of the corticospinal tract. Measures will be collected in 20 patients before and after hospitalization (2 days, 3 months and 12 months) and 20 age and disease severity matched controls at similar time points. In summary, there are long-term impairments that result from hospitalization in older adults that are not explained by the illness alone. This pilot study will result in subsequent larger NIH funded studies because the research is distinct from all others being conducted on muscle function, aging and effects of hospitalization.

Project Title: ACE inhibitors combine with Exercise for Seniors—Mechanisms (ACES-M)
Project Leader: Thomas Buford, Ph.D.

With persons aged > 65 years representing the fastest growing segment of the U.S. population, the prevention of age-related functional decline and disability is an important public health priority. The loss of functional abilities in advanced age is associated with not only the onset of disability and the loss of independence but also with increased rates of morbidity and mortality. Compared to normotensive counterparts, older persons with hypertension experience accelerated functional decline. To date, physical exercise is the primary strategy for preventing functional decline. Yet despite the general benefits of training, exercise alone appears to be insufficient for preventing this decline. Thus, alternative or adjuvant strategies are needed to optimize the functional benefits of exercise for seniors with hypertension. Our preliminary data suggest that angiotensin converting enzyme inhibitors (ACEi) are efficacious in enhancing exercise-derived improvements in function. Despite these promising initial findings, the hypothesis that ACEi improve older adults' functional responses to exercise has not to our knowledge been tested in a randomized controlled trial (RCT). The long-term goal of this research is to conduct a RCT to appropriately test the hypothesis that ACEi improve older adults' functional responses to exercise. The specific objective of this proposal is to provide proof-of-mechanism to strengthen the rationale for the future trial. A total of 36 sedentary men and women > 65 years of age with physical limitations and hypertension will be recruited to participate in a 12 week intervention study. Participants will be randomly assigned to one of three conditions: (1) ACEi plus exercise training, (2) thiazide diuretic plus exercise training, or (3) AT1 receptor antagonist plus exercise training. The exercise intervention will include both multi-modal, center-based training and home-based walking. The specific aims are to: (1) assess the relative effect of the interventions on changes in exercise capacity, (2) characterize the effect of the interventions on circulating concentrations of angiotensin-related peptides, and (3) evaluate the impact of the interventions on relevant molecular and cellular skeletal muscle characteristics.

Project Title: Effects of Oxytocin on Physical and Cognitive Functioning in the Elders
Project Leader: Natalie Ebner, Ph.D.

The pilot project is a first step toward integrating two important lines of research: 1) broad evidence of age-associated decline across functional domains and 2) increasing evidence of beneficial effects of the neuropeptide oxytocin on health, cognition, and socioemotional functioning. This line of research specifically brings together a team of junior and senior experts on physical and cognitive aging, neuroscience, and psychopharmacology for a comprehensive investigation of the anti-inflammatory effects of oxytocin and effects of oxytocin on improvement of physical health and cognition in old age. The study will comprise older men of varying cognitive status, who either self-administer intranasal oxytocin or placebo over a period of three weeks. Inflammation markers, physical and cognitive performance, and brain activity during cognitive tasks will be assessed pre- and post-intervention in order to determine intervention effects of oxytocin treatment on these functional measures. By combining neuroendocrine with behavioral and pharmacological approaches, this project constitutes an example of best practice in combining different scientific techniques, offering different levels of analysis and different perspectives on the phenomenon of interest. The primary goal of the current proposal is to establish high quality pilot data that will contribute to extramural funding of this line of research. In this endeavor the pilot will also leverage the ongoing data collection in the OXT Faces Study (with a focus on oxytocin's effects on socioemotional functioning in aging). Findings from this this project will increase understanding of the role of the neuropeptide oxytocin in physical and cognitive function in aging, and in interaction with socioemotional functioning. Furthermore, information gained from this project will have the potential to inform pharmacological interventions targeted at preventing or delaying physical decline, cognitive deficits, and socioemotional dysfunction, working towards improved independence and quality of life in old age.

Project Title: Effects of Vitamin D Supplementation on Fall Risk and Functional Outcomes in Older Adults with Insufficient Vitamin D Levels: A Pilot Study (DSAFE)
Project Leader: Stephen Anton, Ph.D.

The potential role of Vitamin D deficiency and/or insufficiency in increased risk for falls and physical dysfunction, cardiovascular disease, autoimmune disorders, and immune functioning is not clear at the present time. Currently, evidence regarding the role of Vitamin D in age-related health conditions and functional decline is mixed. It is also unclear if Vitamin D supplementation has beneficial effects on improving physical function and reducing fall risk in older adults. Thus, studies are needed to determine the potential effects of different doses of Vitamin D supplementation on falls and physical function in older adults. However, before large-scale randomized controlled trials can be conducted, pilot studies are needed to assess the feasibility of identifying and enrolling a sufficient number of older adults with Vitamin D insufficiency into longer-term trials, as well as to assess their is to determine the feasibility of recruiting the target population of older adults with low Vitamin D levels (<30 ng/mL) for such a trial, assess compliance with Vitamin D supplementation, and gather preliminary data for estimating power and sample-size for a future randomized controlled trial. A total of 50 individuals with low Vitamin D levels (i.e., serum 25-hydroxy Vitamin D range 10 ng/mL to 30 ng/mL) will be enrolled into the present six-month study. After completing a baseline assessment in which blood pressure and fall risk are assessed, participants will be provided with a three-month supply of capsules containing Vitamin D (800 IU per capsule) and will be instructed to consume one capsule per day prior to returning to the clinic for a three-month assessment visit. Following completion of their three-month assessment visit, participants will be provided with a second three-month supply of Vitamin D capsules and will be instructed to continue following the same dosing regimen prior to returning to the clinic for a six-month assessment visit. Thus, the present study will directly address the Institute of Medicine's recommendation regarding the collection of pilot data to assess the feasibility of identifying and enrolling a sufficient number of participants at an adequate rate and cost, as well as adherence to the study intervention, for the planned future trial.

PRE-CLINICAL

Project Title: Critical role of Sirtuin 1-Mitofusin 2 axis in aged livers
Project Leader: Sooyeon Lee, Ph.D.

Ischemia-Reperfusion (I/R) injury 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 suppression. Growing evidence indicate that SIRT1 also serves important roles in cytoprotection against ischemia/reperfusion-mediated injury. In our recent studies, we have identifiied a novel target of SIRT1- a mitochondrial protein Mitofusin-2 (MFN2), that interacts with SIRT1 and is potentially deactylated by this enzyme. In this study, we will extend our original findings that SIRT1-MFN2 interaction directly impacts multiple essential processess during I/R in young cells, and investigate how the status of this SIRT1- MFN2 axis is impacted by aging. Our principal hypothesis is that premature SIRT1 loss by short ischemia in old hepatocytes precipiates an accelerated sequential chain of defective mitophagy, mitochondrial permeability transition (MPT) onset and hepatocyte death after I/R. Furthermore, we will establish whether MFN2 acetylation is a critical signal that bridges SIRT1-mediated cytoprotection with autophagy and/or mitophagy. To test our hypothesis, we will use three age groups (young, middle aged, and old) mice and isolate primary hepatocytes from both SIRT1 wild type (WT) and knockout (KO) mice and characterize the cellular mechanisms including defective mitophagy, and onset of the MPT and cell death after I/R. These studies will provide novel mechanistic knowledge regarding the role of aging and increased suseptiblity for liver damage from I/R, and will establish new directions for therpeutic strategies for improving I/R-mediated liver failure.

