The 2014 Annual Directory and Report of the Claude D. Pepper Older Americans Independence Centers is produced as a resource to provide information on the research activities occurring at the Centers throughout the United States, as well as a record of the publications and projects that have resulted from these research activities.

The Pepper Centers are listed alphabetically with a synopsis of each of their major research programs, supportive core units, training, publications, minority research, and recognition and awards. All information contained in this directory is based upon information supplied by each Center.

This document is searchable through Adobe Acrobat.

The 2014 Directory was prepared by the Claude D. Pepper Older Americans Independence Center Coordinating Unit at Wake Forest University.
Claude Denson Pepper 1900-1989

Claude Denson Pepper was born near Dudleyville, Alabama on September 8, 1900. He graduated from the University of Alabama in 1921 and from Harvard Law School in 1924. After establishing a general law practice in Perry, Florida, Pepper began his political career with his election to the Florida House of Representatives in 1929. While working in the State Capitol in 1931 he met his future wife, Mildred Webster outside the Governor’s office in Tallahassee. Claude and Mildred were married on December 29, 1936 in St. Petersburg, Florida and for 43 years they were inseparable. In 1936, Senior Florida Senator, Duncan Fletcher, died while in office and Pepper was elected to the U.S. Senate to fill the vacant seat. He quickly became a leader of the New Dealers in Congress and a friend and confidant of President Franklin Roosevelt. Against what seemed to be overwhelming opposition from conservative isolationists in 1940 and 1941, he was able to lead the fight to pass the Lend-Lease Act which allowed the U.S. to support the Allied effort in World War II. In domestic affairs, he also made a name for himself as somewhat of a "radical" by sponsoring bills for National Health Care, equal pay for equal work for women, cancer and heart disease research programs, and a minimum wage. Senator Pepper was co-author of legislation that established the National Cancer Institute, the first of many National Institutes of Health. Following his defeat for election to a third full term in the U.S. Senate in 1950, Pepper returned to his law practice in offices in Tallahassee, Washington, and Miami. In 1963, he returned to Congress as the Representative of the newly-created 3rd Congressional District of Florida. Pepper was appointed as the Ranking Democrat on the House Select Committee on Aging when it was created in 1975 and became Chairman of that Committee in 1977. Serving as Chairman of the Committee until 1983, he became known throughout the U.S. as "Spokesman for the Elderly." In this capacity, he crusaded for an end to involuntary retirement, strengthened the Social Security system, fought age discrimination, and pushed for stronger legislation to end abuse of the elderly. He also chaired the U.S. Bipartisan Commission on Comprehensive Health Care, a body created through an amendment of his added to the 1988 Medicare Catastrophic Protection Act, and he worked tirelessly to strengthen the Medicare program.

During Claude Pepper’s five decades of public service, he was a strong and effective advocate for millions of Americans in the areas of health care reform and economic security. His numerous achievements will be felt by generations to come: Americans guaranteed a decent wage, or saved from death or illness by breakthroughs in biotechnology, or protected from age discrimination in the work force or presented with a decent retirement income by the Social Security program. He left monuments such as the National Institutes of Health, a strengthened Medicare program, and a strengthened Social Security system. He achieved his goal, “to lighten the burden upon those who suffer,” many times over. Senator Pepper died in Washington, D.C. on May 30, 1989.
Boston University  
Shalender Bhasin, MD  
670 Albany St, 2nd floor  
Boston, MA 02118  
Email: bhasin@bu.edu

Duke University  
Harvey Jay Cohen, MD  
Box 3003, DUMC  
Durham, North Carolina, 27710  
Email: hjc@geri.duke.edu

Johns Hopkins University  
Jeremy Walston, MD  
Karen Bandeen-Roche, Ph.D.  
Johns Hopkins Medical Institution  
2024 E. Monument St., Suite 2-700  
Baltimore, MD 21205  
Email: jwalston@jhmi.edu

Mount Sinai Medical Center  
Albert L. Sui, MD  
10th Floor, Annenberg Building  
One Gustave L. Levy Place, Box 1070  
New York, NY 10029  
Email: albert.siu@mssm.edu

University of Arkansas  
Jeanne Wei, MD, PhD  
University of Arkansas for Medical Sciences  
4301 West Markham Street  
Little Rock, Arkansas 72205  
Email: weijeanne@uams.edu

University of California, Los Angeles  
David B. Reuben, MD  
David Geffen School of Medicine at UCLA  
10945 Le Conte Avenue, Suite 2339  
Los Angeles, CA 90095-1687  
E-Mail: dreuben@mednet.ucla.edu

University of California, San Francisco  
Ken Covinsky, MD  
University of California, San Francisco  
4150 Clement Street  
San Francisco, CA 94143  
415-221-4810x4363  
E-Mail: Ken.Covinsky@ucsf.edu

University of Florida  
Marco Pahor, MD  
Department of Aging and Geriatric Research, College of Medicine  
University of Florida  
1329 SW 16th Street, Room 5161  
Gainesville, FL 32608  
E-Mail: mpahor@ufl.edu

University of Maryland, Baltimore  
Andrew P. Goldberg, MD  
VA Medical Center, GRECC (18)  
10 North Greene Street  
Baltimore, MD 21201  
Email: agoldber@grecc.umanryland.edu

University of Michigan  
Jeffrey B. Halter, MD  
University of Michigan  
1500 E. Medical Center Drive  
Ann Arbor, Michigan 48109-0926  
Email: jhalter@umich.edu

University of Pittsburgh  
Susan Greenspan, MD  
3471 Fifth Avenue  
Pittsburgh, PA 15213  
Email: greenspan@pitt.edu

University of Texas Medical Branch  
Elena Volpi, MD, PhD  
301 University Blvd. Rt. 8060  
Galveston, TX 77555-0860  
Email: evolpi@utmb.edu

Wake Forest University  
Stephen Kritchevsky, PhD  
Wake Forest University School of Medicine,  
Medical Center Boulevard  
Winston-Salem, NC 27157-1051  
E-mail: skritche@wakehealth.edu

Yale University  
Thomas M. Gill, MD  
Yale University School of Medicine  
20 York Street, DC-023  
New Haven, Connecticut 06504  
Email: thomas.gill@yale.edu
SECTION I. DESCRIPTION OF CENTER

The overall theme of our center is “to understand and modify multiple pathways of functional decline.” The Duke Claude D. Pepper Older Americans Independence Center (Pepper Center) is based in the Duke Center for the Study of Aging and Human Development, an all-university program with strong multidisciplinary affiliated programs such as the Durham VA GRECC, the RAND/Hartford Interdisciplinary Geriatric Research Center, the Duke Institute for Genomic Sciences and Policy, the Duke Clinical Research Institute, the Duke Center for Living, Trajectories of Aging and Care Center, and the Stedman Nutrition and Metabolism Center. This rich milieu includes 126 faculty as Senior Fellows of the Aging Center and over 21 million dollars of research germane to our center goals.

Over the past twenty-one years, the Duke Pepper Center has been at the forefront of geriatric research and training focused on the development of interventions to improve the functional status of older adults and the support of research that identifies risk factors predictive of functional decline. The Duke Pepper Center originally began its funding as a Geriatric Research and Training Center (GRTC) in 1991. The GRTC was originally funded with three research cores and support for junior faculty and pilot projects, which reflects the organization of the current OAIC structure. One year later, Duke was awarded a Pepper Center and, at the direction of the National Institute on Aging, the two programs were combined into one. Initial Pepper Center support focused on the development of promising interventions to promote the independence of older Americans and faculty development. Since then, the Duke OAIC has produced an impressive portfolio of relevant research and innovations in faculty development.

The specific goals of the Duke Pepper Center are:

1) Support and enhance research related to our Center theme of exploring modifiable pathways to functional decline;

2) Train investigators in the methodologies needed for competence in mechanistic, translational, and outcomes research aimed at exploring modifiable pathways to functional decline;

3) Identify and nurture promising new and transitioning investigators who have an interest in research aimed at modifying functional decline in later life.
SECTION II. RESEARCH, RESOURCES, AND ACTIVITIES

A. CORES

Analysis Core (Resource Core 1)
Carl F. Pieper, D.P.H., Core Leader
Tel: (919) 660-7525  FAX: (919) 684-8569  E-mail: carl.pieper@dm.duke.edu

The Analysis Core provides analytic and technical support to the funded grants, pilots, projects and junior faculty in the Pepper. The Core provides mentoring, consultation and advice to approved projects and people and pursue two general goals: to collaborate with the projects and researchers of the Pepper Center with appropriate and innovative analytic and data management technologies, and to advance statistical science in the study of function and functional decline. The Analysis Core work closely with the Biochemical Pathways and Metabolomics Cores to direct and perform the requisite analyses from the data derived from that Core. Members of this core sit on the Internal Operating Committee and are involved in selecting and assisting in the design of future projects, pilots, and junior faculty. To accomplish these goals, the Analysis Core has the following specific aims:

Aim 1: Provide R01s, pilot projects, and junior faculty investigators with design, analytic, data management, and technical support by which to conduct research and to address hypotheses related to functional and aging;

Aim 2: Further statistical/analytic science in the study of elderly.

Biochemical Pathways Core (Resource Core 2)
Virginia B. Kraus, M.D., Ph.D., Core Leader
Tel: (919) 681-6652  FAX: (919) 684-8907  E-mail: vbk@duke.edu

The overall goal of the Biochemical Pathways Core is to increase scientific knowledge that will lead to more effective strategies to maintain or restore independence in older persons. To this end we perform biomarker and systems pathway analyses to evaluate etiologies of functional decline associated with aging. Our long term goals are to develop tools to predict at-risk groups, and to provide information to monitor efficacy of intervention(s). Our primary focus is on biochemical and inflammatory markers. This core provides a centralized resource for these analyses across the spectrum of Pepper projects: pilot studies, Research Career Development awardees, external projects. The overall approach we utilize combines analyses of multiple excellent studies to advance the understanding of pathways of functional decline.

To accomplish these goals the Biochemical Pathways Core has three specific aims:

Aim 1. Perform biomarker analyses for several independent but inter-related Pepper-designated projects.

Aim 2. Perform systems pathway analyses to identify biological pathways implicated in functional decline and with potential for modifiability via interventions.
Aim 3. Serve as a resource for research-oriented advice and training on principles and methods of biomarker analyses.

The services of this core enhance our center's ability to conduct novel age relevant analyses:

a. To identify biochemical and inflammatory markers indicative of functional status and predictive of functional decline in aging;
b. To generate data for the Analysis Core to evaluate the generalizability of markers of functional decline in aging;
c. To generate data to evaluate specific disease associations with markers of functional decline;
d. To gain insights into biological pathways implicated in functional decline;
e. To aid identification of targets for interventions to slow, halt or reverse functional decline;
f. To generate data to monitor the efficacy of interventions designed to combat functional decline in aging.

Metabolomics Core (Resource Core 3)
James Bain, Ph.D., Core Leader
Tel: (919) 479-2320, FAX: (919) 477-0632, E-mail: james.bain@duke.edu

Comprehensive metabolite profiling, or “metabolomics”, can define chemical phenotypes and has unique potential for discovering biomarkers that predict disease incidence, severity, and progression and for casting new light on underlying biochemical and metabolic abnormalities associated with such conditions. While genomic and transcriptomic technologies have matured to the point that core laboratories providing these services are commonplace, the complexity inherent in metabolomics still requires a specialized resource to measure large numbers of intermediary metabolites with diverse chemical properties in a quantitatively rigorous and reproducible fashion. Underlying issues include a) the wide-ranging concentrations of metabolites in tissues and bodily fluids (ranging from sub-nanomolar to millimolar), b) the variety of biological matrices that are surveyed, and c) the chemical diversity of the analytes. Given these variables, it is not surprising that no single technology exists for measurement of all of the metabolites in the “metabolome”.

Our focus is on metabolic signatures associated with functional decline in aging. The goal of the Metabolomics Research Core (RC3) is to apply a diverse set of complementary metabolomics technologies that provide a rare combination of broad coverage and analytical precision to the study of aging and its associated morbidities in support of the overall theme to understand and modify the multiple pathways of functional decline. Using a suite of seven research-dedicated mass spectrometers, our team analyzes small-molecule metabolites in samples from aging studies in humans, laboratory animals, and cultured cells, with an emphasis on understanding how changes in metabolism relate to functional decline. We take a two-pronged approach, performing both targeted and non-targeted ("shotgun" or exploratory) metabolomics. We currently offer fifteen targeted assays, which make quantitative measurements of more than 400 individual metabolites in such diverse chemical classes as amino acids, ceramides, and acyl coenzyme As. Our non-targeted work employs both gas chromatography/mass spectrometry (GC/MS) and liquid chromatography/MS. Duke's Pepper Center has supported development of several of our assays. We are always open to forming new collaborations with intra- and extramural Pepper investigators.
Aim 1) To provide both targeted and non-targeted MS-based metabolomic measurements that might help explain functional decline in samples from studies funded by the Duke Pepper OAIC and its collaborators.

Aim 2) To develop new targeted metabolomics methods for measurement of a broader array of acylcarnitine and acylglycine species.

Aim 3) To support young investigators in the Duke Pepper OAIC in planning, execution, and interpretation of metabolomics measurements in the context of their clinical and/or basic studies, and to integrate the resultant findings with other biochemical and clinical data to enhance our understanding of metabolic changes associated with functional outcomes.

Aim 4) To serve as a vehicle for connection of the Duke Pepper OAIC to other Pepper Centers and the aging research community at large.

Research Career Development Core
Kenneth W. Lyles, M.D., and Cathleen Colon-Emeric, MD, MHS, Core Leaders
Tel: (919) 660-7520 (Lyles) (919) 660-7517 (Colon-Emeric) FAX: (919) 684-8569
E-mail: kenneth.lyles@dm.duke.edu; cathleen.colonemeric@dm.duke.edu

The goal of the Research Career Development Core (RCD Core) is to recruit, train, mentor, and develop future research leaders with skills in translational research and clinical investigation directed at exploring approaches to understand and modify multiple pathways of functional decline. Promising scientists are recruited to develop and/or expand their investigative skills with an emphasis on translating basic research findings into clinical studies or, taking clinical research findings and posing new basic research questions. RCD Core awardees take courses tailored to their specific career needs, receive mentoring from senior faculty members, and receive leadership training to prepare them for key positions in geriatrics and gerontology. Our mentoring plan is designed to motivate clinical investigators to explore basic research principles and basic scientists to interface with clinical researchers. The RCD Core ensures its awardees to take advantage of other Pepper Center research cores and other experienced investigators at Duke University Medical Center. RCD Core awardees participate in seminars and conferences where interdisciplinary investigators discuss their work. In these settings, ideas for translational collaborations are raised and discussed, resulting in new projects and studies. Close collaborative links with other programs and centers at Duke University are available to RCD Core awardees, e.g., Duke Clinical Research Institute; Health Services Research Program, VAMC; Geriatric Research Education and Clinical Center VAMC; the Duke Clinical Translational Science Award Center; the Institute for Genome Sciences and Policy, and the Duke University Medical Center Mentored Clinical Research Scholar Program (MSRSP). The RCD Core helps awardees develop interdisciplinary projects and use these programs, Center and Institutes to foster translational research studies. A listing of past and current awardees is listed in section III.

Pilot/ Exploratory Studies Core
Kenneth E. Schmader, M.D., Core Leader
Tel: (919) 286-6932 FAX: (919)286-6823 E-mail: kenneth.schmader@dm.duke.edu
The overall objective of the Pilot/Exploratory Studies Core (P/E Studies Core) is to conduct pilot studies to acquire information needed to select or design future crucial studies in the Duke Pepper’s area of research focus. The P/E Studies Core orchestrates several key activities to generate productive pilot studies. These activities include formal methods to solicit and select pilot studies via the Duke Pepper Pilot Grants Program and Pilot Studies Workshop Series and a multifaceted plan for monitoring study progress and larger proposal development. There are six specific aims associated with this core:
1) Generate ideas and enhance the intellectual environment for the development of pilot/exploratory studies of approaches to understand and modify multiple pathways of functional decline;
2) Solicit, select and provide research funding for the highest quality pilot studies and investigators;
3) Facilitate successful completion of the pilot studies and their development into externally funded, larger grants;
4) Attract, support, and further develop promising junior investigators to aging research in coordination with activities of the Research Career Development Core;
5) Grow areas of research foci for future Duke Pepper OAIC applications;
6) Educate developing investigators about the logistics and science of pilot studies via pilot studies workshops.

Leadership/ Administrative Core
Harvey J. Cohen, M.D., Core Leader and Principle Investigator
Tel: (919) 660-7500          FAX: (919) 684-8569   E-mail: harvey.cohen@duke.edu

Miriam C. Morey, Ph.D., Co-Director and Principle Investigator
Tel: (919) 286-0411-1-6776 FAX: (919) 286-6823   E-mail: miriam.morey@.duke.edu

Jamazina Smith, Staff Assistant
Tel:  (919) 660-7502        FAX:  (919) 684-8569     E-mail: jamazina.smith@duke.edu

The Leadership/Administrative Core (L/AC) has responsibility for the overall direction and operation of the Duke Pepper Center. The L/AC will provide the leadership necessary to harness and direct the creative energy of this complex research activity. The Core will have input from, and interaction with, key members of other units of the Medical Center, the University, and the Durham VA and relies on two panels, Independent Review Panel and External Advisory Committee for expertise and direction in selection of future projects, pilots and junior faculty awardees. The Pepper Center Operating Committee is the primary mechanism for problem solving and planning. Monthly meetings composed of core leaders, key program advisors and administrative staff which are Co-chaired by Drs. Cohen and Morey to review the status of all center related activities and strategies to move forward with the proposed work. The specific goals of the L/AC are:

1) Assure overall coordination, integration, and administration of the Duke Pepper Center;
2) Assure integration with other affiliated programs;
3) Assure efficient and appropriate use of core facilities by investigators and programs;
4) Plan and develop funding strategies for cores and support of projects related to cores;
(5) Plan and coordinate future core activities and integrate Pepper Center activities with new programs established at Duke Medical Center.

**B. RESEARCH:**
The Duke Pepper Center supports three resource cores which have evolved from prior support: (1) Analysis, (2) Biochemical Pathways, and (3) Metabolomics. Externally funded NIH/VA grants, with study aims and study populations that integrate into our thematic focus, receive support from these cores. New specific research aims relevant to our Center are developed for each externally funded grant which we support. The Research Career Development Core and the Pilot/Exploratory Studies Core facilitates career development with established post-doctoral Research and Geriatric Training and Pilot Programs. Support for career development and pilot projects are selected on a competitive basis using criteria clearly defined in the Pepper Center guidelines. The Leadership/ Administrative Core directs and coordinates activities to ensure continued integration of center activities. Collectively, the resources and activities surrounding these resources contribute towards the advancement of our center theme of “to understand and modify multiple pathways of functional decline.” Our resource cores provide comprehensive profiling capabilities that allow us to explore an integrated and multi-system approach to understanding multiple pathways of functional decline. Over the past few years, we have identified and begun to address crucial problems in statistical methodology to reduce, analyze, and synthesize large volumes of biologic and genetic data (RC1). We also have identified novel biochemical and metabolic factors underlying organ and tissue impairment that are associated with dysfunction at the level of the whole person (RC2), and we have identified and developed new technologies in metabolomics (RC3). This strengthened metabolomics influence within the OAIC has resulted from several key investigations that provide innovative linkages between metabolic signatures, premature disease, heritability of premature disease, and functional decline. Our metabolic profiling capability is unique among Pepper Centers and is a valuable collaborative resource to the overarching Pepper OAIC program nationally

**PEPPER CENTER SCHOLARS**
Since its inception, the Duke Pepper Center has produced an impressive portfolio of relevant research and innovations in faculty development. One of its many accomplishments is support and mentoring of numerous promising investigators whose careers focus on relevant aging related research at Duke. In 2009 in recognition of the contributions of these young investigators, career development and pilot project awardees, and the Duke Pepper Center established a *Duke Pepper Scholars Program.*

The 2013-2014 Pepper Center Scholars are:

**Mehri McKellar, M.D.** Assistant Professor, Department of Medicine, Division of Infectious Diseases  
**Work in Progress:** To examine whether the degree of immunosuppression and underlying inflammation in HIV-infected patients affects physical performance and whether physical decline is mediated through metabolic dysregulation.

**Richard Lee, MD., MPH** Medical Instructor, Department of Medicine, Division of Endocrinology and Metabolism  
**Work in Progress:** Two investigations to explore his hypothesis that increased functional impairment contributes significantly to the increased fracture risk in older patients with diabetes.
Rasheeda Hall, MD, Department of Medicine, Division of Endocrinology and Metabolism

Work in Progress: To determine if chronic kidney disease is an independent predictor of recurrent falls and injurious falls in nursing home residents with a history of falls and to examine potential mediators of recurrent falls.