Project Title: A Novel Rodent Model of Age-related Motor-Cognition Dual-Task Deficits
Project Leader: Sara Burke, Ph.D.
The loss of independence in the elderly can manifest from impairments in both physical and cognitive abilities. Importantly, a bi-directional relationship exists between these modalities such that dysfunction in one produces declines in the other. Moreover, even in normal aging, latent motor deficits can be unmasked when subjects perform a "dual-task", which requires walking while using working memory. This presents a significant problem, as instrumental and basic activities of daily living often necessitate simultaneous motor and cognitive functioning. Critically, a fundamental gap exists regarding the biological mechanisms that are responsible for the strong association between physical performance and cognition and why the aged brain has insufficient resources for supporting dual-task performance. The long-term goal of the proposed research plan is to determine the interactive mechanisms of declining physical function and cognition in order to develop therapeutic strategies that promote successful aging. The objective of the current application is to obtain critical pilot data that defines the interactions between walking gait and memory in a Brown Norway x Fischer 344 rat model of aging and begin to determine if a ketogenic diet intervention leads to better performance on a motor-cognitive dual-task. Additionally, we will measure peripheral markers for inflammation and oxidative stress in aged rats to uncover the biological factors that impact motor-cognitive function. These pilot data will be used to support an R01 application. A novel device for assessing rodent gait has been developed in order to achieve these aims. This gait tracker provides the unprecedented technological advancement of being able to integrate with other behavioral test apparati, which is not possible with commercially available tools. The significance of the proposed project is that the development of an animal model of cognitive-motor interactions will vertically advance aging research by enabling investigations into the mechanisms of this association in the elderly. The rationale is that at the completion of these experiments the field of aging research will be better poised to test potential interventions for promoting the abilities of elderly individuals to live fulfilling and independent lives.

<u>The completed pilot/exploratory projects are:</u>

Project Title: A new adaptive physical activity technology in nursing home older adults
Project Leader: Vincenzo Valiani, M.D.
The primary aim of the proposed research is to determine the feasibility and acceptability of a new physical activity technology (JINTRONIX) on a small population of nursing home older adults. The secondary aim is to explore the physical performance of the participants at the baseline, at the end and after two weeks by the end of the physical exercise program. The tertiary aim is to explore the gender related difference in the feasibility and acceptability of the nursing home physical activity technology. The long-term objective of the proposed work is to enhance late-life health and independence through interdisciplinary and innovative approaches to optimize physical performance and mobility among older adults. Ten men and ten women aged > 80 years and living in a nursing home will be enrolled and assigned to a specific cycle of home independent physical activity program of 4 weeks using type tools, virtual games, and motion tracking sensors. A team of a physician and a kinesiologist will help the participants to learn the interface at the beginning of the program and will check the results by tracking the data via the JINTRONIX web interface. The feasibility and acceptability to physical exercises will be evaluated through the daily diary of the participants and the data registered by the JINTRONIX software. The physical performance and the functional status of each participant will be measured at the baseline, at the end and after two weeks by the end of the cycle of exercise program through the SPPB (Short Physical Performance Battery) test, ADL and IADL. The proposed research will be a pilot study for a larger work.

Project Title: Age related post-transcriptional regulation of translation in skeletal muscle
Project Leader: Luciano Brocchieri, Ph.D.
Sarcopenia, a muscle atrophy condition associated with weakness and loss of strength leading to a decline

in physical capacity, is commonly observed in the elderly population. A progressive increase with age in the concentration of damaged macromolecules, especially proteins, is likely to play a central role in senescent decline. Classic studies in diverse organisms, including humans, have established a link between the aging process and the regulation of protein synthesis and degradation. Eukaryotic cells must invest in an extensive network of factors, comprising ~800 proteins in human cells (~200 chaperones and co-chaperones and ~600 ubiquitin-proteasome and autophagy components), which cooperate to maintain the conformational integrity of the proteome. Thus, to understand the causalities of loss of proteostasis with aging requires a global understanding of how regulation of the quantities and quality of the protein product is affected by aging. Recent applications of the newly developed deep-sequencing technique of "ribosome profiling" have demonstrated on a transcriptomic level how protein production strongly depends on stress-related posttranscriptional mechanisms of translational control. The purpose of this study will be to provide first-time characterization of how age-related muscle function decline (sarcopenia) is regulated and affected by the deterioration of control of translational processes. We will use a well established rat model of mammalian translational control of individual genes in muscle tissue at different stages of aging in comparison to young animals and to modifications induced in muscle cell by mild and severe oxidative stress treatment, a known condition associated with aging. Using the transcriptomewide information provided by ribosome profiling we will be able to identify age and stress related mechanisms of translational control, to quantify gene-by-gene translational activities, and to formulate hypotheses on how failure of translational control may lead to proteostasis collapse with aging. muscle aging to investigate modifications in

Project Title: Role of Mitochondrial DNA Repair in Sarcopenia
Project Leader: Silvia Tornaletti, Ph.D.

Sarcopenia, the age-related loss of functionality of skeletal muscle, is characterized by high levels of apoptosis, by accumulation of oxidative damage, and by mitochondrial (mt) DNA abnormalities. In addition, aging muscle shows decreased levels of the mitochondrial transcription factor A (TFAM), a 25 KDa nuclearencoded protein that has central roles in maintaining mtDNA structural integrity and functionality. These observations indicate that in aging muscle DNA repair pathways inefficiently remove DNA lesions from mitochondrial DNA. However, little is known about DNA repair in muscle tissue and its changes in efficiency with aging. We propose to fill this knowledge gap by testing two possible hypotheses on how DNA repair and TFAM may be involved in sarcopenia. A first hypothesis is that the efficiency of repair of oxidative DNA damage in skeletal muscle decreases with age. A second hypothesis is that accumulation of oxidative DNA damage in mtDNA in aged muscle affects the efficiency and/or the fidelity of TFAM binding to its target sequences with deleterious effects on mtDNA maintenance, replication and transcription. Specifically, we propose to: 1) Measure the efficiency of repair of oxidative DNA damage in skeletal muscle comparing repair efficiency in muscle from young and old Fisher 344xBrown Norway rats. Repair kinetics of base excision repair enzymes will be measured on mtDNA sequences (D loop, common deletion sequence) containing specifically positioned single-base modifications, abasic sites, or nucleotide gaps. 2) Measure binding efficiency of TFAM to damaged and undamaged mtDNA sequences in skeletal muscle. Our molecular analyses will be supported by measurements of functional activities on animals of different age groups, thus providing us with a comprehensive view of how molecular deficiencies affect muscle function. Our studies for the first time will provide a comprehensive analysis of DNA repair and DNA maintenance mechanisms in an animal model system that most closely resembles the sarcopenia observed in humans. This innovative approach will bring a new level of scientific discovery to the unresolved question of how muscle mass and function declines with sarcopenia.

Project Title: Age-related iron accumulation and its role in mitochondrial dysfunction
Project Leader: Jinze Xu, Ph.D.

Although iron is essential for normal cellular and enzymatic functions, age-related iron dyshomeostasis

may be responsible for cellular and mitochondrial dysfunction, which likely contributes to aging and several age-related diseases. We hypothesize that age-related non-heme iron accumulation is associated with increased skeletal muscle labile iron levels and/or greater release of iron from storage sites, causing oxidative damage and mitochondrial dysfunction. Therefore, increasing cellular iron export by genetic manipulation of over-expression of ferroportin could improve muscular mitochondrial function and reduce oxidative damage in skeletal muscle of aged rats. To reduce iron levels, levels of ferroportin (a cellular transmembrane iron exporter) will be increased by using innovative transfection techniques directly applied to the muscle. Experiments will be performed on intact muscle fibers of Fischer 344 × Brown Norway (F344BN) rats at two different ages (8 and 26 months). Muscles will be transfected to increases ferroportin one week prior to a standard hind-limb suspension protocol. To substantiate our hypothesis, we will use novel intravital multiphoton excitation laser-scanning microscopy to assess mitochondrial membrane potential. Additional mitochondrial bioenergetics parameters will be determined with high-resolution respirometry, which does not require isolation of mitochondria from skeletal muscle tissues. We hypothesize that cellular iron levels in soleus muscles of animals exposed to ferroportin transfection will be reduced and show an improvement in mitochondrial function and reduced levels of apoptosis. Hence, for the first time, using highly translational interventions and novel biological and imaging methods, we will determine the effects of reduced cellular iron levels on skeletal muscle mitochondrial bioenergetics, oxidative damage and apoptosis in aged animals. Thus, we will determine the therapeutic potential of these genetic manipulations to reduce myocyte iron levels at advanced age to improve skeletal muscle mitochondrial and physical function with aging.

Project Title: Aging induced pluripotent stem cell (iPSC) study
Project Leader: Anna-Maria Joseph, Ph.D.

Human aging is associated with a progressive decline in the functional capacity of most tissues and organs of the body. Skeletal muscle is highly affected with aging, typically experiencing a 1% loss per year after the age of 40 and accelerating with each passing decade. This muscle atrophy referred to as sarcopenia, is associated with weakness and loss of strength leading to a decline in physical capacity that is observed in the elderly population. Currently, the mechanisms associated with these age-related changes are under investigation but research is limited due to the lack of available models that mimic aging conditions in humans. Thus, the main focus of this project is to establish a new experimental model of human aging using induced pluripotent stem (iPS) cells derived from skin biopsies of healthy elderly participants (> 70 yr), as well as young healthy adults (20-35 yr). iPS cells are adult cells reprogrammed to an embryonic stem (ES) cell-like state by forced expression of several factors that are vital for maintaining ES cell function. Human iPS cells maintain the properties of ES cells, including pluripotency that refers to their ability to form any type of tissue in the human body. While iPS cells resemble ES stem cells they have less ethical concerns and immune rejection issues. Moreover, due to the fact that human iPS cells retain the properties of the donor cells they can be used to establish "patient-specific" iPS cells that exhibit the disease characteristics of the individual. For this reason, we will establish iPS cells from young and elderly individuals of disparate ages that retain the aging phenotype of the subject and can be studied in the laboratory to investigate the mechanisms associated with aging. Furthermore, given the impact of reduced muscle mass on physical capacity, we will use these iPS cells to generate muscle cells that will also express the aging phenotype of the subject. Altogether, we anticipate that iPS cells and iPS-derived muscle cells generated from this study will maintain the aging characteristics of the subjects and will provide a highly innovative model to study human aging. More importantly, these age-specific iPS cells could potentially allow the opportunity for fast track drug screening and the development of stem cell-based therapies for age-related diseases.

Project Title: Gut-Microbiome Interactions, Aging and Intervention
Project Leader: Drake Morgan, Ph.D.

There is increasing evidence linking gut microbiota to a variety of behaviors. As this is a relatively new area of study, essentially all experiments to this point have investigated the difference between "germ-free" and

conventionally-housed mice. Germ-free mice are typically born via Caesarean section and raised in an environment that eliminates the possibility of becoming infected with any bacteria (i.e. sterile housing conditions, food, and water), and therefore have no endogenous bacterial flora. The acquisition of microbiota in the immediate postnatal period has been demonstrated to have a defining impact on the development and function of the gastrointestinal, immune, neuroendocrine, and metabolic systems of an animal. The impact on behavior is less known, although several studies have demonstrated that germ-free mice are considerably less anxious than animals with gut flora. Little is known about other behaviors (e.g. learning and memory, locomotor activity). The primary goals of this application are to establish that variations in the microbial community are related to behavioral outcomes (as opposed to the presence versus absence of a microbiome), that the behavioral phenotype is transmissible via the microbiome, to determine the mechanisms linking gut flora and behavior, and to assess whether older animals are differentially sensitive to these manipulations.

Project Title: Automaticity of walking: Age-related impairment and functional implications
Project Leader: David J. Clark, Sc.D.
Coordinated control of walking is compromised with aging, and this is likely an important determinant of mobility function. Evidence from dual-task paradigms indicate that older adults rely to a greater extent on the brain to control walking. This lack of automaticity during walking may be detrimental because the brain becomes burdened with controlling walking and is thus less able to perform other important information processing task and to assist with motor control under challenging walking conditions. Peripheral sensory deficits may be an important factor, as these deficits are common in older adults and sensory input is known to be critical for the spinal circuitry that facilitates coordinated walking. The overall hypothesis of this proposal is that compromised mobility in older adults is associated with reduced automaticity of walking due in part to impaired peripheral sensory function. We will address the following specific aims:
Specific Aim 1: Examine the association between automaticity and mobility function in older adults with high, moderate and low mobility function. We hypothesize that automaticity will be associated with walking ability.
Specific Aim 2: Examine whether neuromuscular activation measurements improve upon gait biomechanical measurements for identifying individuals with deficient automaticity of walking. Advanced analysis of surface electromyography (EMG) will be used to quantify automaticity by examining: (a) inter-muscular coordination using "spinal cord map" analysis and b) estimated supraspinal contribution to control of leg muscles using wavelet analysis of EMG frequency content. We hypothesize that neural measures will detect deficient automaticity more frequently than biomechanical measures. Specific Aim 3: Assess whether peripheral sensory deficits and muscular weakness in the legs are associated with deficient automaticity. We hypothesize that the presence of sensory deficits (determined by clinical assessment) will be a significant factor accounting for deficient automaticity, but that muscular weakness will not.