C. PILOT PROJECTS

The 2013-2014 Pilot Projects are:

Role of Protein Scaffolding in Sarcopenia
John Stiber, MD, Associate Professor, Medicine, Cardiology
(Funded 2013-2014)

A Pilot Study to Identify Physiological Vulnerabilities to Accelerated Functional Decline
Dan Belsky, PH.D., Assistant Professor, Medicine, Geriatrics
(Funded 2014-2015)

Epigenetic Modification of Stem Cells with Aging and Obesity
Farshid Guilak, Ph.D., Professor, Orthopedic Surgery and Cell Biology
(Funded 2014-2015)

Skeletal Muscle Mass and Strength Trajectories in Older Patients Hospitalized with Medical Illness
Susan Nichole Hastings, M.D., Associate Professor, Medicine, Geriatrics
(Funded 2014-2015)

Determining the Role of Protein Quality Control in Mitochondrial Dysfunction and Disease in Aging
Matthew Hirschey, Ph.D., Assistant Professor, Chemistry and Biochemistry
(Funded 2014-2015)

Racial Differences in Outcomes of Older Adults Receiving Inpatient Palliative Care Consultation
Kimberly Johnson, M.D. Associate Professor, Medicine, Geriatrics
(Funded 2014-2015)

Accelerometry Data for Physical Activity and Sedentary Behavior in Older Adults: Data Processing and Analysis
Katherine Hall. PhD, Assistant Professor, Medicine, Geriatrics
(Core Resource Utilization 2013-2014)

Improving Venous Thromboembolism Prophylaxis in Hospitalized Elders
Juliessa Pavon, MD, Assistant Professor, Medicine, Geriatrics
(Core Resource Utilization 2013-2014)

SECTION III. CAREER DEVELOPMENT (RECENT) AND SUBSEQUENT FUNDING
Mehri McKellar, MD,
Medicine – Geriatrics/ Endocrinology
Duke University Medical Center
Durham, NC
RCD Supported (2013-2015)
**Work in Progress:** To examine whether the degree of immunosuppression and underlying inflammation in HIV-infected patients affects physical performance and whether physical decline is mediated through metabolic dysregulation.

**Subsequent funding**
1.5P30-AI064518-08, Duke Center for AIDS Research (CFAR) Small Award, Physical Function and the Role of Metabolomics in HIV and Aging Study, awarded 2013. Role: PI.
2.5P30-AI064518, Duke Center for AIDS Research, renewal for 5 years, awarded 2015. To establish and support an academic environment that promotes and encourages the intramural collaboration and coordination of all AIDS-related research activities at Duke, thus serving the requirements of all AIDS investigators and their research programs. Role: Executive Committee member and leader of the HIV and Aging Scientific Working Group.
3.1R24AG044325-01, HIV/Aging Pilot Program, Rapid Cycle award, awarded 2014. To study racial differences in change in physical function in older male veterans with HIV, using the national Veterans Aging Cohort Study database.
4. R13, conference funding, sponsored by Emory University. HIV & Aging: From Mitochondrial to the Metropolis, October 2104. Role: Executive Committee member.

Richard Lee, MD,
Medicine – Geriatrics/ Endocrinology
Duke University Medical Center
Durham, NC
RCD Supported (2013-2015)
Applied for GEMSSTAR 2013
**Work in Progress:** Two investigations to explore his hypothesis that increased functional impairment contributes significantly to the increased fracture risk in older patients with diabetes.

**Subsequent funding**
GEMSSTAR award 10/1/14-9/30/16: Aim: To identify potential novel biomarkers or pathways using metabolomics, associated with increased fracture risk, independent of bone mineral density, among older adults with diabetes.
American Diabetes Association 7/1/14-6/30/16
NIH Loan Repayment Program 7/1/14-6/30/16

Rasheeda Hall, M.D., Pepper Center Diversity Supplement Awardee (2012-2013)
Medicine – Nephrology
Duke University Medical Center
Durham, NC
**Subsequent funding**
Research Award of Excellence: VA Institute of Medical Research
Work in Progress: To determine if chronic kidney disease is an independent predictor of recurrent falls and injurious falls in nursing home residents with a history of falls and to examine potential mediators of recurrent falls.

SECTION IV. DUKE PEPPER CENTER PUBLICATIONS –2014-2015

2014


SECTION V. EXTERNAL ADVISORY BOARD MEMBERS

Karen Bandeen-Roche, Ph.D. Johns Hopkins
Chair of Duke External Advisory Board,
Years of service: 6

Roger Fielding, Ph.D Boston University School of Public Health
Years of Service: 6

Mary Tinetti, M.D., Yale School of Medicine
Years of Service: 1
2014

Farshid Guilak, Ph.D.  Professor of Orthopedic Surgery, Department of Orthopedic Medicine
Duke University Medical Center
Honors:
Arthritis Foundation Investigator Award, 2014
Cell and Molecular Bioengineering Innovator Award, Biomedical Engineering Society, 2014
Finalist, Healthcare Heroes Award, Triangle Business Journal, 2014

Connie Bales, Ph.D. Professor in Medicine, Division of Geriatrics, Duke University Medical Center
Honors:
Elected Chair (beginning June 2014) of the Medical Nutrition Council and thus also a member of the Executive Board of the American Society for Nutrition
Minority Research

The Duke University Pepper Center
(2014)

General Brief Description of Minority Activities:
The Duke Pepper Center has a rich tradition of minority research that includes support of minority trainees and a broad depth of research yielding extensive publications of relevance.

Special Projects

Genetic Ascertainment of Large African American Family for Osteoarthritis and Early Onset Cardiovascular Disease.

Virginia Kraus, M.D., Ph.D., William Kraus, M.D., Project Leaders:
Years 2001-ongoing

Drs. Virginia Byers Kraus and William E. Kraus, in collaboration with the Duke Pepper Center and the Duke Center for Human Genetics, have genetically ascertained one of the largest intact extended families in the United States. Particular emphasis was placed on evaluating this family (Family C) for osteoarthritis and early onset heart disease. This family celebrated a reunion in Durham, NC, July 24-28, 2002. A total of 500 adults participated from 35 states. This family traces its origin back to 1773 and consists of a mixture of ethnicities: primarily American Indian mixed with Anglo-Saxon and African-American. This is believed to represent one of the oldest intact extended families in the United States. Large family reunions have been held every two years since 1978 and every four years in North Carolina. A family genealogy has been published encompassing the years 1773 to approximately 1950. Of note, the author, approximately aged 86, is still living in North Carolina. We ascertained 239 members of this family at a Health Fair. We obtained health information, family history information along with laboratory data for use as quantitative traits including glucose and lipids. In addition, a physical exam was obtained which included body mass index, weight, height, calcaneal bone mineral density, hand exam for OA, blood pressure, eye exam for glaucoma and retinopathy, and a physical function measure on the over 65 age group. A pedigree has been constructed consisting of four generations. In addition to phenotyping and genetic ascertainment, we provided educational medical workshops on osteoporosis, osteoarthritis and cardiovascular disease. We are working to connect the four generations in the pedigree back to the original founders utilizing information provided in the Family C genealogy and information provided by the family geneologist who has kept current records for the family. We now have these in hand. We plan to proceed with interviews of older family members remaining in North Carolina to try to fill in any pedigree gaps. We will also proceed with evaluating the pedigree for medical conditions that appear to run in the family. We will then proceed to apply for funding to support genetics research on this family.
Gene-environment Interactions in Aging, Functional Decline and Disease
Svati Shah, M.D., Project Leader       Years 2007-Ongoing

The overall goal of this work is to study the interactions between aging, genetics and environment on the risk and development of (or protection from) complex diseases that commonly cause disability and loss of independence in older adults. The study of risk factors and heritability of key diseases in older adults directly relates and leads to functional decline. Furthermore, multiple disease pathologies and risk factors likely interact to produce disability and functional decline in older adults. Moreover, these interactions are not localized to old age alone, but occur throughout the life span, making the study of complex diseases in younger individuals (e.g., mid-life) as important as older individuals for advancing the understanding of how these diseases produce functional decline in late life.

For this pilot study, we will study metabolic risk factors for the complex diseases of cardiovascular disease (CVD) and osteoarthritis (OA). We have chosen to study CVD and OA risk for several reasons. First, CVD and OA are the two of the most common disabling conditions affecting older adults in the US. Second, aging is identified as a major risk element contributing to the development of each of these conditions. Third, ascertainment of samples from a large family structure four generations will provide a unique opportunity to study the interactive effects of aging, genetics and environment on the development of arguably the two most influential conditions affecting functional decline in the aging US population.

We have the extraordinary opportunity to address these issues through access to medical information, biomarker and genetic sampling in a large complex ethnically-diverse (primarily African and Native American) family. The family under study (Family C) is one of the oldest existing extended families in the United States and has a prevalence of disease that mirrors the rates in the general population, making it valuable for generalizing findings to the US population. This large multi-generational family resource will provide an innovative means to study the effects of aging, trait heritability, genetic and environmental factors, and interactions among these elements for common inherited conditions. There are three specific aims related to this project:

1). Quantitative measurement of CVD and OA disease-related biomarkers in all sampled family members;
2). Quantitative assessment of the heritability of metabolic risk factors for CVD and OA biomarkers, and their interaction with aging in this family;
3). Perform a genome-wide linkage analysis in this Family to map metabolic risk factors for CVD and OA susceptibility genes.

Johnston County Osteoarthritis Project
Virginia Kraus, M.D., Ph.D., Investigator.       Years 2001 - Ongoing

The Johnston County Osteoarthritis Project is an ongoing, community-based study of the occurrence of knee and hip OA in African American and Caucasian residents in a rural county in North Carolina. Details of this study have been reported previously 24. Briefly, this study involved civilian, non-institutionalized adults aged 45 years and older who resided in six townships in Johnston County. Participants were recruited by probability sampling, with over-
sampling of African Americans. A total of 3,187 individuals were recruited between May 1991 and December 1997. All participants completed a baseline clinical evaluation. Among the 3,187 participants with baseline data, 1,329 were not eligible or available for follow-up assessments. Reasons that participants were not eligible or available included emigration from study area (N=161), refusal (N=435), inability to participate due to physical or mental conditions (N=234), death (N=411), and inability to contact or find (N=88). Assessments at follow-up were completed from 1999-2003.

Dr. Kraus’s research in musculoskeletal disease has identified important racial differences in several biomarkers and pain responses. These results impact the use and interpretation of biomarkers for personalized medicine applications. While Caucasians had higher serum Hyaluronan levels (an indicator of knee synovitis) than African Americans, African-Americans had higher levels of the systemic inflammatory biomarker high-sensitivity C-reactive protein (hsCRP). In individuals with hip and knee OA, African Americans had higher pain scores. Racial differences in pain and function were related to psychological factors, including arthritis self-efficacy, affect, and use of emotion-focused coping. These symptom and biomarker data will be of increasing importance for early identification of individuals at risk for disease onset and progression in order to initiate treatment at very early times to avoid irreversible stages of disease and functional impairment.

**Increasing access to hospice care for older African Americas: a National study**

Kimberly Johnson, M.D.,
R01 (Ongoing)

African Americans use hospice at lower rates than Whites. Additionally, African Americans are more likely to experience inadequate symptom management and poor communication which may be improved with hospice care. The overall goal of this work is to identify best practices among hospice providers in reaching African Americans. The study will include a national sample of hospice providers. Participants provide information about their community education and outreach practices, admission practices beyond those required in Medicare Hospice Benefit, cultural sensitive training, goals and strategies to increase service to African Americans, and identify barriers and facilitators of these efforts. The specific aims of the project are:

1: Determine the association between the organizational characteristics of hospice providers and rates of hospice use by older African Americans in their service area.
2: Determine the association between the community engagement and marketing practices of hospice providers and rates of hospice use by older African Americans in their service area.
3: Determine the association between the admission practices of hospice providers and rates of hospice use by older African Americans in their service area.

The finding of this work will be used to design interventions to increase use of hospice care by older African Americans.

**Funded Pepper Pilot 2014-2015**

Racial Differences in Outcomes of Older Adults Receiving Inpatient Palliative Care Consultation
Over the last decade, there has been tremendous growth in inpatient palliative care consultation programs. These programs reduce symptoms, improve doctor-patient communication, increase satisfaction with care, and decrease costs. Inpatient palliative care consultation programs are especially relevant to improving the care of older adults hospitalized with restricting symptoms and progressive functional decline because nearly 70% of Medicare beneficiaries spend some time in the hospital in the last year of life. Because older African Americans with advanced illness are more likely than Whites to be hospitalized in the last year of life and to die in the hospital, inpatient palliative care consultation may provide an opportunity for them to receive interventions which address major threats to independence and the quality of end-of-life care (ex: uncontrolled symptoms, spiritual, emotional, and social well-being). Using a combination of chart review and interviews with patients and caregivers, the specific aims of this pilot study are:

1) Evaluate the feasibility of recruiting, enrolling, and following a sample of older African Americans and Whites receiving inpatient palliative care consultation.

2) Evaluate the feasibility of using standardized chart review to document reason and characteristics of patients receiving palliative care consultation, and to measure outcomes of palliative care consultation (ex: reduction in symptoms, improved psychosocial well-being, advance directives, patient disposition).

3) Examine beliefs, attitudes, and perceptions regarding benefits of and/or concerns about inpatient palliative care consultation through qualitative interviews with patients and their caregivers.

To-date, we have identified 666 consults among older adults (≥ age 65) between January 1, 2011 and December 31, 2011; 29.6% were African American. African Americans were slightly older than Whites (mean age 79.5 vs. 77.8) and a greater proportion (40.1% vs. 29%) were on the General Medicine service and a lower proportion in the ICU (19.8% vs. 25.8%) at the time of the consultation. Among African Americans, the reasons for consultation more often included a request to assist with communication (80.2% vs. 69.3%) and symptom management (69.5% vs. 58.9%). More older whites than African Americans who received palliative care consultation died during the hospitalization (31.1% vs. 18.3%) and more African Americans than whites were discharged to skilled nursing facility or rehab (29.4% vs. 19.6%). Similar proportions of patients in both racial groups were discharged with hospice. These findings suggest that there are important racial differences in inpatient consultation. Some of these differences may reflect attempts by referring providers to improve the care of seriously ill African Americans across domains where African Americans are known to experience lower quality care than whites, such as communication and symptom management (both more common reasons for consultation among blacks than whites). They may also indicate cultural differences which healthcare providers find more challenging to navigate and for which palliative care consultation may assist (such as communication in the face of poor prognosis and preferences for ongoing life-sustaining treatments). This pilot will provide preliminary data for a larger study to evaluate racial differences in outcomes of older adults receiving inpatient palliative care consultation.

Duke Pepper Center Minority Supplement Awardee
Dr. Rasheeda Hall is a Fellow in Nephrology with an interest in exploring solutions to health system problems for vulnerable populations, such as low-income, elderly, and uninsured patients with chronic kidney disease (CKD) that rely on Medicare and Medicaid for healthcare coverage. Her career goal is to become an established independently funded investigator that conducts health services research to improve the efficiency, quality, and costs of healthcare delivery for this vulnerable subset of patients. To attain this goal, she has incorporated her prior educational and clinical training into research training under NRSA’s Comparative Effectiveness Post-doctoral Fellowship Program while completing her clinical fellowship in Nephrology. Her diversity supplement will allow her to build on this training and allow protected time for immersion in aging research and geriatric nephrology. She will develop a deep understanding of the health system problems that impact the vulnerable population of nursing home (NH) residents with CKD. Her proposed research project is summarized below.

CONNECT for Quality is a 5-year randomized controlled trial of 2 different approaches to fall prevention in nursing homes (NHs). Sixteen NHs (including approximately 1600 NH residents with falls) will be randomized to either a novel nursing home staff intervention (CONNECT) plus a standard falls QI program (FALLS), or FALLS alone. Change in fall rates at the facility level is the primary outcome. Secondary outcome measures include risk of recurrent falls, injurious falls, fall-related quality indicators measured by chart abstraction, and staff perceptions of care.

2. CANDIDATE’S PROPOSED RESEARCH PLAN
a. Background and design: The proposed supplemental study focuses on the impact of chronic kidney disease (CKD) on falls in NH residents. Falls are the leading cause of serious injury in NH residents, and result in substantial morbidity, mortality, and increased healthcare costs. At least 50% of NH residents have CKD, and CKD progression leads to worsened functional status which persists after dialysis initiation. Older community dwellers with either CKD or end stage renal disease (ESRD) have higher fall rates than elderly community-dwellers without CKD, although this association has not been examined in the NH setting. We postulate that CKD contributes to falls in NH residents through multiple mechanisms including functional decline, disease-specific metabolic derangements such as anemia and vitamin D deficiency, and disease-specific altered pharmacokinetics such as increased sensitivity to psychoactive medications. Since fall reduction programs target individual patient risk factors, there is a critical need to uncover if and how CKD impacts falls in NH residents. Without this information, current fall risk reduction strategies such as those implemented in CONNECT for Quality may not be effective for preventing injury and disability in NH residents with CKD. Therefore, the specific aims of the supplementary study are:

Aim 1: Determine if CKD is an independent predictor of recurrent falls and injurious falls in NH residents with a history of falls.
Hypothesis 1A: NH residents with CKD will have a higher risk of recurrent falls and injurious falls than NH residents without CKD.
Hypothesis 1B: CKD independently predicts recurrent falls and injurious falls in NH residents after controlling for other known fall risk factors among NH residents.

Aim 2: Explore potential mediators of recurrent falls and injurious falls in NH fallers with CKD.
Hypothesis 2A: The association between falls and CKD is mediated in part by anemia.
Hypothesis 2B: The association between falls and CKD is mediated in part by increased sensitivity to renally cleared psychoactive medications.
Hypothesis 2C: The association between falls and CKD is mediated in part by vitamin D status.
Hypothesis 2D: The association between falls and CKD is mediated in part by increased levels of ambulatory dysfunction. This will be a secondary data analysis of a prospective study. Dr. Hall will utilize the resident-level data collected in the first year of CONNECT for Quality, and data from a pilot test of CONNECT for Quality in 4 Veterans Affairs nursing homes which was completed in 2011. Specifically, she will use baseline data from a sample of approximately 600 NH residents who are at least 65 years old and have at least 1 fall in a 6 month study period. Data elements include fall events and injuries over 6 months, ambulation status, fall-related comorbidities, psychotropic medications, and vitamin D supplementation. In order to allow her to complete her specific aims, serum creatinine and hemoglobin will be collected routinely from new residents enrolled in the CONNECT for Quality study (estimated n=300 between 4/1/12 and 12/31/12), and will be obtained for the completed VA sample through abstraction of the electronic medical record system (n=300). CKD status will be determined by calculation of estimated glomerular filtration rate from the serum creatinine, gender, race, and age. Given the immediate availability of resident-level data and the minimal steps required to obtain additional variables for each NH resident, it is feasible for Dr. Hall to conduct this study during the 1-year funding period.

b. Significance: Understanding the impact of CKD on falls in NH residents is important to individual patient care and healthcare policy. Results from this study will make a significant contribution to the practice of NH fall risk reduction by increasing our understanding of the impact of CKD on NH resident fall rates and fall severity. This study also has policy implications as the evidence could lead to novel fall risk reduction strategies that positively impact the rate of potentially avoidable hospitalizations for NH residents.

Two papers resulting from this work are currently in press (see bibliography).

New Pepper Center Scholars’ Mentored Minority Trainees

Heather Whitson, MD
Minority Trainee(s):
Liza Genao, M.D., She is doing research-comparing outcomes in Medicare Beneficiaries with COPD, and she is considering race-based disparity
Publications Pertaining to Minority Research:

2014
None

2015

Section I. DESCRIPTION OF CENTER

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

With the renewal of the center in July 2013, the JHU OAIC builds upon its driving frailty hypotheses, its high quality, committed, frailty-focused biological and biostatistical core expertise and training, and institutional commitment that have been cornerstones of this OAIC since its inception. It further builds on key frailty-related biological studies from the last cycle of this OAIC, which have provided focus on inflammation, mitochondrial biology, and the angiotensin system as intervention development targets. It now includes the addition of a transformative clinical translational and recruitment resource core to accelerate the translation of JHU OAIC frailty-related discoveries into clinical interventions. This evolution has greatly facilitated the mission of OAIC: To provide a hypothesis driven, frailty-focused, highly interdisciplinary center where supported investigators are supplied with the expertise, resources, and training necessary to make fundamental etiological discoveries related to frailty and then move these discoveries towards frailty-focused interventions. We propose to accomplish this through the following specific aims.

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

1) To stimulate, lead and develop effective frailty-focused interdisciplinary research programs that promote the maintenance of independence. Frailty will be the framework from which biological discovery and intervention development will be built.
2) To translate the frailty-focused new knowledge generated in this OAIC into targeted prevention and treatment strategies that help older adults maintain independence. A new clinical
translational and recruitment resource core and a continuing frailty registry will facilitate this effort.