Project Title: Immune Mechanisms in the Elderly in Response to Severe Sepsis and Trauma
Project Leader: Philip Efron, M.D.
Our overarching hypothesis is that aging is associated with an inappropriate emergency myelopoietic response that contributes to increased inflammation, immune suppression and organ injury. The project will have two specific aims: 1) to characterize the emergency myelopoietic response during severe sepsis and severe trauma in the aged versus the young adult mouse; and (2) to examine whether increased dysregulation and delay in the emergency myelopoiesis response after sepsis or trauma is responsible, in part, for the immune suppression that leads to increased susceptibility and/or mortality to secondary infections in the elderly as compared to the young. Sepsis and trauma remain two of the leading causes of death in the United States. Besides early resuscitation and source control, little progress has been made in either field over the past two decades. One of the consistent risk factors for mortality in either disease state is a patient age of greater than 55-65 years old. Preliminary work in both animal models and human translational research illustrates that the immunological response of the elderly significantly differs from that of the younger population, and that this is in part responsible for the increased morbidity and mortality seen with older severe sepsis and severe trauma patients.

With the increasing age of the hospital population, the requirement for a better understanding of the innate and acquired immune responses in the elderly in situations of extreme inflammation, including trauma, infection and hemorrhage, has become particularly important.

Project Title: Inflammatory Mediators of Ethnic Differences in OA Pain and Functional Impairment
Project Leader: Roger Fillingim, Ph.D.

Osteoarthritis (OA) represents the leading cause of disability worldwide, and the knee is the most commonly affected joint [3]. Knee OA is more common and produces greater pain and disability African American (AAs) than non-Hispanic whites (NHWs) [1]. Indeed, our findings from the UPLOAD (Understanding Pain and Limitations in Osteoarthritic Disease) Study demonstrate greater pain and functional impairment among AAs [2]. However, the mechanisms underlying these ethnic group differences in pain and reduced function remain unknown. Biomarkers reflecting non-specific inflammation (C-reactive protein, CRP) and neutrophil activation (myeloperoxidase, MPO) have previously been associated with OA-related pain [4;5], however, no investigator to date has determined whether these markers contribute to ethnic group differences in knee OA-related pain and functional impairment. Therefore, we propose in this exploratory study, to determine whether CRP and MPO differ for AAs versus NHWs with knee OA, and whether levels of these biomarkers contribute to ethnic group differences in knee OA-related pain and functional impairment. We will test the following hypotheses: 1) Patients with knee OA will show higher CRP and MPO compared to pain-free controls, and CRP and MPO will be positively associated with OA related pain and functional performance; 2) African Americans with knee OA will show higher CRP and MPO compared to non-Hispanic whites; and 3) These group differences in CRP and MPO will partially mediate ethnic group differences in OA related pain and functional impairment.

Project Title: Role of Curcumin and Methotrexate in Improving Physical Function in Older Adults with Elevated Levels of Inflammation (ICE)
Project Leader: Stephen Anton, Ph.D.

Given the increasing number of older adults with chronically elevated levels of systemic inflammation, new therapies are urgently needed to reduce chronic inflammation and improve functional ability in this high risk population. Botanical and pharmaceutical compounds represent important and underexplored source of potential new therapies for improving both cognitive and physical function because of their anti-inflammatory properties. Curcumin, a bioactive polyphenolic extract of Turmeric, has been found to lower CRP levels in patients with rheumatoid arthritis. Methotrexate has been found to reduce a number of markers of systemic inflammation including CRP and IL-6 (as well as TNF-alpha) in patients with rheumatoid arthritis and psoriasis. Although these compounds have potent anti-inflammatory effects, the effects these compounds have on functional outcomes, have been largely unexplored. Moreover, experimental data in older adults (age > 70 years) with elevated levels of inflammation, who are at highest risk of functional decline, are lacking. The proposed randomized, placebo-controlled study will determine whether supplementation with selected anti-inflammatory agents (i.e., curcumin and methotrexate) in low to moderate functioning older men and women (> 70 years) with elevated levels of inflammation [interleukin-6 (IL-6) > 2.54 pg/mL)]4 is associated with the following outcomes: (1) reductions in markers of systemic and intramuscular inflammation, (2) improvements in physical function, (3) improvements in cognitive performance, and (4) reductions in pain and experimental pain sensitivity. To achieve these aims, eligible participants (N = 90) will initially complete a baseline assessment visit and will then be randomized to receive curcumin (1000 mg/day), methotrexate (10 mg/week) or a placebo (n=30 per group) for a period of 6 months. Because methotrexate is a folate-depleting drug, participants in this study arm also need to take 1 mg of folate six days per week. In order to ensure that the results of the study are related to the methotrexate or the curcumin, all study participants will be instructed to take 1 mg of folate six days per week. Following this 6-month supplementation period, participants will complete a post-treatment assessment visit. Within each condition, a subgroup of participants will undergo a functional MRI and a muscle biopsy before and after treatment. The proposed study will be the first to test

whether selected anti-inflammatory agents reduce systemic and cellular inflammation, improve cognitive and physical function, and reduce pain levels in older adults at risk for functional decline due to high levels of systemic inflammation.

Project Title: Locomotor reserve: a novel approach for detecting mobility deficits with aging
Project Leader: David J. Clark

This goal of the project is to produce high-quality pilot data to support an externally funded line of research for early detection of age-related mobility deficits, specifically with regard to emerging neuromuscular impairment. We propose the concept of a "locomotor reserve" to provide a novel and promising approach by which physical assessments can be used to detect and probe the neuromuscular determinants of emerging mobility disability. Locomotor reserve is operationally defined here as the ability to increase locomotor output over and above usual locomotor output. This proposal will focus on walking speed reserve (% difference between usual and fastest walking speeds) and step length reserve (% difference between usual and longest step lengths while walking). We expect that increasing speed and step length during a brief walking assessment primarily challenges the neuromuscular system, and may thus provide unique insight to neuromuscular factors affecting mobility function. We will recruit older adults to two experimental groups (n=10 participants per group). Participants in both groups will have usual walking speed in the range of 1.0-1.4 m/s, which has been described as a "normal" range. The decision to recruit relatively high functioning participants is consistent with our objective of establishing assessments for early detection of mobility deficits. The difference between the groups will be the magnitude of walking speed reserve. The group with higher walking speed reserve ("HIGH") will be capable of increasing walking speed by at least .8 m/s. The group with lower walking speed reserve ("LOW") will be capable of increasing walking speed by .6 m/s or less. Muscle volume, intermuscular adipose, walking biomechanics and neural control will be assessed in order to determine the factors underlying differences in locomotor reserve.

Project Title: Epigenetic model of accelerated late life obesity and decline in muscle quality
Project Leader: Philip Scarpace

Obesity, including age-related obesity has become a national problem (1). Age-related obesity is a major link to insulin resistance, diabetes, increased cardiac risk, atherosclerosis, and stroke, ultimately leading to impaired physical performance and disability (2). Obesity in males and females over 70 years of age dramatically increases by nearly two-fold the number of remaining years spent disabled (3). There are several potential causes of obesity, including genetic and epigenetic factors, as well as lifestyle factors (6). A relatively small number of preclinical (mostly rodent) studies have examined the role of maternal obesity on the susceptibility of offspring to develop obesity. Most have studied the offspring at a young age, but the implications of the maternal environment for later life susceptibility to dietary obesity remain unexplored. Aging is associated with a number of factors that may contribute to a decline in physical performance with age (4), two of which are obesity and a decline in muscle quality, and these may be interdependent as HF-feeding contributes to a decline in muscle function (Fig 5). We discovered that with increasing age, rats demonstrate a greater susceptibility to high fat (HF) diet-induced weight gain and this is related to the presence of leptin resistance (5). Our umbrella hypothesis is that maternal HF-induced obesity predisposes the offspring to accelerated age-related dietary obesity and the associated decline in muscle quality. Put simply, at every age, offspring from obese dams will demonstrate greater susceptibility to diet-induced obesity (DIO) than corresponding offspring from lean dams, and this will accelerate the age-related decline in muscle quality leading to loss of physical function at an early age. The underlying mechanisms are hypothesized to be maternal leptin resistance hastens the onset of age-related leptin resistance in offspring, thus increasing the susceptibility to DIO.

Project Title: A Network Based Analysis of Systemic Inflammation
Project Leader: Paul Borsa, Ph.D.
This exploratory study will examine the temporal response of gene expression in the innate immune system following acute muscle injury. In this exploratory project we will evaluate with newly developed micro-array technology the gene expression of inflammation biology in low functioning and high functioning old age-matched subjects in response to acute muscle injury (pre and 24-hours post-injury). We will use a novel technology that combines genomics, statistics and precise signaling transduction pathways of inflammation, which will allow us to visualize and understand the complexity of the inflammation responses and may provide us with additional biomarkers to monitor inflammation in humans. We will correlate biomarkers of inflammation (gene expression) with measures of muscle function (ROM, strength) to evaluate the inflammatory response and rate of recovery between subjects. This exploratory study will generate pilot data that will be used to determine variances and effect sizes for sample size calculations for a future large-scale clinical study.

Project Title: ACE inhibition and muscle quality
Project Leader: Christy Carter, Ph.D.
This exploratory project is designed to use a rodent model of age-related physical decline to conduct Preclinical testing of two pharmacologic interventions with the potential to forestall age-associated physical decline: angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), and to study pathophysiologic changes postulated to play important roles in disability. In this Exploratory Study we will assess this relationship by cross-sectionally assessing long-term ACEi and ARB treatment in aged F344xBN male rats (24 to 30 months of age) and the impact on oxidative stress (carbonyl proteins), inflammation (TNF-α IL-6) and apoptosis (caspases). We have observed that high does ACEi treatment attenuates apoptotic signaling in skeletal muscle. Carter's award of a translational supplement to her R01 ACE inhibition and physical performance in aged rats is addressing mechanistic hypotheses associated with this finding and several papers are published.

Project Title: Feasibility of Computer Adaptive Testing in Elders
Project Leader: Craig Velozo, Ph.D.
One of the most promising areas of outcome measurements in healthcare is the use of computer adaptive testing (CAT). CAT tailors the testing situation to individual respondent, to achieve a combined efficiency and precision unattainable with traditional paper-and-pencil test. Several CAT studies have shown promising psychometrics with administration of as few as 6 items in per construct. In addition, Velozo and colleagues have developed a computer adaptive test, the ICF Activity Measure, with an underlying extensive item bank (264 items) designed to measure physical function for individuals with disabilities. The ICF measure has the potential to provide an efficient and precise measure of physical functioning outcomes for sarcopenia interventions in the older adults. However, the feasibility of CAT with the older adults is questionable. Some characteristics of the older adult population, such as visual deficits and unfamiliarity/unease with technology may affect the feasibility of CAT with this population.

Project Title: Leptin Inhibition, Blood Flow and Sarcopenia
Project Leader: Nihal Tümer, Ph.D.
This exploratory study will test the hypothesis that inhibition of leptin signaling in obese rats would lead to a decreased sympathetic nervous activity, improved vascular function and reduced blood pressure without significantly affecting the already reduced metabolic effects of leptin. In the proposed studies, lean young and obese senescent F-344xBN rats will be treated peripherally with this leptin antagonist. Arterial blood pressure and heart rate will be followed with radiotelemetry and vascular reactivity will be assessed at the end of the treatment period *in vitro* using isolated skeletal muscle arteries. We will examine the responsiveness of the arteries to changes in intraluminal pressure and to several vasoactive substances mediating endothelium-

dependent and independent dilator responses.

Project Title: Autophagy and Sarcopenia in a Transgenic Mouse Model
Project Leader: Stephanie Wohlgemuth, Ph.D.
This pilot study is designed to investigate the extent and correlation of autophagy, sarcopenia and decline in physical performance with age. We hypothesize that the incidence of sarcopenia and decline in physical performance is associated with a decrease in autophagy and a consequential increase in abnormal mitochondria. We will test our hypothesis in a prematurely aging transgenic mouse model that specifically accumulates mitochondrial DNA mutations, reflecting age-related mitochondrial damage. Our hypothesis will be assessed using the following specific aims: 1. Determine correlation between decreased physical function and incidence of sarcopenia in new aging model. 2. Determine age-related differences in autophagy in skeletal muscle of this new aging model. 3. Explore the correlation between the incidence of sarcopenia and the decrease in autophagy and physical function. The long-term goal of this study is to elucidate the cellular and molecular mechanisms of autophagy, its role in age-related decline in skeletal muscle performance and disablement process, and to investigate possible interventions for prevention and rehabilitation of disability.

Project Title: Acute Responses to Blood Flow Restricted Exercise
Project Leader: Todd Manini, Ph.D.
There is a fundamental gap to understanding the ability to promote muscle function (mass, strength and endurance) without high mechanical loading. The long-term goal is to develop a safe and effective intervention without excessive tissue strain that increases muscle function. This project's objective is to determine the acute neuroendocrine and hemostatic responses to a novel approach for promoting muscle function involving low-intensity exercise with blood flow restriction (BFRExercise). The central hypothesis is that BFRExercise is a safe intervention that acutely upregulates growth factors (i.e. serum growth hormone). The rationale for this study is that rehabilitation protocols involving high-intensity exercise are not tolerated well by some individuals (i.e. elderly), can't be performed by some (i.e. Parkinsonian patients), and is contraindicated for others (i.e. post-injury/surgery); thus, the development of low-strain interventions to increase muscle function would dramatically change the fields of neurologic, geriatric, orthopedic and rehabilitation medicine. This hypothesis will be tested by pursuing 2 specific aims: 1) To compare acute neuroendocrine and hemostatic responses to BFR exercise in young and old adults; 2) To compare acute neuroendocrine and hemostatic responses to BFR exercise in Parkinsonian patients and healthy older adults. We will also pursue an exploratory aim; 3) to evaluate the hemodynamic and inflammatory changes as a result of BFRexercise. This research is significant because it is expected to result in the development of a novel, safe and practical intervention that promotes muscle function in the absence of high-intensity exercise that will enhance overall health and physical function in numerous populations.