3) To provide the highest quality interdisciplinary expertise, support, infrastructure and technology in biological, data analytic and clinical research methodologies relevant to frailty research to OAIC supported trainees and investigators. These are offered to accelerate progress in frailty research.

4) To support the development of new and innovative methodologies, research strategies and technologies essential to the study of frailty. Special focus will be placed to leverage areas in which this OAIC has made substantial progress in the previous funding cycle.

5) To provide tailored frailty-related training and mentorship to junior investigators interested in developing careers focused on maintaining independence in older adults. We continue with a leadership team that is highly expert and committed to training the next generation of frailty-focused investigators.

6) To attract outstanding investigators and trainees to frailty research from across the Johns Hopkins University and beyond. We will do this in part by providing highly visible educational and training activities on a local and national level.

Section II. RESEARCH, RESOURCES AND ACTIVITIES

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

Karen Bandeen-Roche, Ph.D., Core Leader
410-955-1166  410-955-0958 FAX  kbandee1@jhu.edu

Qian-Li Xue, Ph.D., Core Director
410-502-7808  410-614-3755 FAX  qxue1@jhu.edu

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

To accomplish (A), we provide analytic and data management support for high priority research on frailty by assisting researchers in the design, development, and implementation of data systems; data acquisition and cleaning; refinement of study hypotheses; study design; design and implementation of data analyses; and preparation of manuscripts, presentations, and applications for research funding.

To accomplish (B), we develop and test new methodologies for data analysis needed to translate basic research into clinical practice (see §B.2.2 below).

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

A major contribution of our work is to provide analytic and data management support to OAIC-supported scholars and investigators. The work of OAIC scholars is detailed in the RCDC and Pilot Project sections of this report and our contributions outlined under key outcomes and publications below, and our contributions to other work is summarized in Table 1 and the publications listing below. In the past year, we additionally have provided scientific leadership in three emerging topics that are key to the advancement of frailty research:

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

**Project 1 Major findings in the past year**: All abbreviated PFPs exhibit high specificity and negative predictive value for identifying frailty syndrome, but differ in their sensitivity and positive predicted value (PPV). Three-item PFPs proved insensitive but were best performers for PPV, well exceeding the original PFP on this metric. Regarding predictive validity, it was not merely the number of manifestations constituting the abbreviated PFPs but the specific manifestation combinations that distinguished the risk of adverse outcomes. Our findings support the need to tailor the choice of frailty tool to the intended use and purpose. A manuscript summarizing these findings is under revision. Efforts are underway to validate the results in the Cardiovascular Health Study.

The 2nd project we initiated develops new, nationally representative estimates of frailty prevalence among older adults in the U.S., using data from the National Health and Aging Trends Study (NHATS). It also characterized by frailty status the risk of multiple adverse events affecting health care costs and quality of life for older adults.

**Project 2 Major findings in the past year**: We found 15% of the older U.S. non-nursing home population to be frail, and 45% to be pre-frail. Age-related increases in frailty prevalence were from 9% in persons 65 to 69 to 38% of those 90 or older. Sizable race, income and regional disparities in frailty prevalence were observed. Adverse health outcomes were 2 to several times more common among frail vs. robust individuals. Frail individuals frequently exhibited disability, but considerably often did not, whereas robust individuals only rarely were disabled. Pursuit of findings regarding frailty disparities and progression among the pre-frail has potential to reduce disparities and extend the robust health span in older adults. A manuscript is under review.

The 3rd project initiated in the current reporting period studies the intersection between physical frailty and cognitive impairments. Epidemiologic and experimental studies have found that physical function and cognition are associated in older adults, which has led to the popular view of cognitive impairments as components of frailty. However, the nature of their associations with physical frailty is not well-characterized. This new project aims to provide descriptive and theory-informed, model-based
evidence that we hope will reinvigorate the discussion on whether cognitive impairments and physical frailty belong to the same syndromic construct. Specifically, we used the National Health and Aging Trends Study (NHATS) to estimate the prevalence of frailty and cognitive impairment in the United States, separately and jointly. We explored population characteristics that may distinguish physical from cognitive impairments. Next, we used latent class analysis (LCA) to assess the internal construct validity of a possible unified syndrome that includes both physical frailty criteria and cognitive impairments. The analysis was conducted initially in the Women’s Health and Aging Study II (WHAS II) and cross-validated using NHATS. Thirdly, we explored the mechanistic link between domain-specific preclinical cognitive impairments and the development of physical frailty in the WHAS II.

Preliminary findings: NHATS data show that physical frailty and cognitive impairments frequently do not coexist in older adults, and meaningfully different profiles of individual characteristics emerge with their separate versus joint occurrence. The analysis further provides preliminary evidence consistent with the hypothesis that dementia in old age and Alzheimer disease-related pathology in particular may contribute to the coexistence of physical frailty and cognitive impairments. Findings from the LCA provided further validation of the dissociation between physical frailty and cognitive impairments in certain subgroups. The longitudinal study linking cognitive functioning to the development of physical frailty found that cognitive decline over time, and decline in executive functioning in particular, explains extra between-person heterogeneity in frailty development beyond baseline performance and age, suggesting potential causal links. Taken together, these findings highlight the complexity of the cognition-frailty relationship and the need for a more refined approach to the study of the integration between cognition and frailty. Progress on the clinical assessment, treatment, and management of frailty would benefit from a better understanding of overlapping and distinct pathophysiology underlying cognitive impairments and physical frailty, as well as improved specificity of frailty phenotype by distinguishing the frailty syndrome as its own entity from secondary signs and symptoms of other age-related diseases. Findings were presented at the International Conference on Frailty and Sarcopenia Research held April 23-25, 2015.

During this reporting period, this Core has assisted 34 researchers in 21 projects and 9 grants on frailty and other aging phenotypes, including the design, development, and implementation of data systems; data acquisition and cleaning; refinement of study hypotheses; study design; design and implementation of data analyses; and preparation of manuscripts, presentations, and applications for research funding. This support has resulted in 16 publications to date. Seven grants led by Hopkins investigators have been submitted and 1 U01, 1 R01 and 1 R03 have been funded. In addition, we’ve provided statistical consultation to two other U01s led by other Pepper center PIs (see Aim 4 outcomes below).

In the following, we summarize key outcomes for each specific aim.

Aim 1. Mentoring: We comprehensively support research led by each RCDC investigator. Support provided in the current year has been outlined in the RCDC progress report. Dr. Bandeen-Roche (Agrawal, McAdams-DeMarco, Gross, Pustavoitau,) or Dr. Xue (Kalyani, Gross) has mentored and collaborated with each RCDC awardee, providing individualized explication of statistical techniques as well as more general mentoring. Support has spanned study design, analytic design and implementation, and data management. In addition, our core continues to play a central role in the Pepper Scholars program. Accomplishments are detailed in the Leadership / Administrative Core section of our report.
**Aim 2. Data Infrastructure:** We continue to provide ongoing support to the frailty registry including data storage, data checking, data cleaning, and results report. Additionally, we continue to provide direct programming support for data collection and management of ongoing (e.g., the Losartan and Vitamin D intervention studies) as well as new studies. In collaboration with the Clinical Translation Core, we have also played a critical role in the development of a new APP to facilitate physical frailty assessment by researchers and clinicians (see details in section C.3 of the LAC report).

**Aim 3a. Analytic and Data Management Support:** The details of the projects that we have supported and types of support are summarized in Table 1 of the overall progress report. To minimize redundancy, we summarize in the Table 1 below only projects that are not already reported by the other OAIC cores. The topics covered span the entire spectrum of basic biology of frailty (e.g., energy production and utilization) to frailty instrument selection and validation.

**Aim 3b. Methods Development:** see §B2.2.t

**Aim 4. Partnership and Outreach:** We have detailed our collaboration in supporting the research and mentoring activities of the OAIC Cores throughout the previous narrative. Dr. Bandeen-Roche and Dr. Xue regularly. To disseminate new ideas and research findings, Drs. Varadhan and Xue organized/chaired two symposia at the 2014 GSA and the 2015 International Conference on Frailty and Sarcopenia Research, respectively, to study the intersection between physical frailty and cognitive impairments – a topic of great significance to frailty research. The symposia attracted collectively close to 200 attendees. To strengthen existing and build new partnerships with other OAICs, we provided methodological and scientific expertise in the design and development of three multi-institution-sponsored research projects. First, in Oct. 2014, we jointly led the development of a U01 proposal (PI. Jeremy Walston) to define and validate measures of chronic inflammation, and evaluate them through pilot anti-inflammatory interventions to inform the design of an ultimate efficacy trial for improving gait speed. There was crucial collaboration by three OAICs (Duke, Michigan, Hopkins) and the Universities of Nebraska and Vermont. In the 2nd project, we partnered with biostatisticians at the Boston OAIC (Thomas Travison) and NIA (Michelle Shardell) in the development of the analytic plan for another U01 (PI. Shaleneder Bhasin) aiming to develop and evaluate diagnostic cut-points for low muscle mass and muscle strength that predict an increased risk of mobility disability among older adults. In the 3rd project, Dr. Bandeen-Roche facilitated the design of the NIH and PCORI funded "Randomized Trial of a Multifactorial Fall Injury Prevention Strategy” led jointly by Pepper centers at Boston, UCLA, and Yale.

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

Aravinda Chakravarti, Ph.D., Core Leader  
410-502-7525  410-502-7544  aravinda@jhmi.edu

Jeremy Walston, M.D., Core Co-Director  
410-550-1003  410-550-2116 FAX  jwalston@jhmi.edu

Dan-Arking, Ph.D., Core Co-Director  
410-502-7531  410-502-7544 FAX  arking@jhmi.edu
In Year 12 of our award, the RC-2 continues to expand its scope of support into a comprehensive molecular core that builds on the evolving science, infrastructure, and expertise across the Johns Hopkins Medical Institution. This evolution has facilitated the leveraging of additional human, technological, and infrastructure resources from across the Johns Hopkins Medical Institutions towards frailty and aging research. Multiple senior leaders from across the JHMI have been engaged to supply the necessary expertise and infrastructure and to a) facilitate analytical strategies needed to analyze genetics and epigenetics data being generated, b) incorporate measurements of oxidative stress, mitochondrial function, inflammatory cytokines, senescent T-Cell markers, DNA methylation, and gene expression as needed into RC-2 sponsored frailty research, and c) develop improved access to human and/or animal biological samples and phenotypic data for needed for additional frailty research. This expansion has allowed RC-2 to support and develop integration of key biological and technological advances into frailty related studies. We continue to provide assay development support, access to samples and rodent models, sample processing, and biological expertise to all of our RCDC supported and PESC supported scholars and continue to provide a wide range of external support and expertise to individual investigators from across JHU regarding frailty endo-phenotype development, frailty measurement, human genetics, mouse model development, renin-angiotensin system measurement, DNA methylation measurement, biomarkers related to frailty, and in the use of frailty and the biomarkers of frailty as a risk factor for organ transplantation failure, surgery, and anesthesia.

Important new findings that help to differentiate between the impact of aging and chronic inflammation on renin-angiotensin system activity, novel insights into the frail mouse metabolism and metabolomics measures. Dr. Arking and colleagues found a crucial link between mitochondrial copy number and mortality and frailty. Please see the following:

- Dr. Walston, OAIC Principal Investigator, and colleagues found that Losartan improved activity levels and parameters related to inflammation and oxidative stress in older mice. Their study was published in Experimental Gerontology.
- JHU OAIC Development Project led by Dr. Dan Arking of the Biological Mechanisms core found that the amount of mitochondrial DNA, otherwise known as mitochondrial copy number, predicts frailty and mortality. This study was published in the Journal of Molecular Medicine.

In the following, we summarize key outcomes for each specific aim.

Specific Aim 1: To provide state-of-the-art scientific expertise, technology and infrastructure necessary to facilitate cost-effective and efficient use of omics, other molecular approaches, and downstream computational technologies relevant to frailty research. Genetic Studies: We continue to supply internal and external support in this area, with ongoing external support to the Long Life Family Study (LLFS; U01AG023744) through phenotype development and through the development of novel mitochondrial copy number analyses. A grip strength manuscript has been submitted at present that represents a collaborative effort between investigators in 20 large aging cohort studies. Important new findings related to mitochondrial copy number, frailty, and mortality were published in the past year. Epigenetic studies: For the further development and adaptation of DNA methylation technologies we continue to provide recruitment and phenotypic development to external support to Dr. Andrew Feinberg and postdoctoral fellow Dr. Amy Vandiver (R01 AG042187). Altered gene and protein expression: This support is provided through our leverage of state-of-the art technology and genomic analysis, senior expertise, mentorship, and leadership available at JHMI towards frailty research via the laboratory of Drs. Arking and Chakravarti. Mitochondrial and oxidative stress: We have developed a panel of mitochondrial measurements that facilitated the funding of R-01
applications for Drs. Abadir and provide the basis of methodology development for another R01. Bioinformatics necessary to integrate and interpret biological data: We continue to engage Dr. Alkalesh Pandey and Dr. Jeff Leek in ongoing analytical challenges represented by multiple layers of biological data from the above realms. This is embedded in the DP2.

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

We continue to provide and facilitate access to human and animal tissue samples on an as needed basis to trainees and supported investigators from established studies previously supported by the NIA including the Cardiovascular Health Study (CHS), the Women’s Health and Aging Study (WHAS), and the Baltimore Longitudinal Study on Aging (BLSA). We also providing ready access to mouse models of frailty and biological samples derived from frail mouse models, including the IL-10−/− frail mouse and ATR1 and ATR2 KO mice developed in part by RC-2 support. We continue support ongoing work by EP investigator Abadir, AFAR supported investigator Tyesha Burks, DP investigator Westbrook, and multiple other external investigators. We continue to provide access to an institutionally supported mouse phenotyping data base related to frailty in order to facilitate the identification and utilization of other mouse models with frailty or related phenotypes. Finally, we continue efforts to develop access to merged national, population-based data sets relevant to molecular and genetic frailty. We continue broad collaborations with CHARGE working group around aging and inflammation phenotypes, and have recently finished a GWAS analysis of grip strength in older adults.

Specific Aim 3: To facilitate the translation of RC-2 frailty research findings into intervention- or prevention-focused clinical studies in collaboration with the leadership of all other cores. This aim focuses on molecular and computational methods for translational projects that are similar to aim 1 (discovery) but will usually differ in matters of scale and access to biological materials. We continue to focus on the development of clinical trials, on measurements important to the outcomes and biological discovery within those clinical trials. These include the U01 led by Dr. Appel Vitamin D study, “Vitamin D Supplements to Prevent Falls in Older Adults: A Dose-Response Trial,” and the losartan study detailed below in the PESC, where we provide inflammatory measurement expertise, and a pending U01 focused on inflammatory phenotype and intervention development.

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

Specific Aim 5: To continue to provide institutional, national, and international access and visibility for RC-2-related science and activities. This aim seeks to identify at Johns Hopkins both biologically motivated junior faculty who value omics technology and technologically motivated junior faculty who value frailty research to contribute to this area. We have established this core as the ‘go to’ place for collaboration and expertise development across surgical, medical, and now
engineering disciplines over the past year through provisions of services and expertise listed above. We continue to provide broad exposure to our work through outreach efforts at the Gerontological Society of America Annual Meetings, the annual International Frailty and Sarcopenia Meetings. We will also played leading roles in the 2014 Glenn Foundation meetings, and in the 2014 Kogod Annual Aging symposium at Mayo Clinic, and grand rounds at the University of Arizona.

Additional Projects:

**Inflammatory Phenotype Development:** We developed and published an inflammatory index published last year by Varadhan et al. This important phenotype has now been utilized in the development of a clinical trial for sub-acute inflammation and in HIV phenotypes by EP supported investigator Damani Piggott and by other investigators studying mobility declines.

**Genome-wide Association Study of Grip Strength** (Amy Matteini, PhD, RC-2 supported project): In collaboration with the Cohorts for Heart and Aging Research in Genetic Epidemiology (CHARGE) consortium research associate Amy Matteini (working with Dani Fallin and Jeremy Walston) have developed and led analysis of the cross-sectional association between maximal grip strength and 2.1 million single nucleotide polymorphisms (SNPs) utilized in this GWAS study. Data from twelve prospective cohorts were used in this analysis. Main effects were estimated using multiple linear regression models, adjusted for age, gender, weight and height. Additional models were built to test for SNP by gender and SNP by age interactions. Inverse variance weighted meta-analysis will be performed for a fixed effects model of beta and standard errors from all studies.

**Biology of Healthy Aging Program:** This Johns Hopkins Division of Geriatric Medicine based research group consists of 4 faculty members, 4 postdoctoral fellows, and 5 technicians who focus on aging biology and how it impacts frailty and vulnerability. Multiple EP supported basic science to clinical translational protocols are underway related to mitochondria, inflammation, RAS, and immune system decline.

**Year 8 RC-2 Development Project: Genome-wide Association Study of Grip Strength** (Amy Matteini, PhD, RC-2 supported project): In collaboration with the Cohorts for Heart and Aging Research in Genetic Epidemiology (CHARGE) consortium research associate Amy Matteini has led a GWAS analysis of 14 prospective cohorts evaluating the association between maximal strength and 2.1 million single nucleotide polymorphisms (SNPs). Two genome-wide significant associations were observed in regions of chromosomes 7 and 8 (p-value<5x10^-8). These findings are being submitted to Aging Cell and suggest common genetic variation may regulate myotube differentiation and muscle repair in older adults.

**Mouse Model of Frailty and the Development of other Relevant Animal Models.** RC-2 has continued to provide support to many investigators in the other cores for animal model development. Five manuscripts have now been published as a result of this effort, and 6 more are under development that characterize bone, metabolism, cognition, behavior, and skeletal muscle changes.

**Years 9-10 RC-2 Development Project, Dan Arking, PhD:** “The role of mitochondrial copy number and genetic variation in frailty” Energy metabolism has long been hypothesized to play a role in human disease and aging. We have shown association of a mitochondrial allele variation in the D-loop hypervariable region of the mitochondrial genome with the frailty phenotype in older adults (Moore et al., 2010). Given the central role of the D-loop in replication and maintenance of the mitochondrial genome, we hypothesize that this associated variant is likely to affect mitochondrial
stability and copy number of the mitochondrial genome, and thereby influence the frailty phenotype. A manuscript demonstrating these relationships is now published.

**Year 11-12 RC-2 Development Project: “Integrative omics analyses of the IL10\textsuperscript{Tm/Tm} frail mouse”** PI. Dan Arking, PhD; co-investigator: Dr. Reyhan Westbrook, OAIC Diversity Supplement Awardee

The IL10\textsuperscript{Tm/Tm} mouse, like frail humans, develops age-related skeletal muscle weakness, endocrine abnormalities, inflammatory pathway activation, mitochondrial abnormalities, and early mortality. These findings support the further use of this mouse to dissect molecular pathways that may impact frailty. Metabolomic profiling has been completed and analysis is underway with Dr. Pandey and Arking.

**RC-2 Interactions with Other Cores and with Supported Faculty and Additional Molecular Expertise Provided to OAIC Scholars:** In addition to the projects listed above, present or past OAIC supported scholars Sean Leng and George Wang have received External Project (EP) support for performance of assays related to their ongoing immune system studies related to frailty and immunosenescence (see Pilot and RCDC pages). Ronald Cohn, Sevil Yasar, Tyesha Burks, Rhondalyn Mclean, Reyhan Westbrook, and Peter Abadir, supported by Pilot, Diversity supplement, and RCDC respectively, have received ongoing advice and molecular support for their projects related to the renin-angiotensin system and intervention development with losartan. This is a rapidly expanding area within our OAIC and is a system that helps to explain connections between energy production, mitochondria, and inflammation and frailty.

**Project 1 – Losartan and wound healing** (Jessica Lee, Peter Abadir, Jeremy Walston): The study hypothesizes that blocking angiotensin 1 receptors in wounds with a losartan-based cream will facilitate healing of skin injuries and chronic wounds in older mice. The objective of this R21 grant proposal is to compare efficacy and safety of a losartan based cream at doses of 5%, 10% and 15% with a placebo cream in a mouse wound healing model. RC-2 provided aging mice for pilot data that helped to secure this award, which is funded with the starting date of April 1, 2013.

**Project 2 – CMV and immune function** (Sean Leng): To test the hypothesis that the presence of CMV DNA in monocytes predicts T-cell immunosenescence and chronic inflammation in older adults better than anti-CMV IgG serology (seropositivity and absolute IgG antibody titers), this study proposes to assess CMV DNA in monocytes and its immune consequences longitudinally using available peripheral blood mononuclear cells (PBMCs) and sera that were banked over 12 years in the Women’s Health and Aging Study II. RC-2 personnel and Dr. Walston collaborated with Dr. Leng in refining study aims and hypotheses and designing measurement plan. This grant was revised and resubmitted as a R21 and funding began in July of 2013.

**Project 3 – Age-related changes in Mitochondrial Angiotensin System** (Peter Abadir): Age-related mitochondrial abnormalities contribute to a wide range of age-related conditions, including Type 2 diabetes, frailty, heart failure, neurodegeneration, and sarcopenia. Dysfunctional mitochondria in older organisms generate ROS that damage mitochondrial DNA, which in turn leads to reduced ATP supply to the cell. Although multiple potential etiologies for this mitochondrial decline have been proposed, no clear aging-related etiological mechanisms for this have been identified. The overall research objective is to determine how age-related changes in the newly identified Mitochondrial Angiotensin System (MAS) influences late-life mitochondrial dysfunction. Dr. Walston and other RC-2 personnel helped to generate preliminary evidence and provided aging mice for the development of this study. This is follow-up work from PESC and RCDC supported efforts in prior years.
Project 4 – Assessing the Clinical Validity of a Novel Inflammatory Index in Geriatrics (Ravi Varadhan): A low grade pro-inflammatory state characterized by increased levels of cytokines and acute phase proteins has been associated with adverse outcomes. Dr. Varadhan and his colleagues have recently developed a novel inflammatory index score (IIS = log(IL-6) + 2 log(sTNFαR1)). IIS predicted 10-year all-cause mortality better than any other single or aggregate measure developed from 15 commonly measured serum markers of inflammation. Using data from a large, national cohort of older adults followed annually for more than twenty years, this new proposal is designed to test the hypothesis that the IIS independently and consistently predicts declines in measures of physical and cognitive function, as well as the incidence of frailty, mobility disability, and dementia in community-based older adults (age> 65 years). A demonstration that IIS consistently predicts age-related declines and adverse outcomes across several major physical and cognitive domains important to older adults would further establish it as a measure of chronic inflammatory burden with clinical validity and move it closer to potential integration into clinical practice.

Project 5 – Influenza vaccine failure in older adults over 75: role of chronic CMV infection (Sean Leng): Seasonal influenza causes significant morbidity and mortality and is the fourth leading cause of death for older Americans. Annual immunization with a trivalent inactivated vaccine (TIV) is recommended for all adults 50 years and older. However, despite improved vaccination coverage in older adults over time, influenza-related mortality has actually increased. This study evaluates chronic CMV infection as a contributing factor to influenza vaccine failure in older adults over 75. Dr. Walston and other RC-2 personnel helped with study design and measurement efforts for pilot data. Dr. Leng’s R01 grant, ‘Influenza Vaccine Failure in Adults over Age 75: Role of Chronic CMV Infection” was funded by NIAID as January 2014. The OAIC RC-3 and its clinical will provide additional recruitment assistance.

External Support:

Sean Leng, MD, PhD. NIH/NIAID R01 AI108907. Influenza Vaccine Failure in Adults over Age 75: Role of Chronic CMV Infection. Funded 2014. This project receives ongoing support.

Dorry Segev, MD, PhD. NIH/NIA R01 AG042504. Frailty and Risk Prediction in Older Adults Considering Kidney Transplantation. Funded 2013. This project receives ongoing support.

Sean Leng, MD, PhD. NIH/NIA R21 AG043874. Chronic CMV Infection in the Elderly: Diagnosis and Link to Chronic Inflammation. Funded 2013. This project receives ongoing support.

Jeremy Walston, MD, and Peter Abadir, MD. NIH/NIA R21 AG043284. Novel Formulation of ARB based for Treatment of Wounds in Aging. This project receives ongoing laboratory and animal model support.

Peter Abadir, MD. NIH/NIA R01 AG046441: Age Related Changes in Angiotsin Receptors and its Role in Chronic Inflammation. This project receives ongoing support.

Andy Feinberg, MD. NIH/NIA R01 AG042187: The Role and Genetic Mechanism of Epigenetic Plasticity in Age-Related Disease. This project receives ongoing support.
II.C. RESOURCE CORE-3 (RC-3): CLINICAL TRANSLATION AND RECRUITMENT CORE

Robert Wise, M.D., Core Leader
(410) 550-0546  rwise@jhmi.edu

The renewal of the center fostered the development of a new JHU OAIC resource core that has evolved from a highly successful RCDC-based Clinical Translational Unit. In order to more effectively meet this center’s goal of translating frailty-related etiological discoveries into clinical studies that help maintain independence in older adults, and to overcome the substantial barriers to success in clinical investigation for junior investigators, the leadership of this OAIC made a strategic decision to develop this resource core. RC-3 provides to supported OAIC investigators: 1) comprehensive training and mentorship in clinical research that spans from study design through implementation through outcome interpretation, 2) clinical research space and assistance with all aspects of forms and protocol development, data collection, and recruitment of human subjects, 3) a large and active registry of well over 900 older adults that have been characterized for frailty and who have consented to be contacted for aging and frailty related studies, and 4) synergy with other cores in order to optimize all aspects of frailty-related study design, data collection, and biological measurement and junior faculty training. This synergy is greatly augmented by the recruitment of core leader, Dr. Robert Wise, who has considerable expertise in the development, implementation, and conduct of both clinical physiological studies and clinical trials. In addition, the daily operations are led by a highly skilled and experienced research program manager with expertise in the measurement of frailty, mobility, and cognition, as well as expertise in protocol development and implementation and in minority subject recruitment and retention. This initiative, which is closely aligned with the JHU Division of Geriatric Medicine and Gerontology goals of better integrating clinical practice with clinical research, is in large part funded by philanthropic resources from the Division. RC3 supports the study design, implementation, training, mentorship, and recruitment needs of PES-1 (Dr. Lee), the recruitment and coordinating needs of PES-2 (Dr. Weiss), and the coordinating and measurement needs of our RCDC candidates, and our ongoing Vitamin D intervention (Dr. Yasar). In addition, the core supports external projects that require frailty-related recruitment and clinical research study support, including: support to the R01 award and the K-23 award of former Pilot / RCDC supported investigators, Dr. Leng and Dr. Abadir, respectively; support for recruitment into an NIH supported clinical trial for anemia of unexplained etiology in older adults; and recruitment, minority outreach, and frailty measurement expertise to an R-01 focused on reducing disability in community dwelling older adults. The goals of RC-3 are outlined in the following specific aims:

1) To provide mentorship and training in all aspects of human subjects research to OAIC supported investigators, including study conceptualization, study design and outcomes, definition of interventions, measurement, protocol development and implementation, regulatory approval, quality assessment procedures, and standard operating procedures related to frailty and the maintenance of independence for all RC-3 supported investigators

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

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

Clinical Translation Unit: The central hub of RC-3 is the Clinical Translational Unit. In the most recent cycle preparation for the conduct of frailty-related clinical and clinical intervention studies, we recognized the value of creating a unit broadly aimed at aiding investigators in the design, recruitment, and implementation of clinical studies involving human subjects. This Clinical Translation Unit (CTU) was founded on the Bayview Medical Campus, adjacent to the Division of Geriatric Medicine and Gerontology clinical sites and adjacent to the Biology of Healthy Aging laboratories. It supports recruitment and clinical translation for RCDC and PESC supported investigators Abadir, Lee, and Weiss and EP supported project led by Feinberg, Leng, and Walston.

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

There are currently 1127 participants in registry database who have been characterized for frailty, many of whom have agreed to be re-contacted for additional research studies.

Current projects supported by the RC-3:

OAIC Pilot Study: Jessica Lee, MD and Peter Abadir, MD: “A Study of Muscle Strength Maintenance in Older Adults.” Please see full description provided in the Pilot Core report. RC-3 provides recruitment, scheduling and measurement support.
**OAIC Pilot Study: Robert Weiss, MD:** “Energy Production in Frailty: Skeletal Muscle ATP Kinetics in Frail, Older Adults.” Please see full description provided in the Pilot Core report. RC-3 provides recruitment.

**K23 Grant: Peter Abadir, MD, PhD:** “Age Related Change in Angiotensin Receptors and its Role in Chronic Inflammation.” With this NIA K23 award, Dr. Abadir aims to evaluate specific factors that may play a role in late life weakness, increased morbidity and mortality. Angiotensin receptors 1 and 2 (AT1R and AT2R) are found on the surface and on the inside of virtually all human cells. This study evaluates the relationships among these receptors in immune system cells as people age, and determines how these changes might influence chronic inflammation, frailty and late life vulnerability. RC-3 provides recruitment support.

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

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

**R01: Se-Jin Lee:** ‘Mechanism Underlying Myostatin Regulation and Activity.” Dr. Lee investigates the mechanisms underlying the regulation and activity of myostatin, which is a signaling molecule that plays a critical role in regulating skeletal muscle growth. RC-3 plans to provide recruitment and lab processing support.

**U01: PACTTE (Partnership for Anemia Clinical and Translational Trials in the Elderly):** The NIA recently released an RFA entitled, “Partnership for Anemia Clinical and Translational Trials in the Elderly.” The OAIC-sponsored CTU faculty, former RCDC-supported faculty Dr. Roy, and OAIC-PI Dr. Walston were involved from the very beginning in the development of the scientific and recruitment planning for this. RC3 and CTU personnel provided recruitment and management support for this study until it closed in early 2015.

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

**Data and Safety Monitory Board (DSMB):** An OAIC DSMB was established to provide independent safety review for all OAIC interventional human subjects studies. All five members of the DSMB are external to the OAIC, with two members from the University of Maryland, and all have been approved by the NIA Program Officer. The DSMB meets semi-annually, or more frequently as
needed, to review progress, findings and all potential safety issues related to OAIC human subjects research projects. The DSMB convened in February 2014 to carefully review and discuss its operating charter. The group convened in May 2014 to review the current intervention studies on Losartan and frailty, and Vitamin D and frailty among older adults. The group also re-convened in December 2014 to review the ongoing Losartan pilot study. Reports from each meeting have been submitted to the NIA Program Officer. The next meeting will take place in July 2015.

II.D. RESEARCH CAREER DEVELOPMENT CORE (RCDC)
Gary Gerstenblith, M.D., Core Leader
410-955-6835   410-614-9422 FAX  gblith@jhmi.edu

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

1) To identify, attract, and select for career development support a diverse and interdisciplinary group of junior investigators from across JHU with the greatest potential to become outstanding research leaders focused on frailty and how to ameliorate it, and on maintaining independence with increasing age.
2) To provide the research infrastructure and salary support to these junior investigators so as to enable them to successfully bridge the critical transition to independent research leadership and grant funding. The resources provided will ensure protected research time and access to core resources necessary to advance their productivity and interdisciplinary training.
3) To provide each supported individual with mentorship individualized to his or her needs and to monitor the progress of the research project and career development.
4) To develop for each supported individual a program of subject-area, methodological and leadership training needed to equip them to excel in their career goals, and promote its successful completion.
5) To provide an academic home and an intellectual ‘stimulus zone’ for supported faculty as well as postdoctoral fellows, pre-doctoral students, and junior faculty working on frailty-related projects. Its cornerstones will include an energetic and welcoming senior faculty; a monthly research-in-progress forum fostering interactions among the senior faculty, RCDC supported investigators, all other OAIC supported investigators, and the larger community on aging at JHU; the sponsorship of a seminar series on frailty in collaboration with the LAC and the Johns Hopkins Center on Aging and Health (COAH); and the provision of an informational network facilitating access to the many other intellectual enrichment opportunities at JHU. In all we aim to create the critical mass of investigators needed to spark clinical multidisciplinary research interaction and collaboration among supported faculty.
The RCDC serves as a center of training, mentorship and networking for talented junior investigators spanning 3 levels of development: 1) K-Eligible Investigators: We dedicate our highest level of support for junior faculty members deemed to have promise for K or other career development awards. We have designed our Core to provide salary support to 3 individuals in any given year. These individuals also are provided with material support from all 3 RCs. 2) R-Eligible Investigators: Junior investigators supported by K or other career development awards, and who are actively engaged in research relevant to the goals of this OAIC, are prioritized for external project support from the RCs and encouraged to apply for PESC resources as needed. They also receive ongoing mentorship and education to facilitate the awarding of an independent investigator (e.g. R-01) award. 3) Other Trainees: Interested junior faculty, post-doctoral fellows and pre-doctoral students are encouraged to participate in OAIC-sponsored activities, provided with mentorship, and encouraged to develop research and career goals that will enable them to be eligible for formal OAIC support. In recent years, such trainees have made substantial contributions to the scientific life of this OAIC. Many have become RCDC, PESC, EP, and diversity supplement supported scholars.

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

- Dr. Mara McAdams, an OAIC scholar and former RCDC awardee, found that frailty is a strong, independent risk factor for post-Kidney Transplant mortality. This study was published in the American Journal of Transplantation. In a separate study, Dr. McAdams found an association between frailty and Mycophenolate mofetil dose reduction, which can lead to rejection and possibly graft loss among kidney transplant recipients. This study was published in the journal Transplantation.
- Dr. Rita Kalyani, an OAIC scholar and former RCDC awardee, found associations between hyperglycemia and muscle strength, a key component on the hypothesized frailty pathway. This work was published in the journal Diabetes Care.
- Dr. Devon Dobrosielski, a former RCDC awardee, found that the severity of OSA was reduced after an exercise and weight loss program among older adults. This study was published in the journal Medicine & Science in Sports & Exercise.

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

Current RCDC-supported Junior Faculty in Year 12 (2014-2015)

**Charles Brown, MD. Research Career Development Core (RCDC). “The association between baseline frailty and postoperative delirium or functional decline after cardiac surgery, and a potential intervention to improve outcomes.”** Mentors Name: Charles Hogue, Jeremy Walston

In this project, Dr. Brown leverages resources of an ongoing NIH-funded trial to examine whether frailty in cardiac surgery patients is independently associated with postoperative delirium or 1-month functional decline. He is also measuring depth of anesthesia to determine the feasibility of an intervention to improve outcomes in frail patients by reducing depth of anesthesia. Preliminary data in cardiac surgery patients at Johns Hopkins demonstrate a 31% prevalence of frailty with a markedly increased incidence of delirium in frail patients (41.2%) vs. non-frail patients (2.6%; P<0.001) albeit with small sample size and imprecise delirium measurement. These preliminary data motivate the goals of Aims 1 and 2 to determine the association between frailty and postoperative delirium or functional decline, using rigorous assessments of delirium and functional status. Also, optimizing depth of anesthesia represents a potential intervention, since frail adults
may be vulnerable to a relative anesthetic overdose. However, randomized trials of anesthetic depth in cardiac surgery patients have not been reported, nor has the range of anesthetic depth been examined in frail cardiac surgery patients. This gap in understanding motivates **Aim 3** of this study to measure depth of anesthesia in frail cardiac surgery patients to determine if reducing depth of anesthesia is a modifiable target to improve postoperative outcomes. Dr. Hogue, Dr. Brown’s mentor, is currently enrolling patients in an NIH-funded trial (RO1 HL092259) to determine whether optimizing blood pressure during cardiac surgery can reduce stroke. In this RCDC-supported study, Dr. Brown is enrolling patients from Dr. Hogue’s trial into a nested cohort study. Previously, he has examined delirium in a nested cohort of 60 patients in this trial, thus demonstrating the feasibility of his current approach.

**In this proposal, the Specific Aims are:**

1) **1. To determine whether baseline frailty is independently associated with delirium after cardiac surgery. Hypothesis:** The incidence of delirium is increased in frail patients independently of important confounding variables. To establish this, Dr. Brown aims to enroll 72 patients undergoing coronary artery bypass and/or valve surgery. He will measure baseline frailty using the Cardiovascular Health Study-derived criteria and assess delirium using the rigorous Confusion Assessment Method (CAM) or CAM-ICU.

2) **2. To determine whether frail patients have greater decline in functional status one month after cardiac surgery, compared to non-frail patients. Hypothesis:** Decline in functional status from baseline to one month after cardiac surgery is greater in frail vs. non-frail patients. To establish this, Dr. Brown will assess change in instrumental activities of daily living (IADL), gait speed, and hand-grip strength, in the same patients enrolled for Aim 1.

3) **3. To determine whether depth of anesthesia in frail patients is a modifiable risk factor for delirium and functional decline after cardiac surgery. Hypothesis:** Under standard protocols depth of anesthesia during cardiac surgery is greater in frail vs. non-frail patients, and exceeds levels consistent with general anesthesia. To establish this, Dr. Brown will monitor depth of anesthesia during cardiac surgery using the Bispectral Index (BIS), a non-invasive processed electroencephalogram. BIS values of frail patients will be compared to BIS values of non-frail patients, as well as to accepted cutoffs for general anesthesia (BIS=45-60).

**Progress Summary:**

Dr. Brown and colleagues have established study infrastructure, including identifying a research assistant, creating CRF’s, and building a REDCap database. The study IRB is approved: NA_00027003. Patient enrollment began in August. To date, 45 patients have been enrolled in the study, which is on track for the goal of approximately 1 patient per week over 18 months. Frailty assessments and delirium and functional assessments have been successfully completed in all of these patients. Data analysis has not yet started: Dr. Brown is conferring closely with the Biostatistics Core on his analytic plan. Dr. Brown will continue current recruitment, and will begin preliminary analysis of data shortly. Statistical support will be sought from the Biostatistics Core for this analysis.

Dr. Brown has submitted a manuscript on the association of frailty and delirium based on his preliminary data. He is in the analysis and manuscript preparation phase of three manuscripts (1) the association of delirium and length of stay/ cost after cardiac surgery, (2) the association of brain MRI scans and postoperative delirium, and (3) characterization of delirium after spine surgery. Regarding grants, within the past four months, he submitted a K-23 grant application, a International Anesthesia Research Society grant application, a grant application for a Johns Hopkins Discovery Award, a Johns Hopkins Clinical Scientist Career Development Award Application, and a Doris Duke preliminary grant application. The Biostatistics Core supported Dr. Brown in the development of these
applications. Three abstracts were presented at the 2015 Society Cardiovascular Anesthesia meeting, 2 of which are based on the first two items in this section. Two abstracts were also submitted to the annual meeting of the American Society of Anesthesiologists.

**Alden Gross, PhD, MHS. Research Career Development Core (RCDC). “Intersection of Domain-specific Cognitive Performance and Frailty: An Integrative Data Analysis.” Mentors Name: Drs. Qian-Li Xue, Ravi Varadhan, Michelle Carlson**

The overall goal of this proposed research is to determine the role of global and domain-specific cognitive performance in the development of frailty using a pooled analysis of three large longitudinal observational studies with prospectively measured data on cognitive performance and frailty among more than 6,500 adults over age 70. Dr. Gross hypothesizes that although frailty and cognitive impairment are both age-related phenomena, common but distinct processes underlie them and thus the conditions overlap more with age. His proposed study benefits from a large sample size which will support the ability to detect patterns and afford the opportunity to address mechanistic questions about frailty that cannot be addressed as well in smaller samples. Specifically for this proposal, poor nutrition, cardiovascular risk factors, and depressive symptoms are key risk factors for both cognitive decline and frailty. The proposed research will test empirically whether these mechanisms for frailty are cognitively mediated. Such a finding would have implications for causal understanding and T1 translational research.

Challenges in studying the intersection of cognition and frailty are that participants in epidemiological and clinical studies often are a selected sample, or a sample is too small to make confident statements about generalizability of findings. The Women’s Health and Aging Study II (WHAS-II), for example, was selected to be a healthy cohort of older women and thus has low rates of frailty and cognitive impairment (see Preliminary studies). To address this challenge, Dr. Gross will combine epidemiologic data from the WHAS II, Health ABC, and Ginkgo Evaluation of Memory Study (GEMS). Critically, each study administered comparable frailty measures. Because cognitive decline is itself heterogeneous, and specific cognitive domains – namely, executive functioning and psychomotor speed – have been associated with components of frailty, it is useful to distinguish different cognitive domains from each other. Although cognitive tests differ across studies, Dr. Gross will use a novel approach to harmonize constructs across tests representing global and domain-specific cognitive performance, in particular memory and executive functioning (6). The specific aims are as follows.

- **Specific Aim 1.** To evaluate associations between global and specific cognitive domains (memory, executive functioning) and frailty at baseline in a sample of over 6,500 adults age 70 and over. Hypothesis 1a: Cognitive impairment is not related to physical frailty in the overall sample at baseline, but the two conditions coalesce more over time due to overlapping, but distinct, aging processes. Hypothesis 1b: Consistent with prior research, associations with frailty are stronger for executive functioning than for memory.
- **Specific Aim 2.** To determine whether baseline level and rate of change in domain-specific cognitive performance (memory, executive functioning) is associated with earlier incidence of frailty. Hypothesis 2: Deterioration in executive functioning, but not memory, is associated with earlier incidence of frailty. In planned sensitivity analyses, we will explore whether these associations differ by age, sex, ethnicity, and socioeconomic status (income).
- **Specific Aim 3.** To determine the mediating role of cognitive decline in the association of known frailty risk factors (cardiovascular risk, nutrition, and depressive symptoms) and the development of frailty. Hypothesis. Cognitive decline partially mediates associations between cardiovascular risk, nutrition, and mood-related risk factors for the development of physical frailty.
This research has potential to elucidate part of the role of cognitive performance in frailty by leveraging three well-characterized epidemiologic cohort studies. Characterization of the association of particular cognitive domains with development of frailty may help to target persons at risk for frailty earlier, thus informing their clinical care. Identifying the mediating role of cognitive decline in known mechanistic pathways to frailty may also facilitate translational research by informing the design of interventions to prevent or delay physical frailty.