Resveratrol for Reduced Muscle Lipid Content in Older Adults/ Resveratrol for Improved Performance: The RIPE Trial
Project Leaders: Todd Manini, Ph.D./ Stephen D. Anton
In this project, we aim to conduct a double-blind randomized placebo controlled pilot study to determine whether resveratrol, a dietary ingredient, supplementation improves memory and physical performance in older adults. Loss in memory and physical performance is a frequent complaint in older adults and a growing public health issue. Additionally, later adulthood is associated with a normative decline in both working and primary memory as well as domains including attention, speed of processing and executive function. A key link to these processes may be related to the deleterious effects of oxidative stress and chronic inflammation.

Dose-Response Effects of Weight Loss on Systemic Levels of Inflammation and Oxidative Stress
Project Leader: Stephen Anton, Ph.D.

Obesity is associated with an elevated levels of inflammation and oxidative stress that may contribute to muscle loss (sarcopenia), declines in physical functioning, and physical impairments in older adults. Lifestyle interventions targeting weight loss through reductions in caloric intake and increased physical activity may reduce systemic levels of inflammation and oxidative stress and thereby improve physical functioning in obese, older adults. However, the mechanisms by which weight change and exercise influence physical functioning and muscle loss remain largely understudied. Work in basic science suggests that weight loss and exercise may avert sarcopenia by reducing inflammation, oxidative damage, and the consequent atrophy and apoptosis (programmed cell death) of skeletal muscle myocites. Thus, studies are needed to investigate the potential molecular links between obesity, weight loss, and systemic levels of inflammation and oxidative stress. Findings from these studies may identify novel therapeutic targets and therapies for improving health and decreasing the incidence of age-related diseases associated with obesity and sarcopenia. The proposed study will utilize a large sample of obese, older adults (N = 100) from rural communities to examine: 1) the dose response relation between weight loss programs of varying intensity on changes in markers of systemic inflammation (i.e., CRP, IL-6, and TNF-alpha), oxidative stress levels (i.e., oxLDL, myloperoxidase), and vascular inflammation (E-selectin, VCAM-1) over six months, and 2) whether weight loss versus changes in physical activity are related to improvements in biomarkers of inflammation and oxidative stress, as well as physical function. Rural adults represent an ideal population to examine these relationships since they have higher rates of obesity and obesity related comorbidities than urban adults. The proposed study will take advantage of a large-scale NIH funded weight loss trial; thus, all measurements can be completed in a cost-effective and timely manner.

The Role of Heat Shock Protein 70 Overexpression on the Recovery of Muscle Mass and Function Following Cast Immobilization

Project Leader: Andrew Judge, Ph.D.

The elderly often encounter more, and extended, periods of skeletal muscle disuse, such as bed rest or cast immobilization, due to an increased likelihood of falls, disease and surgery. During these periods of disuse significant muscle atrophy occurs, which may be exaggerated in the elderly compared to young. Furthermore, during recovery following disuse, or reloading, muscles from the elderly fail to recover mass and function. These combined effects of muscle atrophy and the inability of old muscle to regrow leads to a significant loss of functional independence in the elderly. The central hypothesis of the proposed work is that overexpression of Hsp70 will promote skeletal muscle regrowth and improved function in old animals following a period of muscle disuse. The rationale for the proposed work is based on the role that Hsp70 may play in enhancing protein synthesis and activating satellite cells. Furthermore, muscles from adult rats increase Hsp70 expression during reloading and completely regrow, whereas the ability of muscles from old rats to increase Hsp70 is significantly compromised. To test this central hypothesis, we cast immobilized rats for 10 days to cause significant skeletal muscle atrophy and then used gene transfer to overexpress Hsp70 in the soleus muscle of one limb, with the contralateral limb serving as a control. Hsp70 overexpression significantly enhanced skeletal muscle fiber regrowth in old rats. In a separate group of rats we tested “physical performance” via incline plane and a swim test prior to cast immobilization, immediately following 10 days of cast immobilization, and following 10 days of cast immobilization plus 10 days of reloading. Overexpression of Hsp70 increased the mean time to failure on the incline plane test in old rats but not young rats and increased the swim distance during repeated swim trials in young rats but not old rats. Ongoing biochemical analyses will determine whether Hsp70 overexpression enhances markers of protein synthesis and/or satellite cell activation during muscle regrowth.

Biological Effect of Weight Loss and Exercise in Elders
Project Leader: Stephen D. Anton, Ph.D.
This study will lay the groundwork for a randomized controlled trial (RCT) of the effects of weight loss plus exercise (WL+E) on inflammation, oxidative stress, apoptosis, body composition, intramuscular fat, sarcopenia, muscle strength, and physical functioning in obese older adults.

Physical Exercise to Prevent Disability Pilot Study (The LIFE Study)
Project Leader: Marco Pahor, M.D.
To refine key trial design benchmarks (including sample size calculations to demonstrate the feasibility of a full-scale trial and refining/developing recruitment, procedures, materials and organizational infrastructure), the LIFE (Lifestyle Interventions for Independence in Elders) study conducted a pilot, single-blind randomized, controlled trial involving comparison of a physical activity program of moderate intensity to a successful aging program. A total of 400 sedentary persons aged 70-<90 years who are at risk of disability were followed for at least one year at four intervention sites: Wake Forest University School of Medicine in Winston Salem, NC, the University of Pittsburgh, Pittsburgh, PA, the Cooper Institute in Dallas, TX, and the Stanford University in Palo Alto, CA. The Administrative Coordinating Center and the Data Management and Quality Control Center are at Wake Forest University School of Medicine. The LIFE study assessed the combined outcome of major mobility disability defined as the incapacity to walk 400 m, or death, which will be the primary outcome of the full-scale study. This outcome has not been used in previous randomized, controlled trials, and therefore, a pilot study is needed to assess its incidence rate. Secondary outcomes include ADL disability, major fall injuries and cardiovascular events. LIFE explored the effects of the intervention on physical performance measures, cognitive function, health-related quality of life, and use of health care services. In addition, LIFE explored and performed cost-effectiveness analyses of the intervention.
This pilot study will yield the necessary preliminary data to design a definitive Phase 3 randomized, controlled trial. By providing a conclusive answer regarding whether physical activity is effective for preventing major mobility disability or death, the results of the full-scale trial will have relevant clinical and public health implications, and will fill an important gap in knowledge for practicing evidence-based geriatric medicine.
Study is complete. Secondary analyses are in progress. Phase 3 clinical trial has been awarded.