**Progress Summary:**

Related to Aim 1 of the project, he presented preliminary findings from WHAS II, with a replication using Health ABC data, at a 1/7/15 Pepper Scholars Program research in progress meeting. He worked with mentors to prepare an abstract for the International Conference on Frailty & Sarcopenia Research in Boston, which was accepted as part of a symposium led by Dr. Xue. His paper was presented on April 24, 2015, and he presented a poster on the work at the Annual OAIC Meeting on April 27, 2015. He has drafted a manuscript to be circulated to co-authors, and received encouragement from the editor at Journal of Gerontology: Medical Sciences to submit there.

As of April 2015, Dr. Gross has downloaded and processed much of the Health ABC data, which came in 199 separate pieces. He has begun analyzing biomarker data in Health ABC as they relate to the frailty phenotype, and gave a presentation at the Frailty Working Group on April 8, 2015. This work is ongoing. Dr. Gross has also submitted a proposal to use CHS data, which is currently being revised.

Dr. Gross received a priority score of 24 on a K01 submission to NIA that partly extends this proposal into physiologic measurement of frailty (Title: Intersection of Physiologic Frailty and Cognitive Performance in Older Adults: An Integrative Data Analysis). He is currently revising the submission. It was originally submitted October 10, 2014. Drs. Bandeen-Roche and Walston are co-mentors.

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

Senile calcific aortic valve stenosis (AS) is a progressive degenerative disease that is most prevalent among elderly individuals and is associated with considerable morbidity and mortality without surgical aortic valve replacement (SAVR). Unfortunately, approximately one-third of elderly patients are deemed ineligible for this therapy due to comorbidities. Transcatheter aortic valve replacement (TAVR) has emerged as an effective alternative to SAVR among AS patients with prohibitive or high surgical risk, with similar improvements in survival and quality of life when compared to SAVR. Current studies are in progress to better characterize clinical features that provide the most useful information regarding the risks and benefits of TAVR, but there is very limited literature on the prognostic impact of frailty among patients undergoing TAVR. Furthermore, no studies have investigated whether TAVR alters the frailty phenotype in these patients and whether any change is associated with improved outcomes, including quality of life and independent living. Dr. Hasan proposes to:

1. **Evaluate the prognostic impact of frailty on outcomes following TAVR.** To date, 132 patients have undergone the TAVR procedure at Johns Hopkins; all 132 patients have had complete pre-procedure frailty assessments. Dr. Hasan proposes to perform a retrospective analysis of this patient group to evaluate whether pre-procedure frailty is independently associated with adverse outcomes among elderly patients undergoing TAVR for AS. He will also address this aim via a prospective analysis as part of the study proposed in Specific Aim 2. He hypothesizes that frailty is independently associated with risk of post-TAVR early mortality, hospital length of stay, discharge to
a nursing facility, discharge to a rehabilitation facility, progressive heart failure, renal failure, days before return to home from the nursing or rehabilitation facility, and heart failure-specific quality of life as assessed using Minnesota Living with Heart Failure (MLHF) questionnaire.

2. **Evaluate the impact of TAVR on frailty.** Dr. Hasan proposes to conduct a prospective observational study of elderly patients with AS undergoing TAVR at JHMI with serial assessment of frailty before and at one month and six months after TAVR. He hypothesizes that frailty, evaluated as a scoring of the components of the phenotype, will improve following TAVR and that the extent of improvement will be associated with improved hemodynamic status.

3. **Investigate inflammation as a pathophysiologic link between aortic stenosis and frailty.** As part of the observational study described in Specific Aim 2, Dr. Hasan proposes to evaluate pre- and post-TAVR levels of inflammatory markers that are implicated as a possible link between the pathophysiology of AS and frailty. He hypothesizes that pre-procedure levels of these markers will be correlated with frailty scores in this patient population, that the levels will decrease following TAVR, and that the extent of decrease will be associated with the extent of improvement in frailty score at one month and six months post-procedure.

**Progress Summary:**
Dr. Hasan has revised and resubmitted the IRB protocol for his proposed studies, which is now approved: IRB00054646. There have been no adverse events to date. Dr. Hasan met and reviewed statistical plans with Biostatistics Core Leader, Dr. Bandeen-Roche. He is now in the process of preparing a retrospective data set for analysis as proposed in Specific Aim #1 of this RCDC proposal, and he is organizing staff and other resources to initiate prospective data collection as proposed in Specific Aims #2 and #3.

**Former RCDC-supported Junior Faculty, supported in Year 11 (2013-2014)**

**Mara McAdams-DeMarco, PhD, Assistant Professor, Departments of Surgery and Epidemiology; Mentor: Dorry Segev, MD, PhD, MHS, Associate Professor, Departments of Surgery and Epidemiology**

Dr. McAdams-DeMarco aims to improve the clinical management of older ESRD patients undergoing kidney transplantation (KT) through the development of adverse outcome metrics and risk prediction relevant to older adults. In an ongoing cohort of older KT recipients, she evaluated adverse geriatric outcomes such as activities of daily living (ADL) and instrumental ADL (IADL) disability and frailty as a risk stratifier that has shown promise in her preliminary data. Her aims were to: 1) estimate the trajectories of frailty and the factors associated with this trajectory over 5 years; 2) determine the association of frailty and incident adverse health outcomes of aging; 3) evaluate the inflammatory pathway linking frailty and adverse health outcomes of aging. **Contributions of OAIC Resources:** Dr. McAdams-DeMarco received material support from RC-1 in the implementation of her statistical analysis, and she was mentored by Drs. Walston and Bandeen-Roche.

**Progress Updates:** Dr. McAdams-DeMarco has continued analyses of frailty in patients undergoing kidney transplantation (KT). She is currently working on two main projects: 1) the association of frailty and change in HRQOL while waiting for KT, 2) frailty as a predictor of KT length of stay. She has submitted abstracts to the Gerontological Society Annual meeting, as well as abstracts to the American Transplant Congress. Dr. McAdams-DeMarco was successfully awarded a K01 career development grant from the National Institute on Aging, starting December 1, 2013. Dr. McAdams-DeMarco’s RCDC salary support officially ended in December 2013 with receipt of this K-award. The OAIC has continued to provide her with core support from RC1 and RC2. Dr. McAdams-DeMarco attended and presented a poster at the OAIC National Meeting in April 2014. During the current grant year, she has remained an active participant in the Frailty Working Group and participated in the OAIC Retreat in February 2015.
Recent Awards and Publications related to OAIC:

- April 2014: The Arthritis National Research Foundation (ANRF) and the American Federation for Aging Research (AFAR) jointly funded Dr. McAdams-Demarco’s work in their first-time collaboration of the Arthritis and Aging Research Grant.
- K01 award, NIA, “Frailty and Adverse Health Outcomes of Aging in Older Adults with Kidney Failure”; start date December 1, 2013.
- Faculty Innovations Fund, JHSPH.

Yuri Agrawal, MD. Assistant Professor, Department of Otolaryngology-Head and Neck Surgery
Mentor: John Carey, MD. Professor, Department of Otolaryngology-Head and Neck Surgery.

With this RCDC award, Dr. Agrawal built upon her OAIC pilot work to study the implications of specific vestibular impairments for postural instability, gait impairments, frailty and falls for older adults. Her study aims, carried out in a sample of 70 community-dwelling adults, age ≥70: were to 1) characterize specific vestibular physiologic changes associated with aging; 2) determine the association of vestibular deficits with gait and posture; 3) characterize vestibular function, posture, gait, frailty, and incident falls longitudinally. To address 1) she evaluated semicircular canal and otolith dysfunction, “phasic” (fast-movement) and “tonic” (sustained-movement) stabilization, vestibulo-spinal reflex (VSR; maintains postural stability) and mean vestibulo-autonomic reflex (VAR; maintains autonomic stability). To address 2) she evaluated associations between specific vestibular deficits and quantitative measures of posture and gait, anticipating that specific deficits in otolith, phasic, and VSR function will be most strongly implicated. To address 3) the cohort was assessed at baseline and 1 year, and longitudinal associations of vestibular deficits and posture / gait abnormalities with incident frailty and falls will be assessed. Contributions from OAIC Resources: Dr. Agrawal’s data analyses were mentored by Dr. Bandeen-Roche and materially supported by RC-1. Hypotheses related to biological or physiological etiology of her findings, and the development of etiological studies, were developed in collaboration with RC-2 core leaders. Her recruitment and study conduct were carried out in the BLSA.

Progress Updates: Dr. Agrawal received her K23 career development grant from the NIDCD in March 2014. Dr. Agrawal’s RCDC salary support officially ended at that time with receipt of this K-award. The OAIC continue to provide mentorship and core support, as needed.
Dr. Agrawal has partnered with the Baltimore Longitudinal Study of Aging (PI: Luigi Ferrucci), which has added vestibular testing to the BLSA battery. Dr. Agrawal is continuing with vestibular physiologic testing in the Baltimore Longitudinal study of Aging. New directions for research include:

1) Developing additional tools to measure otolith dysfunction:
   a. She is working with an engineer in the Department of Neuroscience to develop a computerized test of the subjective visual vertical (SVV) to measure utricular function. Based on prior pilot work, she observed a significant association between SVV and oVEMP testing, another measure of utricular function, and SVV may have a higher correlation with function. It is hoped to have this test operational in 3-4 months, and will start collecting data at that point.
   b. She is performing a literature review to understand whether otolith dysfunction presents with specific types of symptoms as opposed to semicircular canal dysfunction. This work will provide a potential outcome measure when evaluating treatment regimens for otolith dysfunction. The timeline for completion of this project is 1 year.

2) Dr. Agrawal and colleagues have started to investigate whether poor vestibular function may be associated with hip fractures. The study design is a case-control study; they are testing older subjects who have sustained a hip fracture and testing their vestibular function, and will be comparing with vestibular function test results in age- and gender-matched controls.

Recent Publications related to OAIC:

- Harun A, Agrawal Y. The Use of Fall Risk Increasing Drugs (FRIDs) in Patients with Dizziness Presenting to a Neurotology Clinic. Otol Neurotol. 2015 Mar 30.

Updates on Grants / Awards / Presentations related to OAIC

- K23 award, NIDCD; March 14, 2014.
- American Otological Society Clinician-Scientist Award, successfully renewed for 2013-2014 academic year
- Co-investigator on NIA-PCORI U01 Multicenter RCT on fall-related injury prevention
II.E. PILOT / EXPLORATORY STUDIES CORE
Neal Fedarko, Ph.D., Core Leader
410-955-2632 ndarko@jhmi.edu

The overall goal of Pilot and Exploratory Studies Core (PESC) is to cultivate and support cutting edge pilot and exploratory studies that will advance the development of effective prevention and/or therapies for frailty and hence facilitate independence in older adults. The PESC provides funding, access to biostatistical, biological, and clinical research core resources, and mentoring and oversight to completion of pilot and exploratory studies. Because of the importance of these studies to the development of new scientific priorities, institutional resources have been added to this core to help maximize productivity and development around frailty science. The PESC Core leaders, in close collaboration with the OAIC Leadership Council, set scientific goals for the next stages of frailty research, and then work to identify investigators whose expertise and career goals would be applicable to furthering knowledge in these target areas. The leadership and resources of these cores are then focused on the development, conduct and eventual translation of high impact pilot studies. The proposed studies must be novel, hypothesis-driven research that establishes potential mechanisms, etiologies, screening approaches or evaluates potential therapies to prevent or ameliorate the syndrome of frailty and related endophenotypes and hence maintain independence. It is expected that PESC supported studies will establish preliminary data that will lead to substantive, long term external funding that can bring this research to completion. Given the recent progress of OAIC supported investigators findings related to mitochondria, inflammation, and angiotensin dysregulation in frailty and aging, special focus was given to these areas for the choices of pilot and exploratory studies articulated in Year 11, the first year of the renewal cycle. The specific aims of this Pilot core are:

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

2. To support development of well-designed and informative PES, by providing intellectual leadership that articulates the scientific vision, goals and priorities of the center, and ensures optimal study design and utilization of the extensive intellectual and research resources offered by other OAIC cores.

3. To provide and conduct longitudinal mentorship and oversight, from conception to translation, for investigators whose pilot proposals are supported by the OAIC. This includes content and career mentorship, assistance in helping the awardee understand how the project fits into the overall theme of frailty-related research, facilitating successful, timely completion of projects, and guiding the awardee in developing further independent funding of PESC supported research.

4. Guide the translation of pilot and exploratory study results developed within this core into a deeper understanding of the basic biology of frailty, or into interventions that will prevent or treat frailty and improve independence in older adults through fostering interdisciplinary communication and collaboration between supported investigators and participants in other OAIC cores.
5. To expand the research environment and network of investigators focused on frailty research by bringing the scientific progress of pilot and other OAIC supported studies to the attention of individuals with the potential to contribute to the study of frailty, by helping awardees present their research at local and national forums, by placing awardees in contact with other individuals at Johns Hopkins and nationally whose interests intersect with the topic they are researching, and by encouraging discussion of frailty and the potential application of the pilot studies being supported in clinical, epidemiological and basic science forums throughout the medical institutions and nationally.

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

- OAIC Pilot investigator, Dr. Honggang Cui and colleagues developed an innovative method for the delivery of therapeutic and diagnostic agents into mitochondria, critical regulators of cellular function and survival that are associated with frailty. Their work was published in the journal, Bioconjugate Chemistry.
- Dr. Walston, OAIC Principal Investigator, and colleagues found that Losartan improved activity levels and parameters related to inflammation and oxidative stress in older mice. Their study was published in Experimental Gerontology.

The PESC studies in Years 11-12 have been both methodologically and substantively innovative. The PES-1 concerns a potential novel treatment for frailty and frailty related conditions. PES-2 and PES-3 utilized state-of-the art technologies (magnetic resonance spectroscopy, nanotechnology), applied them to frailty research, and specifically to core areas of frailty-related biological focus of this OAIC.

**PES 1: A Study of Muscle Strength Maintenance in Older Adults**

**PI: Jessica Lee, PhD; Peter Abadir, MD, Co-Investigator**

**Overview:** JHU OAIC investigators Burks and Cohn found that blocking the angiotensin type 1 receptors (AT1R) with losartan in older mice markedly accelerated injured skeletal muscle healing and decreased vulnerability to disuse atrophy and strength decline. These findings provide a potent rationale for testing the hypothesis that losartan attenuates strength decline and other frailty-related measures in older adults. To test this hypothesis, a randomized, placebo-controlled pilot clinical trial of losartan in prefrail adults over age 70 is proposed that aims to assess whether losartan can maintain muscle strength in older adults. The specific aims of this study are:

1) To assess the safety, tolerability and dosing range of losartan treatment in 24 pre-frail adults age 70 and older using a blinded, placebo-controlled study design.

2) To determine if there are differences in lower extremity peak force measurements (primary outcome) and 6 minute walk time, frailty phenotype, serum markers of inflammation, and TGF-beta activity (secondary outcomes) between treatment and control groups.

Losartan is a medication that is commonly utilized in older adults for the treatment of hypertension, congestive heart failure, and protection of the kidneys in diabetics and is generally well tolerated.

**Significance and Innovation:** Although a component of the angiotensin system and its relationship to skeletal muscle in aging has been studied with ACE inhibitors, no prior studies have been published that look at the effect of ARBs such as losartan on frailty or muscle function. Successful completion of these aims will provide the safety, dosing, and outcome measures data necessary to design the pivotal study needed to determine if longer term treatment with losartan can significantly improve frailty and related skeletal muscle degenerations. This study is within this OAIC’s biological focus.
area and within JHU OAIC’s goals to translate important biological discoveries into clinical frailty research.

**Approach:** Dr. Lee is a Clinical Research Fellow who leads this effort. Dr. Abadir, a Geriatrician and former RCDC investigator with extensive expertise in the angiotensin system, provides medical direction and guidance. Dr. Lee works closely with PESC leadership, RC1, RC2, and especially RC3 to develop, refine, and implement all aspects of this clinical trial. The study is being conducted on each participant over 24 weeks in the Clinical Research Unit (CRU) on the Hopkins Bayview Medical Campus. A total of 24 pre-frail subjects will be recruited from the OAIC frailty registry, newspaper advertisements, and community events such as the Senior Expo, by Dr. Lee and RC-3 staff. After the study is complete and study laboratory values are measured by RC2 laboratory and physical measurements are analyzed, Dr. Lee will work closely with RC1 and RC3 leaders and staff to complete the data analysis and apply results to the development of a pivotal clinical intervention to be funded by sources outside of the OAIC.

**Progress Updates:** As of April 2015, Dr. Lee and staff members in the OAIC Clinical Translation Unit have pre-screened 180 participants by phone, and then screened a total of 42 participants and enrolled 24 of them. To date, a total of 8 participants permanently withdrew or were withdrawn after enrollment. One participant withdrew after a serious adverse event that was not related to the study, another withdrew because he had to go back on his ACE inhibitor for blood pressure control, two withdrew because of difficulty getting consistent transportation to Bayview, and two others withdrew because they did not want to have to take a medication on a daily basis for six months. One participant had ongoing issues with weakness and dizziness and an episode of low blood pressure. After some discussion, we felt that these side effects might be related to the study medication so he was withdrawn. The eighth participant was withdrawn because she failed to comply with study protocol, missed appointments and stopped communicating with the investigators.

As of April 2015, 16 participants have completed the study; 1 participant is currently active in the study and active recruitment is ongoing, with a target of 24 completers. The investigators discontinued the treatment for one of the 16 completed participants after an AE. This participant was then followed and completed the remaining study visits. Also, one of the active participants stopped treatment because of transportation difficulty but has agreed to complete the final study visit. This study was reviewed and approved for continuation by the DSMB of the JHU OAIC in December 2014. The DSMB will review the study again in May/June 2015.

**PES 2: Energy Production in Frailty: Skeletal Muscle ATP Kinetics in Frail, Older Adults**  
**PI: Robert G. Weiss, MD**

**Overview:** Declines in energy production have long been hypothesized to be an underlying etiology of frailty. The PI of this PES utilized a small pilot award to identify significant reductions in high-energy phosphate content and ATP synthesis rates that were identified in at rest muscle of frail compared to non-frail background strain mice. Based on these findings, the investigators hypothesize that older, frail adults have lower skeletal muscle phosphocreatine (PCr) levels and reduced rates of ATP synthesis through creatine kinase (CK) at rest and during plantar flexion exercise as compared to those in non-frail, age-matched subjects. To test this hypothesis, they propose to 1) compare first resting gastrocnemius PCr/Pi and the rate of ATP synthesis through CK and then after exercise using $^{31}$P MRS between frail and 20 age- and gender-matched non-frail older adults, and 2) determine the relationship, if any, between serum based inflammatory mediators, and energy related measurements.

**Significance and Innovation:** This is a pilot study designed to provide a proof of principle that reduced high-energy phosphate metabolism occurs in frail human skeletal muscle both at rest and during exercise. It will provide new insights into the magnitude of energetic abnormalities and also into the variability among subjects that will be critical for guiding the design of future studies of interventions designed to improve energy metabolism and/or reduce inflammation in frail subjects. The findings of
this study may also provide clues into any relationships between energetic abnormalities and the extent of chronic, systemic inflammatory pathway and of renin-angiotensin pathway activation, key focus areas of this OAIC. The noninvasive nature of the proposed $^{31}$P MRS approach to repeatedly probe muscle energy metabolism at rest and during lower extremity exercise promises novel insights into metabolic contributors to frailty, and, possibly more important, the first physiologic test to metabolically identify the presence and quantify the extent of skeletal muscle frailty. These energetic indices could become new endpoints for determining the efficacy of targeted interventions such as mild-anti-inflammatory agents or ARBs such as losartan.

**Approach:** Pilot study PI Dr. Weiss developed state-of-the-art noninvasive magnetic resonance spectroscopy (MRS) methods for quantifying high-energy phosphate levels and CK ATP synthesis rates in cardiac and skeletal muscle from mice to humans, and a non-invasive means to make the same energetic measurements in human skeletal muscle both at rest and during plantar flexion exercise. Because of his expertise, he was solicited to study energy metabolism in frail compared to wild type mice, and now in human subjects. Mean frailty-related differences will be analyzed by t-testing (two-sided, alpha=0.05) and analysis of covariance. The study design yields power of 0.80 to detect a difference of 1.0 in the $\text{PCr}/\text{Pi}$ parameter and 1.3 in the CK flux parameter based on estimated population SD from Dr. Weiss' pilot data. Subjects are being recruited from the frailty registry supported by RC-3. RC-2 assists with sample collection, measurement, and translation into future clinical studies. RC-1 will support database and data analysis.

**Progress Updates:** Enrollment and assessment is underway with support from OAIC RC-3 staff. As of April 2015, Dr. Weiss and staff have enrolled and performed the plantar flexion $^{31}$P MRS/MRI stress test in approximately 18 older subjects. We continue to enroll elderly subjects from the OAIC database who are either 1) non-frail or 2) frail by JHU frailty phenotype criteria. To date, 12 non-frail and 6 frail have been studied. Subjects undergo the $^{31}$P MRS/MRI stress test, a six-minute walk test (an objective measure of functional status with an activity of daily living), and a bicycle cardio-pulmonary stress test with oxygen consumption ($\text{MVO}_2$) measures (to assess cardiovascular reserve). The plantar flexion $^{31}$P MRS/MRI stress test was refined to now include MRI measures of 1) lower extremity muscle mass, 2) fat content and lean muscle mass from Dixon MR images, and 3) measures of popliteal blood flow, another factor affecting lower extremity muscle metabolism and performance. There have been no adverse events or safety concerns to date with these studies. Representative $^{31}$P MR spectra from the lower extremity of an older individual obtained at rest (left) and during plantar flexion exercise to fatigue (right) are shown in the figure below and manifest marked changes in muscle high-energy phosphates with exercise that include a dramatic decline in creatine phosphate ("PCr" with blue dotted arrow denoting exercise-induced decline) and an increase in inorganic phosphate ("Pi" with green dashed line denoting increase from rest to exercise).
PES 3: The Specific Delivery of Pharmaceuticals into Mitochondria

PI: Honggang Cui, PhD; Other Key Personnel Pengcheng Zhang, PhD; Ran Lin

Overview: Age-related dysfunction in mitochondria is associated with the development of frailty, disability and chronic disease states. JHU OAIC supported investigators have recently found declines in ATP production and mitophagy in the frail mouse, a functional angiotensin system in the mitochondria that is down-regulated with age and up-regulated with losartan, and mitochondrial DNA variation that associates with frailty. Dr. Honggang Cui was recruited to develop this exploratory study that aims to develop a delivery system that specifically targets mitochondria with pharmaceutical agents. Dr. Cui is a Johns Hopkins School of Engineering faculty with considerable expertise in fabrication of peptide-based supramolecular nanostructures for drug development. The hypothesis states that pharmaceutically active substances linked to a mitochondrial targeting sequence (MTS) used for sorting proteins into mitochondria can be delivered into mitochondria, and that the pharmaceutically active substance can then be cleaved and function as an active substance. The following specific aims are proposed to test this hypothesis: 1) To determine an effective protein sorting sequence at delivering pharmaceutical agents into mitochondria; 2) To determine if those sequences that effectively deliver pharmaceutical agents can be separated from targeting sequences within mitochondrial and become active pharmaceutical agents.

Significance and Innovation: Although clearly an exploratory study, if the approach articulated below allows for the identification of an effective mitochondrial targeting system, this technology could be utilized to develop drugs specifically targeting mitochondrial dysfunction. Directly targeting mitochondria with pharmacological agents for frailty and aging related conditions is novel and represents a new approach to drug development. Given the emerging recognition of the importance of mitochondria in aging-related decline, such pharmaceutical targeting has great potential to profoundly modify drug development approaches. The application of the novel nano-technologies to frailty research is highly innovative as well.
**Approach:** Preliminary studies have already identified a mitochondrial targeting sequence (MTS) (pre-sequence of rat liver aldehyde dehydrogenase) (MLRAALSTARRGPRLSRLL) that can specifically deliver Losartan to mitochondria. Four additional pre-sequences of mitochondrial matrix proteins (F1-ATPase β, COX IV, Rhodanese and Thiolase) were chosen for further study based on their known specificity for mitochondrion delivery. Peptides will be synthesized on an automatic peptide synthesizer and conjugated to pharmaceutical agents that are of mitochondrial delivery relevance, such as glutathione, co-enzyme Q, alpha-tocopherol, and losartan. 5-carboxyfluorescein (5-FAM) will be used to label the MTS-drug conjugates for imaging purpose. MTS Drug conjugates will be compared by calculating the efficiency of translocation into the mitochondria. Quantification of the targeting efficiency will be made using Western blot. The MTS sequence with highest efficacy will be selected for future studies. To evaluate if the delivered mitochondrial drugs effectively separated from the MTS sequence and become active pharmaceutical drugs, functional mitochondrial assays including aerobic respiration and glycolysis measurement using the Biorad XF Extracellular Flux Analyzers in the lab of RC-2 internal consultant O’Rourke. Different doses of the targeted MTS drug conjugate as well as non-conjugated drug control will be compared.

**Progress Updates:** Dr. Cui and colleagues have been trying to introduce negatively charged polymer hyaluronic acid (HA), which was biocompatible and biodegradable, into mitochondrial targeting system to trigger co-assembly with MTS-Los to form nanoparticles with improved cellular uptake and thus better mitochondria targeting. We have shown that MTS-Los demonstrated exciting results showing obvious colocalization with mitochondria. In parallel with our effort to creating a MTS-Los nano-formulations, we have 1) expanded our MTS peptide library by synthesizing three more Los conjugates with MTS peptide of different origin, and 2) utilizing a dual conjugate strategy to improve cellular uptake by incorporating an additional cell penetrating peptide into the MTX-Los conjugates. Further progress in two areas is described as follows:

1. From previous study, MTS (MLRAALSTARRGPRLSRLL) derived from rat liver aldehyde dehydrogenase has demonstrated obvious colocalization with mitochondria according to our confocal imaging studies. In order to confirm and validate the specific mitochondria targeting ability of MTS, three new MTSs derived from mitochondrial matrix proteins were synthesized. MTS-1 (MVHQVLYRALVSTKWLAESIRSG), MTS-2 (MALLRGVFIVAAKRTPFGAYG) and MTS-3 (MVLPRLYTATSRAAFKAAQ) are pre-sequences in Rhodanese, Thiolase and F1-ATPase β-subunit, respectively. 5-FAM was used as fluorescent tracking agent and conjugated onto lysine side chain on peptide C-terminus.

2. Our previous study has demonstrated the significance of the MTS secondary structures on cell penetrating behavior. As a result, circular dichroism was used to investigate secondary structures of MTS-1 and MTS-2. Both ligands have negative absorption as 208 nm and 222 nm in 20 mM sodium phosphate buffer (pH 7.4, with 20 mM SDS) at 37°C, revealing a typical alpha-helices structure as reported MTS. In order to investigate specific mitochondria targeting ability of MTS-1 and MTS-2, 30 μM digitonin was used to permeabilize cell membrane. MTS-1, MTS-2 and MTS were tested under 5 μM on human glioblastoma cell line U87 and cells were imaged after 2 h incubation. From confocal images, both new MTS show intense fluorescence on cell membrane without digitonin, indicating their accumulation on membrane due to alpha-helices structures. After treatment of 30 μM digitonin, all targeting ligands show improved cellular entry capability and partial colocalization of 5-FAM fluorescence with Mitotracker Red, revealing their specific mitochondria capability against U87 cell line. These preliminary studies showed very encouraging results, and detailed evaluation is currently ongoing.

**Short term goals and next steps include:**

a. In further study, we aimed at mitochondria translocation study with TIM/TOM complex inhibitor. Isolated mitochondria can be used to investigate MTS import mechanism with
inhibitor, without interference of cell membrane translocation process. Same inhibitor MitoBlock-6 can be used on isolated mitochondria from MCF-7 cells.

b. Timeline study of MTS intracellular uptake can be studied to investigate transmembrane mechanism. Since we studied series cellular uptake of 1, 2, and 4 h incubation with conjugates, it is interesting to study more time points to get a comprehensive conclusion of transmembrane mechanism of MTS sequence.

Publications and other related progress:


Previously funded PESC Studies:

Pilot Study: “Impact of vitamin D supplementation on functional outcomes in pre-frail older adults with vitamin D.”
**PI:** Sevil Yasar, MD, PhD

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

Pilot Study: “Effects of Inflammation, Hormonal Alteration and mTOR Signaling in Modulating Age-related Declines in Muscle Strength”
**PI:** Qian-Li Xue, PhD

**Specific Aims:** Aging is associated with the progressive loss of skeletal muscle mass and strength referred to as sarcopenia, leading to significant adverse functional and clinical consequences in older adults. Sarcopenia affects approximately 45% of persons aged 65 and older, accounting for 1.8% ($8.5 billion) of total health care expenditures in the US in 2000. Given rapid growth in the nation’s older population, research to better understand the pathophysiology of age-related muscle weakness is of substantial importance.

Building on earlier work on cross-sectional associations of inflammation and endocrine dysregulation with muscle strength and frailty in older adults, and the new evidence of anti-inflammatory and life-extending effects of the Mammalian Target of Rapamycin (mTOR) inhibitor rapamycin in mice, Dr. Xue and colleagues hypothesize that rapamycin may ameliorate decline in muscle strength by suppression of inflammation. They have evaluated this hypothesis by conducting a pilot trial of rapamycin in rats selectively bred for low aerobic running capacity [low capacity runners (LCR)] or high aerobic running capacity [high capacity runners (HCR)].
Results from the pilot trial confirmed the life-extending effects of rapamycin in both LCR and HCR rats. In addition, they found that rapamycin-treated LCR rats experienced significant weight loss, improved grip strength, as well as down-regulation of mTOR activity in terms of less phosphorylation of its downstream effectors p70S6K1 and 4E-BP1 in the muscle. However, the effects of rapamycin on maximum running capacity and inflammatory biomarker and anabolic hormones were inconclusive due to a combination of factors including measurement imperfection and questionable timing of sample collection. Toward the end of the experiment, Dr. Xue also noticed that some of the rapamycin-treated HCR and LCR rats began to exhibit diabetes-like symptoms including increased food intake, weight loss and frequent urination. It has been postulated that the “diabetogenic” effects of chronic rapamycin administration is due to an impaired insulin action on glucose metabolism in skeletal muscles; and the symptoms may be fully reversible with metformin treatment.

To confirm the findings from the pilot, Dr. Xue and colleagues are conducting a new pilot to collect additional data necessary for future grant applications. The trial consists of 24 female LCR rats. LCR rats are selected because they develop an age-related phenotype that closely resembles the frailty syndrome including weakened muscle strength. They also exhibit compromised mitochondrial function and β-adrenergic activation and lipolysis in skeletal muscle, as well as increased levels of inflammation and oxidative stress compared to HCR (unpublished data). The investigators have added a rapamycin+metformin arm to test the hypothesis that metformin may counteract the “diabetogenic” effects of rapamycin. In addition to the measures collected in the 1st pilot, Dr. Xue and colleagues are measuring serum levels of inflammatory biomarkers and anabolic hormones and fasting glucose repeatedly over time, and have added muscle biopsies to measure histologic parameters of Soleus and EDL muscles including fiber type count and protein content.

**Progress Updates:** In October 2012, twenty-four 16-month old female LCR rats were randomized into three groups: control group (n=8), rapamycin only (n=8), and rapamycin+metformin (n=8). Grip strength was measured every month; body weight is recorded every 2 weeks; tr and blood are collected every 2 months. The investigators also monitored fasting (and added non-fasting recently) blood glucose levels every month. They collected muscle tissues for mTOR assay and histological analysis. Initial results of the current study were presented at the Biology of Healthy Aging meeting on April 23, 2013. The experiment was completed in summer 2013, along with blood and assays and data analysis later in 2013. Muscle histology slides reading completed on March 28, 2014. Study findings to date include: Rapa treatment extended lifespan in both male and female LCR rats; helped maintain grip strength; and slowed decline in maximum running capacity in female LCR rats; Rapa treatment led to an increase in Type II muscle fiber size, but a reduction in Type I muscle fiber size; Rapa treatment caused significant weight loss in male LCR rats, but not in female LCR rats. Studies are underway to explore the mechanisms by which rapamycin improved muscle function in the frail rat model including mitochondrial function and autophagy. Dr. Xue presented this work at the April 2014 Annual Pepper Centers Meeting in Bethesda and won the Poster Award in the Basic Science category.

The experiment and sample collection are completed. The mTOR assays were rerun in Sept. 2014 to confirm the previous findings. The Johns Hopkins Biology of Health Aging group (Drs. Leng, Walston, Abadir, Burks, Yang) met in December 2014 to go over the most recent mTOR assay results and concluded that Dr. Xue should write a short report first focusing exclusively on phenotype data only (i.e., grip strength, max running capacity, body weight using data from both male and female LCR rats). The current plan to have this short report written and submitted in the coming months. Then a separate paper will be written to report biological data including mTOR assay, histology of different muscle groups and mitochondrial function. Dr. Burks will help Dr. Xue with the histological data collection and interpretation, which is set to be completed in spring 2015.

**Pilot Study: “Telomere length and Clinical Outcomes in the Women’s Health Aging Study”**
**PI: Mary Armanios**

Hypotheses and Specific Aims: Telomere length is a known determinant of replicative senescence. Dr. Armanios proposes to measure telomeres in the well-characterized Women Health and Aging Study (WHAS) populations to define whether and how telomere length may be used to quantify risk for discrete, clinically useful endpoints.

The goals of this study are to examine the role of telomere length in association with disease-related measures (Aims 1 and 2), as well as functional outcomes (Aim 3). They propose to use a robust, reproducible telomere length assay for the purpose of this population-based study. This assay relies on a robust method which measures telomere length in lymphocytes using flow cytometry and fluorescence in situ hybridization. The goal is to determine whether telomere length measurement can be used clinically for disease and functional risk assessment in geriatric populations. Dr. Armanios and colleagues propose to study the entire WHAS cohort, both I and II, since telomere length is a quantifiable determinant of biological aging, and its use has already been shown to alter clinical decisions in certain settings. By quantifying the association between telomere length and clinical indices using a robust method and in a relevant population of women, the long-term goal is to determine whether telomere length can be added to current risk assessment tools in geriatric practice. Dr. Armanios will test the hypothesis that telomere length, as a single variable, will be associated with co-morbidities of clinical significance through the following Aims:

1. Telomere length is a predictor of lung function and lung disease in WHAS populations
   **Rationale.** Dr. Armanios’ group has shown that lung disease is the most common manifestation of short telomere-associated disorders. Lung function decline is one of the most acute physiologic changes that occur with age, but the biological basis is not understood.
   a. To test whether short telomeres correlate with lower Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), and FEV1/FVC ratios
   b. To determine the association between telomere length and longitudinal decline of lung function in WHAS II
   c. To determine the association of short telomeres with adjudicated diagnoses of lung disease in WHAS

2. Are short telomeres associated with impaired glucose homeostasis?
   **Rationale.** Dr. Armanios’ group has shown that short telomeres cause glucose intolerance in animal models. Here they will examine the association of short telomere length with measures of impaired glucose homeostasis.
   a. To examine whether short telomere length is associated with elevated HgbA1C levels.
   b. To examine whether short telomere length is associated with an adjudicated diagnosis of diabetes.

3. Short telomere length as a predictor of frailty and disability in older adults
   **Rationale.** Physical function is a major determinant of quality of life in older adults. WHAS has some of the best data on relevant populations on functional outcomes and here Dr. Armanios will test whether telomere length correlates with functional disability measures.
   a. Cross-sectionally and prospectively, relationships of telomere length with the following prevalent and incident functional outcomes: i., frailty; ii, activities of daily living (ADL) disability; iii, instrumental activities of daily living (IADL) disability; iv, grip strength decline over time; v, and walking speed decline over time.

**Progress Updates:** This study aims to examine the role of telomere length as a biomarker of clinical outcomes. Dr. Armanios and colleagues are currently in the process of analyzing the telomere length data. She presented early analyses at the April 2014 Pepper Scholars Meeting. There has been no trial of this size previously using the laborious assay used in this project, and Dr. Armanios expects that she will finish generating the data soon. She has completed the telomere length measurement in 462 of 1,100 available samples (42%), with high data quality. She is currently completing an interim analysis.
with support from the OAIC Biostatistics Core.

II. LEADERSHIP AND ADMINISTRATIVE CORE

Jeremy Walston, M.D., Core Leader
410-550-1003  410-550-2513 FAX  jwalston@jhmi.edu

Karen Bandeen-Roche, Ph.D., Co-Core Leader
410-955-3067  410-955-0958 FAX  kbandee1@jhu.edu

Brian Buta, MHS, Administrator
410-502-3412  410-614-9625 FAX  bbuta@jhmi.edu

The Leadership/Administrative Core spearheads the vision for the science of frailty and its translation in this OAIC. It leads in identifying the next generation of research on frailty that should be created, supports research planning, recruitment of investigators, and the setting of goals and benchmarks. It also administrates the OAIC, its Cores, its advisory and safety boards, and creates visibility for the accomplishments of the OAIC. Led by the Co-Principal Investigators of this OAIC, in collaboration with the leaders of all other OAIC Cores and supported by administrative staff, the roles and responsibilities of this LAC include the provision of essential leadership in planning, integrating, sustaining and monitoring OAIC operations, the organization and evaluation of all elements of this OAIC, and reporting. Its goals are to ensure the conduct of these OAIC functions within a broader goal of helping recruit, initiate and nurture creation of a critical mass of investigators dedicated to advancing discoveries essential to prevention and treatment of frailty in older adults, and supporting the creation of innovative, high impact research to this end. The overall goals of workforce development and support of research are to translate the results of OAIC-supported work into new treatments to enhance independence in older Americans, and creation of a new generation of research leaders in the field.

To these ends, the specific aims of the Leadership / Administrative Core (LAC) are provided as follows:

1) Provide the interdisciplinary intellectual leadership needed to stimulate and sustain the development of innovative frailty focused research, facilitate translation between basic and clinical research on frailty, develop innovative intervention and prevention strategies, and ensure effective, high impact utilization of each of the cores of the OAIC.

2) Identify and attract the next generation of frailty-focused research leaders at Johns Hopkins University (JHU) and facilitate training, career development and access to resources to promote their emergence as independent, interdisciplinary investigators in this field. To this end, this LAC is responsible for visibility for research on frailty at our institution and implementing the recruitment activities, based on leadership decisions about target areas for scientific and methodologic development.
3) Lead, administer, and oversee core functions to assure productivity, cost effectiveness, integration, and quality of all aspects of this OAIC program, and to well steward OAIC resources.

4) Prepare reports for non-competing renewal applications, annually, and administrative documents as needed, including data safety monitoring documentation. Organize and conduct scientific sessions to propel the frailty-focused science and career development of participants in OAIC retreats, research in progress meetings, and research planning meetings.

5) Maximize JHU OAIC scholarly visibility locally and nationally via local programming and participation in the annual OAIC scientific meeting and the annual meetings of the aging-related societies (e.g. Gerontological Society of America) and other relevant societies.

6) Organize independent panels for review of:
   a) Resource Core Developmental Projects; Pilot/Exploratory Studies; and for the selection of specific junior faculty to receive salary support from the Research Career Development Core.
   b) Progress towards OAIC goals, conducted annually by an External Advisory Board external to JHU.

To address these aims, please see the following results and outcomes:

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

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

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

The JHU OAIC held a center-wide **Retreat on Strategic Planning and Roadmap Development for Frailty Research** in Baltimore on February 25, 2015. Thirty leaders and investigators from the JHU OAIC participated in working groups and presentations on key agenda setting topics for the field of frailty research and clinical translation. This retreat was organized in direct response to feedback received from the member of our External Advisory Board.

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

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

The LAC has established an **External Advisory Board** for this grant cycle, and as approved by our NIA Program Official, the members of the current EAB are: Dr. Joan Bailey-Wilson; Dr. Gerald Beck; Dr. Howard Bergman; Dr. Harvey Cohen; and Dr. Luigi Ferrucci. The EAB convened on August 25, 2014 to review the first year of the renewal and provide big-picture guidance going forward. The thoughtful and motivating feedback and discussion from this meeting helped to propel our scientific efforts during the remainder of the reporting period, and led to a retreat held in February 2015 focused on strategic planning for frailty research (described below). The next EAB meeting is tentatively planned for late summer / early fall 2015.

The LAC has established its **Data and Safety Monitory Board** to provide independent safety review for all OAIC interventional human subjects studies. All five members of the DSMB are external to the OAIC, with two members from the University of Maryland, and all have been approved by the NIA Program Officer. The DSMB meets semi-annually, or more frequently as needed, to review progress, findings and all potential safety issues related to OAIC human subjects research projects. The DSMB convened in February 2014 to carefully review and discuss its operating charter. The group convened in May and December 2014 to review the current intervention study on Losartan and frailty among older adults. Reports from each meeting have been submitted to the NIA Program Officer. The next meeting will take place in May/June 2015.