Testosterone Trial IVR Pilot
Project Leader: Marco Pahor, M.D.
The purpose of the study was to learn about the use of questionnaires about general health and feelings of well-being in men who are $\geq$ 65 years old, using a telephone system called Interactive Voice Response (IVR). Questionnaires used in this study were the Harbor-UCLA 7-day diary and the FACIT-Fatigue Scale. The study compared answers to questions collected on the phone system to those that are written on paper forms to evaluate whether the IVR phone is an accurate and reliable way to collect data. Information learned in this study will help to develop a study of testosterone use in men $\geq$ 65 years old and the effects various aspects of their lives.

Testosterone Trial IVR Pilot #2
Project Leader: Marco Pahor, M.D.
The purpose of the study is to learn about the use of questionnaires about general health and feelings of well-being in men who are $\geq$ 65 years old, using a telephone system called Interactive Voice Response (IVR). Questionnaires used in this study are the Positive and Negative Affect Scale (PANAS), SF-36 vitality subscale, and the PHQ-9. The study will compare answers to questions collected on the phone system to those that are written on paper forms to evaluate whether the IVR phone is an accurate and reliable way to collect data. Information learned in this study will help to develop a study of testosterone use in men $\geq$ 65 years old and the effects various aspects of their lives.

Chemotherapy, Weakness, Fatigue and Functional Limitation in Older Breast Cancer Survivors
Project Leader: Todd Manini, Ph.D.

Women over the age of 65 years diagnosed with breast cancer will increase by 72% in the next 20 years2. As the effectiveness of adjuvant chemotherapy increases, it will become increasingly recommended to older adults. Yet survivorship studies have primarily focused on young adults, neglecting older women who are now the largest proportion of breast cancer survivors. Functional dependence is a key determinant of poor quality of life, and a major source of health care and social costs. In this project, we will study the biological and physiological characteristics of elderly breast cancer survivors with expertise from a UF's Institute on Aging with expertise on muscular aging and functional decline. This collaboration is a unique breakthrough opportunity for identifying interventions that will help to initiate programs to prevent or rehabilitate the long-term functional impact of chemotherapy in the elderly. Beyond the effects found in breast cancer survivors, this project has a potential for benefiting patients undergoing chemotherapy for any type of cancer. Therefore, this will be the first step in a research pathway studying the long-term biological, functional, psychosocial, geriatric and oncologic events that occur in older women surviving breast cancer, with potential for designing several novel interventions.

Myogenic and Proteolytic Regulators in Response to blood Flow Restricted Exercise
Project Leader: Todd Manini, Ph.D.

The loss of muscle mass and strength due to aging is of serious concern as it can limit physical performance and is thought to act as a common pathway leading to heightened risk for outright physical disability. Therefore, identifying interventions that induce myogenesis while minimizing proteolysis are of major importance for establishing functional independence in older persons. Our interdisciplinary team that includes experts in basic science (Dr.'s Powers & Leeuwenburgh), clinical science (Dr.'s Manini & Vincent), translational clinical science (Dr. Borst), and laboratory methods (Dr. Zhang) is uniquely suited to assess myogenic and proteolytic regulators while also mentoring the PI on techniques used to quantify gene expression. Restricting blood flow during exercise to elicit a muscle regulatory response is contrary to traditional thinking, but a growing literature indicates that blood flow restriction during low intensity exercise (i.e. 20% of maximal strength) is a potent stimulus for systemic growth factors, muscle protein synthesis and even muscle hypertrophy. This finding is somewhat unusual because high intensity exercise exceeding 70% of maximal strength is typically needed to yield this type of response. The mechanisms are unknown, but residual metabolic byproducts from glycolysis are enhanced during ischemia and may act to modulate gene expression in a similar way as high intensity exercise. The *objective of this project* is first, to ask what are the myogenic responses to acute exercise performed at 20% of maximal strength with blood flow restriction when compared to a control exercise performed at 20% of maximal strength without blood flow restriction. Second, we want to investigate the proteolytic responses to acute exercise performed with blood flow restriction when compared to control exercise. Thus, *we offer two hypotheses*: Hypothesis #1: Acute resistance exercise performed at 20% of maximal strength coupled with blood flow restriction will upregulate myogenic gene expression (muscle IGF-1, Myogenin, MyoD, and Myostatin). Hypothesis #2: Acute resistance exercise performed at 20% of maximal strength coupled with blood flow restriction will downregulate proteolytic gene expression (Atrogin-1, MuRF-1, Caspase-3, and FOXO3A). This *research is significant* because it is expected to result in the development of a novel and practical intervention that promotes muscle growth in the absence of high-intensity exercise. However, prior to widespread use of this modality the first step is to investigate an acute bout of exercise to evaluate the potential underlying responses that will help in developing a conceptual model for the mechanisms of action. Once these data are available chronic low intensity exercise coupled with blood flow restriction can be studied in older adults for enhancement of skeletal muscle health in older adults at risk of muscle atrophy.

The Influence of Resistance Exercise on Physical Function Depression, Quality of Life, Muscle Morphology and Bone Metabolism in Stroke Patients
Project Leader: Kevin Vincent, M.D.
Stroke is associated with musculoskeletal adaptations that result in decreased bone mineral density (BM.D.), impaired motor unit activity and muscle weakness. These changes result in an increased risk of osteoporosis and fracture and are associated with impaired mobility and the reduced ability to perform activities of daily living (ADL). Additionally, patients who have experienced a stroke have increased rates of depression and reduced indices of self-efficacy compared to their age matched counterparts. Resistance exercise (RX) has been demonstrated to be a safe and effective means to improve physical function and endurance in many clinical populations including geriatric, congestive heart failure, organ transplant, cardiac, and cancer patients. Additional benefits in these populations include increased BM.D., increased indices of self-efficacy, reduced indices of depression, and reduced blood pressure responses to a given workload. The relative influence of RX on these variables has not been fully characterized in stroke patients. Recently there have been concerns that RX may increase central artery compliance. However, the data regarding the influence of RX on arterial compliance has been inconsistent. Additionally, there is a theoretical concern that RX may increase spasticity in stroke patients, but this has not been demonstrated in any of published studies uses RX in this population. The primary aims of this investigation will be to examine the influence of 24 weeks of Rx on physical function (motor assessment scale six minute waling test), muscle hypertrophy an muscle morphology (b-mode ultrasound measures of hypertrophy, muscle biopsy for fiber typing), bone mineral density (Dual S-Ray Absorptiometry) and bone turnover markers osteocalcin, alkaline phosphatase and N-linked telopeptides) in patients who have experienced a stroke. Secondary aims will be to assess psychological state [anxiety (State Trait Anxiety Scale), depression (Geriatric Depression Scale)], quality of life (SF-36) spasticity (modified Ashwoth scale), an arterial stiffness (assessed by endothelial function and the resistance vessel technique). Adults (n=30) who have experienced a stroke will be recruited for this investigation. Participants will be randomly assigned to either an RX group (n=15) or a standard care group (n=15). Criterion measures will be assessed at baseline and after the 24 weeks of either RX or standard care. It is hypothesized that RX will result in improved physical function, increased muscle strength and muscle mass increase or preserved BM.D., reduced bone resorption markers, and improved psychological state of the participant by attenuating anxiety and depression more than standard care. We also hypothesize that RX will not result in increased spasticity or arterial stiffness.