In partnership with the Division of Geriatric Medicine and the Center on Aging and Health, the Leadership Council sponsors a monthly **Scientific Seminars Series** of invited scientific presentations, including presentations by Dr. Andrew Goldberg, PI of the University of Maryland OAIC in December 2014.
The OAIC continues to interact with the leadership of the University of Maryland OAIC. This has allowed additional regional visibility. During the past couple years, our leadership and that of the University of Maryland OAIC have continued to work together on initiatives by which we might leverage our complementary strengths and foci to enrich the research environment for scholars associated with our OAICs, particularly our junior colleagues. These efforts have led to individual networking connections, joint participation in the annual JHU Research on Aging Showcase poster competition for graduate students, postdoctoral fellows and junior faculty, and four **Jointly-Sponsored Symposia** presented collaboratively by our centers. Most recently in November 2014, our faculty participated in a joint speed-networking event for the aging trainees from UMB, Johns Hopkins, and NIA.

Related to these efforts, the OAIC held **three high profile symposia** during this reporting period. Dr. Walston led the symposium, “Towards the Integration of Frailty into Clinical Practice,” at the 2014 Annual Meeting of The American Geriatrics Society in Orlando, FL on May 15, 2014. The JHU OAIC led a symposium titled, “Should Cognition be Included in the Assessment of Frailty?” at the 2014 Annual Meeting of the Gerontological Society of American in Washington, D.C. on November 8, 2014. Investigators from the OAIC, Drs. Qian-Li Xue (RC1 Core Director), Karen Bandeen-Roche (OAIC co-PI and RC1 Leader) and Alden Gross (RCDC junior faculty) led the symposium, “Intersection and distinction between physical frailty and cognitive impairments among older adults.” at the 2015 International Conference on Frailty and Sarcopenia Research in Boston in April 2015. Dr. Walston presented a keynote address on “Biological Aspects of Aging and Frailty” at this conference.

The JHU OAIC held a center-wide **Retreat on Strategic Planning and Roadmap Development for Frailty Research** in Baltimore on February 25, 2015. Thirty leaders and investigators from the JHU OAIC participated in working groups and presentations on key agenda setting topics for the field of frailty. This retreat was organized in direct response to feedback received from the member of our External Advisory Board. Planned products presently under development from this retreat are a ‘white paper’ on the next generation of priority areas and a draft roadmap for frailty research at our institution and for the field over the next several years is in development, as well as a series of timey review papers. The four major areas slated for development include translation of frailty into clinical practices of generalists and subspecialists, multisystem dysregulation research, basic biological research, and frailty measurement evolution.

We organized strong participation from our OAIC at the **National Pepper Centers Annual Meeting** held in April 2015. Our PI, Dr. Jeremy Walston, co-PI, Dr. Karen Bandeen-Roche, Biostatistics Core Director, Dr. Qian-Li Xue, and RCDC Leader, Dr. Gary Gerstenblith attended, along with supported investigators Drs. Yuri Agrawal (former RCDC), Charles Brown (RCDC), Alden Gross (RCDC), Rani Hasan (RCDC), and Reyhan Westbrook (Diversity Supplement scholar, RC2 Development project). Drs. Walston and Bandeen-Roche participated as Senior Faculty personnel, Drs. Brown, Gross, and Westbrook presented at the poster session, and Dr. Bandeen-Roche served as a judge at the poster session.

We organized strong participation from our OAIC at the **National Pepper Centers Annual Meeting** held in April 2015. Our PI, Dr. Jeremy Walston, co-PI, Dr. Karen Bandeen-Roche, Biostatistics Core Director, Dr. Qian-Li Xue, and RCDC Leader, Dr. Gary Gerstenblith attended, along with supported investigators Drs. Yuri Agrawal (former RCDC), Charles Brown (RCDC), Alden Gross (RCDC), Rani Hasan (RCDC), and Reyhan Westbrook (Diversity Supplement scholar, RC2 Development project). Drs. Walston and Bandeen-Roche participated as Senior Faculty personnel, Drs. Brown, Gross, and Westbrook presented at the poster session, and Dr. Bandeen-Roche served as a judge at the poster session.

These efforts have been highly successful in recent years with improved integration with other disciplines around important questions in frailty research. We have helped to establish the careers of the RCDC supported faculty through the **successful support of K01/K23 funding** to Drs. Abadir, Wang, Lin, Kalyani, McAdams-Demarco, and Agrawal in the past several years. Drs. Abadir and Leng, both former RCDC supported scholars, received their **first R01 awards** with OAIC support in the past year. We continue to support many other present and former scholars for R award development. We have effectively utilized our Pepper Scholars Program, a monthly research in
progress series, and the Frailty Working Group (both described above) as mechanisms to help stimulate and develop a ‘farm team’ of investigators who are committed to developing research in this area, and ensuring that they are able to generate the data necessary to move their science and careers forward with assistance from the OAIC. For example, Damani Piggott, MD, Assistant Professor of Medicine, received a K23 award, “Determinants and Consequences of Frailty Among Aging HIV-Infected Persons,” from NIAID. The development of Dr. Piggott’s K award was supported by the OAIC through the provision of advice to the award application’s writing by our LAC and Biostatistics Core. Dr. Walston is a member of Dr. Piggott’s mentorship team, and Dr. Bandeen-Roche is a member of his Mentorship Advisory Committee. Dr. Piggott plays an active role in the Frailty Working Group at Johns Hopkins, and recently presented at a Pepper Scholars Program research in progress meeting in April 2015.

Dr. Xue, Biostatistics Core Director, has received two R03 grants relevant to the mission of our OAIC. His recent NIA R03, “Frailty Assessment: Matching Simplification Efforts to Clinical Aims” was funded in August 2014. He previously received an NIA R03 focusing on “Clinical Significance of Short-Term Change and Variability of Grip Strength.”

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

Dr. Westbrook received his Ph.D. in Molecular Biology, Microbiology and Biochemistry, August 2012 from the Southern Illinois University (SIU). He has an extensive background in metabolic research using the aging mouse as his model system. He now applies his skill set towards questions related to frailty and furthers his molecular training with investigators at John Hopkins University in the Older American Independence Center (OAIC). The scientific focus of this OAIC is the Geriatric syndrome of frailty, its identifiers and causes, and the translation of this new knowledge into development and testing of interventions to prevent or treat frailty. A major goal of this OAIC is to identify qualified junior investigators and trainees from the Johns Hopkins Medical Institutions and provide them with training and research resources and infrastructure that enable the development and performance of the highest quality aging and frailty-related research. The OAIC resources most relevant to Dr. Westbrook are RC1 and RC2. Dr. Westbrook take part in the ongoing statistical training opportunities and receives direct faculty and staff oversight and mentorship as he develops and analyses data gathered in his projects. Regular meetings between Dr. Westbrook and RC1 staff and faculty will help to facilitate the highest quality study designs, the augmentation of data collection and management, access to statistical computing resources developed within this OAIC. The Biological Mechanism Core (RC-2) offers a broad array of molecular biological expertise and services highly relevant to Dr. Westbrook’s projects, including frail mouse phenotype development and modeling, access to outstanding metabolomics proteomic, genomic methodology, mitochondrial measurement expertise, and direct access to highly expert and committed faculty members in the Institute of Genetic Medicine with expertise in the generation and analysis of complex biological data sets as proposed by Dr. Westbrook. He also benefits from the close integration of the cores and from the milieu of trainees in both biostatistics and basic scientists, and from the junior faculty trainees who meet on a monthly basis to review progress and present new data. He will gain important translational insights in this process as well, and learn how to move his own results towards meaningful interventions. Importantly, this OAIC is also dedicated to the development of a diverse scientific work force, and
Dr. Westbrook is currently embedded in a group of senior and junior investigators and a mentorial panel with expertise in aging biology, mouse model development, frailty and clinical translational research and complex data analysis. He builds on his expertise in molecular biology and metabolism related to aging by applying his skills to the study of frailty and to biological discovery in the frail mouse within our OAIC. Through research and training activities, Dr. Westbrook is currently learning new technologies and techniques, and receiving scientific and research career mentorship from a highly experienced mentorial panel committed to the development of the next generation of investigators focused on aging and frailty research.

**Research Plan Overview:** Dr. Westbrook focuses on two major projects during his post-doctoral fellowship at Johns Hopkins as described below. The first project builds on his considerable metabolic expertise and aims to further develop his skill set in this area and apply it to the frail mouse model developed in our OAIC. For the second project, Dr. Westbrook helps to lead the RC-2 development project on the integration of ‘omic’ analyses in the frail mouse. This enables Dr. Westbrook to learn important new skills in molecular biology and in complex analytical modeling as described below.

**Project 1:** The frail, IL10<sup>Tm/Tm</sup> mice have been utilized as a model of frailty because of their propensity to develop skeletal muscle weakness and chronic activation in NFkB pathways. Previous findings in humans, including some from this OAIC, indicate that aging and frailty are associated with impaired insulin sensitivity and glucose homeostasis, decreased metabolic rate and locomotor activity, as well as altered respiratory quotient (RQ) and body composition. Current research indicates that aging, sarcopenia and frailty are associated with increased inflammation, cytokines and oxidative stress. However, to date, little is known about the body composition and metabolism of this frail mouse model. Further, although caloric restriction (CR) and exercise have been shown to have beneficial effects on sarcopenia and delay aging, it is not known whether these interventions, or an exercise mimetic drug such as the AMPK agonist 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR), will have any effect on the progression of frailty in the IL10<sup>Tm/Tm</sup> mouse. Dr. Westbrook hypothesizes that older, frail mice have substantially altered metabolism including impaired insulin sensitivity and glucose handling, increased fat mass, increased oxidative stress levels, and altered adipokine profiles. Further, he hypothesizes that CR and exercise regimens, as well as exercise mimetics, when started at an early age, will prevent or delay the onset of the adverse metabolic characteristics associated with aging and frailty in the IL10<sup>Tm/Tm</sup> and normal mice. He proposes to test these hypotheses using the following specific aims and methodology:

**Specific Aim 1:** To determine if 20 month old IL10<sup>Tm/Tm</sup> frail mice (n=10 per group) have altered insulin sensitivity, glucose homeostasis, oxygen consumption (VO<sub>2</sub>), respiratory quotient (RQ), spontaneous locomotor activity, and body composition compared to age and gender matched C57Bl/6 control strain.

**Specific Aim 2:** To determine if the exercise mimetic AICAR administered beginning at 10 months of age, has effects on the insulin sensitivity, glucose homeostasis, oxygen consumption (VO<sub>2</sub>), respiratory quotient (RQ), spontaneous locomotor activity, and body composition of 20 month old IL10<sup>Tm/Tm</sup> as well as age and gender matched C57Bl/6 control strain.

**Specific Aim 3:** To characterize adipokine profile and oxidative stress differences between older IL10<sup>Tm/Tm</sup> mice and age and gender matched C57Bl/6 control strain mice which have received either no treatment, exercise or AICAR.
**Project 2:** In order to develop a new skill set in molecular measurement and complex analyses, Dr. Westbrook will play a leading role in the proposed RC-2 development project entitled: “Integrative omics analyses of the IL10\(^{Tm/Tm}\) frail mouse” The IL10\(^{Tm/Tm}\) mouse, like frail humans, develops age-related skeletal muscle weakness, endocrine abnormalities, inflammatory pathway activation, mitochondrial abnormalities, and early mortality. These findings support the further use of this mouse to dissect molecular pathways that may impact frailty. Rapid advances in molecular technology now allow for the comprehensive examination of molecular phenotypes using several powerful ‘omic’ approaches. Dr. Westbrook will work with RC2 leaders to implement these phenotypic measurements and work with RC1 and RC2 faculty members to develop analytical methodology.

Specific Aim 1: To comprehensively evaluate DNA methylation, gene expression, and proteomics in the skeletal muscle and metabolomics and proteomics in the serum of frail versus non-frail IL10 mice.

**Progress Updates:**

As of April 2015, the Metabolic Characterization of the Interleukin-10\(^{tm1Cgn}\) Mouse project consists of three major components: the metabolic characterization, the metabolomics characterization, and the anti-frailty intervention component. The experiments proposed in metabolic component are completed for the “old-age” cohort, and the “middle-age” cohort, and the “young” cohort. Our goal with the metabolomic characterization is to determine if frail IL-10 knockout mice have altered metabolism by comparing insulin sensitivity, glucose homeostasis, oxygen consumption (VO2), respiratory quotient (RQ), spontaneous locomotor activity, body composition and insulin sensitivity to that of normal mice. Thus far, we have measured body composition, VO2, RQ, locomotor activity, blood cell composition, insulin tolerance and glucose tolerance. We have also measured plasma adiponectin, leptin and IL-6. We have seen interesting metabolic differences in the frail mouse at old age including: decreased VO2, altered body composition with notably decreased fat mass, and altered blood cell composition. Interestingly, many of these changes are age dependent and are not present in young and middle age IL-10 KO mice, most notably the change in VO2. Unexpectedly, we have seen no difference in insulin sensitivity or glucose metabolism at either age. Interestingly, fat mass measured both by NMR based body composition scanning and by dissection of fat pads was decreased in old IL 10 KO mice. The adipokines adiponectin and leptin were also decreased with age in IL-10 KO mice while IL-6 was higher in this mutant than control mice. We have discovered that these mice have striking similarities to frail individuals that have very low BMI yet have poor clinical outcomes associated with heart failure and cancer. This condition was coined the “obesity paradox” which highlights the fact that low BMI is usually associated with improved health, yet in some individuals low BMI associated with poor outcomes.

Mice from all three age groups which will be used for the metabolomic component of the project have been sacrificed and tissues harvested. We performed the plasma preparation for the HPLC & mass spectrometry based metabolomics assessment with the help of the Center for Resources in Integrative Biology (CRIB) core at Johns Hopkins. Our metabolomics profiling yielded >3,400 features with 162 differentially expressed features in the old age group alone. Interestingly, many of the identified metabolites were mapped to pathways including Transmembrane transport, TCA cycle nutrient utilization & Nucleotide metabolism according to Reactome & Wikipathway databases. We are currently working on identifying more metabolites from our data and searching for the biological meaning of the identifications.

The experiments proposed in Specific Aim 1 are complete. We have observed decreased metabolic rate, decreased adipokine production decreased and altered body composition of old IL 10 KO mice.
compared to C57Bl/6 mice. Interestingly we've observed normal insulin & glucose handling in the mutant. We are currently performing the experiments proposed in Specific Aim 2 & 3 and have raised the mice to the appropriate ages and we plan to begin AICAR administration in the next few weeks. Further we are examining the cellular structure & composition of fat pads from old IL-10 KO and control mice.

Progress on Paper Development / Publications; Progress on Grant Development / Submissions; Progress on Abstracts / Presentations

Current list of presentations includes:
- 1st prize in the Post-Doctoral Fellow & Junior Faculty category at the 7th Annual Research on Aging Showcase at the Johns Hopkins Bloomberg School of Public Health.
- Poster Presenter at the 7th Annual Research on Aging Showcase at the Johns Hopkins Bloomberg School of Public Health (May 2014) The Metabolic Characterization of Interleukin-10tm1Cgn Mouse Reyhan Westbrook, Rafa de Cabo, Jackie M. Langdon, Cindy N. Roy, Jeremy Walston.
- Presentation at the Pepper Scholars Program Research in Progress: Reyhan Westbrook, PhD, “The Metabolic Characterization of the Interleukin-10tm1Cgn Mouse.” November 5, 2014.
- Oral presenter at the Division of Geriatric Medicine and Gerontology Grand Rounds (March 26, 2015) ”Metabolic Alterations in the Frail Mouse Model”

Short-term goals and timeline for remainder of the project include:
1) Finish writing the Metabolic characterization paper (next month)
2) Complete AICAR trial next (8 months).
3) Continue to examine fat cellular structure using immunohistochemistry (next month)
4) Complete the identification of unknown metabolites and pathway mapping associations (next month)
5) Examine blood chemistry parameters these mice
Section III. CAREER DEVELOPMENT (subsequent to Pepper Funding)

Subsequent funding by supported investigators:

Abadir, Peter (RCDC/Small Pilot)

Agrawal, Yuri (RCDC/Pilot)

Arking, Dan (Pilot)
- Dan Arking. Functional Dissection of the Sudden Cardiac Death Associated BAZ2B Locus, NHLBI, 12/15/2011-12/14/2016

Boyd, Cynthia (RCDC)
- Cynthia Boyd (Principal Investigator). Pfizer/AGS Foundation for Health in Aging Junior Faculty Scholars Program for Research on Health Outcomes in Geriatrics. 07/01/2002 to 12/31/04.
- Cynthia Boyd. Treatment Burden in Older Adults with Diabetes and Multimorbidity. NIA/AFAR/Beeson. Funded. 9/15/2009-8/31/2014

Brown, Charles (RCDC)

Carlson, Michelle (RCDC)
• Michelle C. Carlson, PhD.  Bechtel Foundation Gift: Toward a Cognitive Frailty Screen  

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

Rita Kalyani (RCDC/Pilot)

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

Lin, Frank R. (RCDC)

Makary, Martin (RCDC)
• Martin Makary. Dennis W. Jahnigen Career Development Scholars Award. 2005.

McAdams-Demarco, Mara (RCDC)
• Mara McAdams-Demarco. K01, NIA: Frailty and Adverse Health Outcomes of Aging in Older Adults with Kidney Failure. Funded December 2013.

Mielke, Michelle (Pilot)

Neptune, Enid (Pilot)

Piggott, Damani (External Project)

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

Roy, Cindy (RCDC)

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

Semba, Richard (Pilot)

Seplaki, Christopher (RCDC)

Varadhan, Ravi (Pilot/RCDC)
• Ravi Varadhan (PI). Methods to Study the Heterogeneity of Treatment Effects in Comparative Effectiveness Research. AHRQ. Funded 9/30/2009 to 01/29/2011.
• Ravi Varadhan. 2011 Brookdale Leadership in Aging Fellowship Award: research to better delineate the applicability of intervention trial findings to populations not well-represented in trials, such as older adults. Funded 3/1/2011.

Walston, Jeremy (Pilot/Genetics)
• Jeremy Walston. NIA Long Life Family Study (LLFS). Subcontract to University of Pittsburgh U01AG023744. Funded 5/1/05 – 5/31/10

Wang, George (RCDC)

Xue, Qian-Li (Biostatistics / Pilot)
• Qian-Li Xue. Clinical Significance of Short-Term Change and Variability of Grip Strength (R03). NIA. Funded 4/1/2012 – 3/31/2014.

Yuh, David (RCDC)
Section IV. PUBLICATIONS (directly resulting from Pepper Resources)


## Section V. External Advisory Board Members Names, Institutions and Years of service

<table>
<thead>
<tr>
<th>EAB Member</th>
<th>Affiliation</th>
<th>Years of Service</th>
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<tbody>
<tr>
<td>Joan E. Bailey-Wilson, Ph.D.</td>
<td>Head, Statistical Genetics Section; Co-Branch Chief, Inherited Disease Research Branch; National Human Genome Research Institute; National Institutes of Health</td>
<td>7</td>
</tr>
<tr>
<td>Gerald Beck, Ph.D.</td>
<td>Section Head, Clinical Trials; Design and Analysis, Department of Quantitative Health Sciences, Cleveland Clinic Foundation</td>
<td>2</td>
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<tr>
<td>Howard Bergman, M.D.</td>
<td>Chair, Department of Family Medicine, Professor of Family Medicine, Medicine and Oncology, Dr. Joseph Kaufmann Professor of Geriatric Medicine, McGill University</td>
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<td>Harvey J. Cohen, M.D.</td>
<td>Division Chief of Geriatrics, Director of the Center for the Study of Aging and Human Development, Duke University Medical Center</td>
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<tr>
<td>Luigi Ferrucci, M.D., Ph.D.</td>
<td>NIA Scientific Director, Senior Investigator and Chief, Longitudinal Studies Section</td>
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1. Recognition and Awards (non-grant honors and awards):

- Dr. Karen Bandeen-Roche was named the 2014 Yale Visiting Professor on Aging.
- Dr. Alden Gross, RCDC Junior Faculty, won first place at the 2015 Research on Aging Showcase poster session in the Johns Hopkins Bloomberg School of Public Health.
- Dr. Jeremy Walston was recognized with a 2015 David M Levine Excellence in Mentoring Award by the Johns Hopkins Department of Medicine.