Reversal of Age-related Obesity by an Unexpected Synergy between Leptin and Seemingly Negligible Voluntary Wheel Running
Project Leader: Alexandra Shapiro, Ph.D.
This proposal seeks a successful strategy to prevent diet-induced obesity and functional disability in aged rats. To date, treatments for obesity have been largely ineffective; thus, novel approaches are urgently needed to combat the increasing obesity epidemic, particularly among older populations Leptin treatment exerts potent response in lean rodents, producing impressive weight and fat loss, but is generally ineffective in both dietary obese young and rats with age-related obesity. This phenomenon, known as leptin resistance constitutes a major obstacle in curtailing age- and diet-induced weight gain and has limited the value of leptin as a therapeutic agent for treating obesity. However, treatments that are able to mitigate or circumvent leptin resistance may provide a viable strategy to restore the effectiveness of leptin in treating obesity. Our exciting new data that a surprising synergy between voluntary wheel running (WR) and leptin (two otherwise ineffective treatments in dietary obese rats) restores the effectiveness of leptin therapy. In particular, the combination of WR + leptin therapy was found to reverse the trajectory of HF-induced weight gain in young-obese, otherwise leptin-resistance rats. This synergy is not a direct result of the distance run in the leptin/WR group, because there was correlation between WR and weight loss. It appears that the act of WR and not the distance synergized with leptin. The study expanded on these recent preliminary data by examining if a novel treatment (WR + leptin) prevents HF-induced weight gain and also improves body composition (lean to fat

ratio) in leptin resistant, aged-obese rats. In this project, the physiological responses to voluntary wheel running alone and in combination with central leptin gene delivery compared with sedentary animals with and without leptin gene therapy in 24-months old obese rats will be examined over a 4-week period. Additionally, the mechanisms underlying the synergy will be investigated. Against the backdrop of the increasing obesity epidemic among older adults, evidence continues to accumulate documenting the deleterious effect of excess weight on health and physical function. To date, treatments for obesity have been largely ineffective; thus, novel approaches are urgently needed to combat the increasing obesity epidemic, particularly among older populations. Study is complete. Paper is accepted in Gerontology.

Oxidative Damage, Inflammation and Physical Exercise
Project Leader: Marco Pahor, M.D.
The hypotheses of this study are that a moderate-intensity physical exercise program may a) reduce inflammation and oxidative damage markers, and b) prevent age-related physical performance loss through these decreases. We plan to a) measure myeloperoxidase, 8-iso-prostaglandin F2alpha, and 3-nitrotyrosine in the LIFE study, and 2) explore whether high levels of these biomarkers predict dropouts.

Project Title: Molecular Mechanisms of Skeletal Muscle Loss in HIV-infected Older Persons
Project Leader: Todd Manini, Ph.D.
Successful medical therapy has greatly improved survival for HIV-infected adults and now ¼ of these individuals are over the age of 50 years. Unfortunately, this population faces a difficult challenge, as they will age with a disease associated with severe muscle wasting that will greatly affect their physical function. These individuals will face the aging process at a lower physical capacity and are expected to have elevated rates of disability. Minimizing the loss in muscle mass is at the forefront for reducing physical disability in aging adults. This study will investigate the mechanisms of muscle loss in HIV infected older adults. One of these mechanisms, cellular apoptosis, is a key target that holds promise for explaining the underlying rapid muscle loss seen with HIV infection and aging. We aim to recruit 20 HIV-infected and 20 non-infected adults aged 55 to 99 years of age to undergo tests of physical function, blood work and undergo a muscle tissue sample. Results from this pilot study will be used to develop a research trajectory that begins to uncover the reasons for accelerated muscle loss in aging HIV-infected individuals.

III. CAREER DEVELOPMENT

Following are names of junior scholars who received Pepper pilot funding and the funding received subsequent to Pepper pilot funding.

OAIC Junior Scholar Publications and Grants from 2010 to 2015

	# Pubs	PI on Grant[a]	# Grants as PI[b]	# of R01-Level Awards[c]	Career-Devel. Awards[d]	Tenured and/or Promotion	Women	Minority	Has Clinical Duties
Stephen Anton, PhD	30	Y	6	2	Y	Y		Y	Y
Thomas Buford, PhD[1]	39	Y	3		Y				
David Clark, PhD[2]	20	Y	2	2	Y				
Yenisel Cruz-Almeida, PhD[3]	21	Y	1		Y		Y	Y	
Vonetta Dotson, PhD[4]	7	Y	1				Y	Y	Y
Natalie Ebner, PhD[5]	8	Y	2				Y		
Philip Efron, MD[6]	31	Y	2	2	Y	Y			Y
Anna Maria Joseph, PhD[1]	15						Y		
Andrew Judge, PhD[7]	28	Y	3	1		Y			
Todd Manini, PhD[1]	87	Y	4	3		Y			
Joe Nocera, PhD[2]	22	Y	2		Y				
Kimberly Sibille, PhD[3]	17	Y	4		Y		Y		
Shinichi Someya, PhD[1]	10	Y	4	2		Proposed			
Bridgett Rahim-Williams,PhD[3]	5	Y	1		Y	Y	Y	Y	
Kevin Vincent, MD[8]	32	Y	2		Y	Y			Y
Stephanie Wohlgemuth, PhD[9]	15	Y	1				Y		
Adam Woods, PhD[1]	4	Y	1		Y				
Jinze Xu, PhD[1]	9	Y	1				Y		
Zvinka Zlatar, PhD[4]	14						Y	Y	
Total #	**347[e]**	**17**	**40**	**12**	**10**	**6**	**9**	**5**	**4**
% of Junior Scholars		**89%**			**52%**	**32%**	**47%**	**26%**	**21%**

a=PI on grant extramural grant awarded by NIH, VA, NSF, foundation, or professional society; b=number of grants on which the Junior Scholar served as PI; c=number of R01-equivalent awards (i.e. R01s, Site PI on multicenter trials, VA Merit awards, subprojects on P50 grants); d=NIH K-awards or their equivalent. e=unique publications from 2010 or since appointment as Junior Scholar, whichever is a later date. Total number of publications does not correspond to the sum of individual publications because some publications are co-authored by two or more Junior Scholars. Superscript numbers indicate colleges and departments: 1=Dept Aging & Geriatric Research, College of Medicine (COM); 2=VA; 3=Dept Community Dentistry & Behav Sci, College of Dentistry; 4=Dept Clin & Health Psychol, College of Public Health & Health Professions (PHHP), 5=Dept Psychology, College of Liberal Arts & Sciences; 6=Dept of Surgery, COM; 7=Dept Physical Therapy, PHHP; 8=Dept Orthopedics & Rehabilitation, COM; 9=Dept Animal Sciences, College of Veterinary Medicine.

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Section V. External Advisory Board

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