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

- n/a
Mount Sinai Medical Center  
OAIC Annual Directory

Section I. Description of Center

As the home of the first academic department of Geriatrics in the U.S., the Icahn School of Medicine at Mount Sinai and the Mount Sinai Medical Center are extremely committed to Geriatrics and the success of this OAIC. This OAIC responds to the Institute of Medicine (IOM) report by implementing a rigorous and comprehensive program of research focused on the increasing numbers of patients and families living with serious and chronic illness. Specifically, our OAIC builds upon the foundation of pioneering research in aging and palliative care conducted at Mount Sinai over the past 15 years with the express purpose of developing and fostering research that, in the words of Claude D. Pepper, will “…lighten the burden of those who suffer and improve the quality of life and independence for the millions of older adults living with serious and advanced illness. We intend to accomplish our goal by addressing the following specific aims:

1. To establish a comprehensive trans-disciplinary research program focused on: a) exploring the relationship of pain and other distressing symptoms on quality of life, independence, function, and disability; b) developing interventions directed at the treatment of pain and other distressing symptoms in older adults; and c) exploring models of care for older adults living with serious and chronic illness.

2. To identify, recruit, and train leaders in aging and palliative care research through: a) mentoring relationships with successful investigators; b) strengthening and expanding Mount Sinai’s existing research training programs in aging and palliative care; and c) support for pilot projects, statistical and analytic consultation, and instrument development and measurement.

3. To establish a research infrastructure that will a) support new and ongoing research in aging and palliative care by providing expertise in research design, measurement, and analysis, b) develop and apply innovative research designs, analytic techniques, and measures, and c) apply to aging research, methods not currently in widespread use (e.g. item response theory, propensity score methods) but which are highly applicable to geriatrics and gerontology because of the populations studied.

4. To develop a research center that bridges the transdisciplinary specialties of geriatrics and palliative care that will serve as a model for research that has not been well addressed by these two specialties.

The overall goal of our center is to bring together a diverse, transdisciplinary group of distinguished investigators with a strong history of collaboration and research in pain and other symptoms, functional outcomes, patient-oriented research, research design, biostatistics, and measurement to establish an OAIC focused on palliative care in older adults.
Section II. Research, Resources and Activities

A. Cores

Our OAIC cores are led by 5 scientists with a strong history of collaboration, expertise in the OAIC areas of focus, and leadership experience:

Albert Siu, MD (OAIC leader, Leadership and Administrative Core [LAC] leader) - The Leadership and Administrative Core (LAC) will be housed in the offices of the Chairman of the Mount Sinai Department of Geriatrics. Core staff will be the Center PI and Core Leader (Albert L. Siu, MD), the Leaders of the RCDC (R. Sean Morrison, MD) PESC (Kenneth Boockvar, MD) RC-RDA (Melissa Aldridge, PhD), RD-MDM (Jeanne Teresi, PhD), the Vice-Chair for Education of the Department of Geriatrics (Rosanne Leipzig, MD, PhD) and the Director of the Center to Advance Palliative Care (Diane Meier, MD). Three standing committees advise the Center regarding policy and conduct of its programs: 1) an OAIC Executive Committee (OAIC EC or EC) of OAIC core leaders and institutional leadership; 2) a Research Advisory Committee (RAC) of senior investigators not currently involved in the OAIC as investigators or mentors; and 3) an OAIC External Advisory Board (OAIC EAB) of outside experts which meet annually to review progress.

R. Sean Morrison, MD (Research Career Development Core [RCDC] leader) - The RCDC addresses the need to train investigators in palliative care and aging research through Specific Aim 2 of the OAIC: To identify, recruit, and train academic leaders in geriatrics and palliative care research by: a) establishing formal mentoring relationships with established and successful senior investigators; b) strengthening and expanding Mount Sinai’s existing research training programs in geriatrics and palliative care; and c) by providing core support for pilot projects, design and statistical/analytic consultation, and instrument development and measurement. The RCDC contributes to the overall goals of the OAIC by ensuring the development and sustained availability of well-trained, productive, and established researchers in the field of geriatrics and palliative care. The RCDC supports recruitment, selection, career development activities, infrastructure to support training and conduct of research studies, and structured and consistent advisory and mentoring teams and oversight processes for each investigator. Tailored to the developmental stage and training needs of each junior faculty member, the RCDC provides a didactic research training curriculum; biweekly seminars on academic survival; journal club; monthly research-in-progress seminars for presentation and discussion of on-going research; individual mentoring; support for measurement and statistics from the resource cores; and oversight of pilot and exploratory studies within the OAIC.

Kenneth Boockvar, MD (Pilot and Exploratory Studies Core [PESC] leader) – The PESC builds upon a 15-year foundation of research in palliative care, disability, and function at Mount Sinai; an established record of successful mentorship by the OAIC senior investigators, and a strong and consistent track record in conducting collaborative and interdisciplinary research that will accomplish the following specific aims:
• **Support pilot and exploratory studies that will:** a) examine the relationship of pain and other distressing symptoms to independence, function, and disability; b) develop interventions directed at the treatment of pain and other distressing symptoms in older adults; and c) explore interventions to improve quality of life and promote function and independence for older adults living with serious and chronic illness.

• **Support the development of junior faculty** by providing a mechanism to obtain mentored, hands-on research training and develop preliminary data in aging and palliative care that will lead to the development of larger federal or foundation funded research projects and career development awards focused on improving care and promoting independence for older adults with advanced illness.

• **Support senior and mid-level faculty** who are conducting: studies in palliative care and aging and who are embarking on new research projects requiring pilot data; palliative care research in younger populations and who would like to expand or shift their research into aging; or aging research unrelated to palliative care who would like to refocus their work to fit within our OAIC theme.

• **Foster collaborative research** among investigators from different disciplines, specialties, and institutions.

**Melissa Aldridge, PhD (Research Core–Research Design and Analysis [RC-RDA])** - The Research Design and Analysis Core (RC-RDA) contributes to the goals of the OAIC by providing statistical, methodological and programming expertise, as well as mentoring in those areas, to investigators in the Mount Sinai OAIC. Expertise is provided in a variety of ways and throughout all phases of the research process—from design through interpretation and presentation of findings. The RC-RDA aims are:

- To provide sophisticated, cutting edge methodological, statistical, and recruitment support to new and existing OAIC investigators by supporting new internal OAIC (e.g, PESC, RCDC) and external research applications, RCDC and PESC funded projects, and consultation and services to externally funded research of OAIC faculty for additional analyses not included in the parent grant.
- To collaborate closely with the Research Career Development Core (RCDC) to ensure that junior faculty obtain research methods training to advance their current knowledge and expertise.
- To collaborate with the RC-MDM to obtain data processing and management appropriate for studies by PESC investigators, junior faculty and other OAIC investigators.
- To apply sophisticated research and statistical methodology (propensity score method, instrumental variable estimation, competing risk analysis) used in other fields but not commonly applied to aging-related research.
- To disseminate this information to other researchers in geriatrics and gerontology through presentations at scientific meetings and publications in scientific journals.
- To work with and provide consultation to researchers at other OAICs on methodological challenges of research on older patients with serious and chronic illness.

**Jeanne Teresi, PhD (Research Core –Measurement and Data Management [RC-MDM])** – A major barrier to research in this field has been the questionnaire burden on patients and family members associated with assessing and measuring symptoms, physical impairment, satisfaction, and caregiver burden. The major goal of the RC-MDM is to address such measurement challenges using item banking and the methods of modern psychometric theory through the
following specific aims:

- To assist OAIC investigators (from this and other Centers) in evaluating measures, and, where appropriate, in the selection, use, and construction of item response theory (IRT) derived measures from existing sources (e.g., the Patient Reported Outcomes Measurement Information System (PROMIS) Roadmap Initiative);
- To apply psychometric techniques to items from existing palliative care and related data sets to test model assumptions, examine distributions and prepare data for analyses;
- To conduct IRT analyses using data from ongoing NIH funded palliative care research with the goal of constructing a palliative care item bank as part of a later developmental project in years 3-5 of this OAIC;
- To provide data management, in coordination with RC-RDA, for studies supported by the other OAIC cores;
- To disseminate this information to researchers interested in geriatric palliative care through: a) presentations and publications, b) the National Palliative Care Research Center (www.npcrc.org) and other major national initiatives; and c) development of a web site with links to PROMIS and related web sites.

B. Research

1. Palliative Care for Hospitalized Patients with Advanced Cancer (PI: Meier, NCI/NINR funded). This series of analyses will contribute to the overall OAIC theme by examining the effect of inpatient palliative care consultation teams (PCCT) on hospital costs, hospital and intensive care unit lengths of stay, and readmission rates using sophisticated statistical methods not commonly applied to aging-related research. The parent study is a multi-site, observational controlled trial of PCCT compared to usual care for 6900 patients hospitalized with advanced cancer in five U.S. hospitals. RC-RDA will provide cost and use data collection, and analyses of cost effects using propensity score matching.

2. Pain and Delirium in an RCT of Perioperative Cognitive Protection (PI: Silverstein, NIA funded). This series of analyses will contribute to the overall OAIC theme by examining the relationships among postoperative pain, pain treatment, delirium and cognitive impairment in older adults using sophisticated statistical methods. The parent study is an RCT of the effect of perioperative infusion of dexmedetomidine, an α2A-adrenergic agonist, compared with standard care on postoperative delirium and cognitive dysfunction in 706 older adults undergoing major non-cardiac surgery at 7 U.S. hospitals. We will conduct analyses not funded by the parent grant first to test the hypothesis that higher pain scores are associated with an increased incidence of post-operative delirium by the CAM assessment, using multivariable logistic regression. Second, we will test the hypotheses that patients receiving patient-controlled analgesia (PCA) will have lower opioid requirements, reduced pain, and a lower incidence of post-operative delirium, using propensity score methodology to match patients receiving PCA to those receiving clinician controlled analgesia and using multivariate logistic regression to examine the association of PCA with post-operative delirium. Third, we will test the hypothesis that opioids with active metabolites (oxycodone, morphine) are associated with an increased risk of delirium as compared to opioids without active metabolites (fentanyl, hydromorphone), and examine the relationship between opioid dose and delirium. We hypothesize a U-shaped relationship between opioid dose and delirium such that low and high doses of opioids will increase the risk of
delirium whereas moderate doses will be protective. We will use propensity score methodology to match patients receiving each opioid type and multivariable logistic regression to examine the relationship between drug type and post-operative delirium. To test whether both low and high doses of opioids are associated with greater delirium, we will include a squared opioid dose term in the model. The signs on the estimate of the dose and dose squared terms indicate whether the relationship is U shaped. All models will control for delirium risk factors, treatment group, opioid dose, and other important covariates. RC-RDA will provide propensity score methodology, modeling consultation and data analysis.

3. **EP-3: Symptoms and Function during Acute Illness in Nursing Home Residents (PI: Boockvar; Co-PI Hung, VA funded).** This series of analyses will contribute to the overall OAIC theme by examining the relationships between pain and other symptoms, medication use, acute illness and function in nursing home residents using sophisticated statistical methods. The parent study is a prospective observational cohort of residents of 2 nursing homes in New York City who have experienced 150 acute illness episodes (e.g., urinary and respiratory infections). We will conduct analyses not funded by the parent study to describe the impact on pain, function, and other symptoms of 2 exposures: 1) periods of acute illness and 2) periods of interruption in opioid analgesics which are common. Levels of pain, function, and other symptoms during exposure periods will be compared with pre-exposure periods, controlling for repeated observations of subjects over time and clustering of subject observations by provider and nursing home, using GEE. RC-RDA will provide modeling consultation accounting for clustered observations, and statistical programming for data analysis.

4. **EP-4: Analgesic Safety and Effectiveness in Older Veterans with Arthritis; PI: Ula Huang; VA Merit Award; external support period: 07/01/14 - 06/30/18; Description:** Recent studies have raised concerns about the safety of opioids versus non-steroidal anti-inflammatory drugs (NSAIDs) of analgesics in older adults, medications commonly prescribed to veterans. Research gaps in optimal older adult pain treatment remain and more evidence-based research is needed before conclusive recommendations and guidelines can be endorsed. The objectives of this study are to evaluate the safety and effectiveness of 3 commonly used analgesic medication types (opioids, NSAIDs, coxibs) for older veterans diagnosed with arthritis. Two projects will accomplish these objectives. The first study will prospectively survey older veterans with arthritis recruited from primary care clinics at four VA centers with geographic and prescribing pattern diversity. The second study uses Veterans Health Administrative data, linked to Medicare and Medicaid claims data on a longitudinal cohort of veterans from 2010-2014 to compare the safety of NSAIDs, selective coxibs, and opioids using both propensity score-matched cohorts and instrumental variable analyses. This study directly relates to the objective of the OAIC by examining the safety and effectiveness of analgesic medications in reducing pain for older adults with chronic arthritis. The RC-RDA will support this project through consultations with biostatistical experts regarding both propensity score and instrumental variable analyses.

5. **EP-5: The Impact of Mental Illness on Veterans’ Palliative Care Access and Outcomes PI: Melissa Garrido; VA Career Development Award; external support period: 10/2012-09/2017;** This study focuses on the intersection of depression and anxiety (DEP/ANX) and palliative care (PC) for veteran inpatients with serious illnesses. First, this study will examine the relationship between pre-existing and newly diagnosed DEP/ANX and outcomes (ICU admissions and readmissions and costs of care) including the relative effect of PC versus PC+mental healthcare (MHC) for veterans with different combinations of physical illnesses and DEP/ANX. Aims will
utilize secondary analysis of 2010-2011 veteran inpatient administrative data for 30,000 inpatient veterans with advanced cancer, HIV/AIDS, CHF or COPD supplemented with EMRs of 200 veterans eligible for an inpatient PC consultation during 2010-2011. Analyses will account for repeated hospitalizations and clustered data, and will address the fact that similar factors may influence both likelihood of PC and MHC as well as ICU admissions and costs. Second, a case-finding intervention will be developed that identifies which veterans receiving PC may exhibit reduced symptom burden and reduced ICU use following a MHC consult. The case-finder criteria will be validated in administrative data, and the intervention will be refined with input from clinician stakeholders. The intervention will then be pilot tested at the facility level. This study directly relates to the objectives of the OAIC by examining the distressing symptoms of depression and anxiety and its impact on quality of life outcomes such as hospitalizations and will test an intervention of PC+MHC to improve these outcomes for older veterans. The RC-RDA will support this project through consultations with biostatistical experts regarding analyses accounting for endogeneity and in the creation of prediction models.

6. **EP-3 Effects of 30-day Bundled Payment of Hospital at Home on Outcomes, Satisfaction and Costs.** PI: Al Siu; CMMI innovation Award; 7/1/2014-6/30/17. Studies have demonstrated the effectiveness of providing acute-level hospital care at home for older persons who would otherwise be admitted to the hospital for acute conditions such as community-acquired pneumonia or decompensated heart failure; however, dissemination of these programs has been limited due to the absence of a payment model. As part of a Health Care Innovation Award, hospital at home (renamed the Mobile Acute Care Team) will be implemented in the Mount Sinai Health System using an expanded innovative package of services as part of a 30-day payment bundle. With the assistance of RC-PRE, a quasi-experimental design has been developed to assess the effects of the intervention on patient outcomes, satisfaction, and costs by comparing patients in the intervention to otherwise eligible patients at other Mount Sinai Health System hospitals that will not have such services. This project will involve Tacara Soones, MD (RCDSC candidate). The RC-RDA is assisting in the assembly of a comparison cohort, construction of an analysis plan to account for comorbidity, and analysis of Medicare data.

C. **Pilots**

**Project 1: Cohort Study of Patients with Ventricular Assist Devices to Determine Symptoms of Patients and their Caregivers**

Principal Investigator: Nathan Goldstein, MD Brookdale Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai

Co-Investigators: 1) R. Sean Morrison, MD, Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai 2) Deborah Ascheim, MD, Department of Health Evidence and Policy, Icahn School of Medicine at Mount Sinai

Background and Specific Aims: Heart Failure (HF) is a chronic illness typically associated with multiple co-morbidities, and it is a leading cause of death in the United States. While medical management is the mainstay therapy for patients with HF, ventricular assist devices (VADs) are
Increasingly used to treat HF patients with end-stage disease. Originally approved as a temporary therapy to “bridge” patients as they waited for cardiac transplantation, VADs are now implanted in patients whose eligibility for transplant is unclear (bridge to candidacy) or ineligible for transplantation (destination therapy). The use of LVADs is expected to increase in the years to come, especially as devices become smaller and are increasingly associated with better survival and fewer post-implantation complications (e.g. infection, bleeding, stroke). While these devices have been shown to improve survival and quality of life in patients with advanced HF, there are little data exploring the non-HF physical symptoms (e.g. pain) of patients with these devices or the psychological symptoms of these patients and their caregivers. This project is a 4-center prospective cohort study of patients with recently implanted VADs and their caregivers to:

**Aim 1:** Evaluate baseline prevalence and change over time of physical (pain and quality of life) and psychological (depression, anxiety, panic disorder) characteristics and symptoms in patients with VADs.

**Aim 2:** Evaluate baseline prevalence and change over time of psychological (depression, anxiety, posttraumatic stress disorder) symptoms in caregivers of patients with ventricular assist devices.

**Aim 2.1:** Determine prevalence of prolonged grief disorder among caregivers of patients with VADs who die.

The project will enroll 100 patients immediately after VAD implantation at Mount Sinai, Columbia-Presbyterian, University of Pennsylvania, and Jewish Hospital (Louisville, KY) Medical Centers to determine baseline prevalence of symptoms of both patients and their caregivers using validated instruments, and then follow them for up to 12 months to determine how these characteristics change. For those patients who die during the course of the study, the project will perform after-death interviews with caregivers. This project will be the first comprehensive exploration dedicated to determining the non-HF-related physical and psychological symptoms of patients with VADs and their caregivers. These data will be also be used to support a future R01 grant application for a randomized controlled trial evaluating whether automatic palliative care consultation at time of device implant improves outcomes for patients with VADs and their caregivers.

Products: the PI received funding from the Greenwall/Kornfeld Foundations to conduct a small scale randomized controlled trial of palliative care for patients with VADs. Data from the project were also used to apply for 1) a K02 application which was originally submitted in 2012 (not funded) and 2) National Palliative Care Research Funding (funded). Two manuscripts are currently under review for this project.

**Project 2:** Couple-focused Symptom Management Intervention for Older Lung Cancer Patients & Their Spousal Caregivers

Principal investigator: Hoda Badr, PhD, Department of Oncological Sciences, Icahn School of Medicine at Mount Sinai

Co-Investigators: 1) Juan Wisnivesky, MD; General Internal Medicine, Icahn School of Medicine at Mount Sinai; 2) William H. Redd, PhD; Department of Oncological Sciences, Icahn School of Medicine at Mount Sinai
Background and specific aims:
Cancer is a disease of the elderly; 50% of all cancer patients are over the age of 65, and this number is growing rapidly as the population ages. LC patients experience more debilitating symptoms than other cancer patients and better approaches to symptom management are needed in this population. With the increasing reliance on outpatient care, spouses and intimate partners are playing a more critical role in the care of cancer patients. However, the spousal caregivers of LC patients are also likely to be elderly and LC couples often leave the hospital with knowledge deficits that can impede effective symptom management and care. Currently, there are no programs that: a) take a couples’ approach to LC pain and symptom management; b) provide practical strategies couples can use to discuss cancer-related symptoms and concerns; and c) are designed to specifically address the pain/symptom management needs of older LC patients and their partners.
Thus, the specific aims of this study are to:

1) Use focus groups to develop and refine a couple-focused intervention for older lung cancer (LC) patients and their partners that prepares and educates couples about LC symptoms, teaches them techniques for effective symptom management and home care, and teaches communication skills that couples can use to effectively problem-solve cancer-related concerns and coordinate care.

2) Pilot test the intervention in a small randomized controlled trial (RCT) vs. a usual care control group and to explore whether couples in the intervention group experience better patient (i.e., symptom burden, symptom distress, functional disability, general QOL), partner (caregiver strain, competence, QOL), and relationship outcomes (i.e., relationship satisfaction and intimacy).

The study consists of 2 parts. Part 1 uses 4 focus groups comprising 30 LC patients and their partners to develop and refine a symptom management intervention for older LC couples. Preliminary intervention content is based on Dr. Badr’s previously published studies of couples’ psychosocial adjustment to LC and her research on pain in advanced cancer. The proposed intervention will encourage couples to view LC as a ‘we’ disease, work together as a team to problem-solve and effectively manage symptoms at home, and openly and supportively communicate about both the practical and emotional challenges that can arise as LC progresses. Through its focus on communication and the coordination of care between patients and their partners, the goal of the intervention is to improve patient (i.e., symptom burden, symptom distress, general QOL), partner (caregiver strain, competence, QOL), and relationship outcomes (i.e., relationship satisfaction and intimacy) in LC. Part 2 will pilot test the intervention in a small randomized controlled trial (RCT) vs. a usual care control group (50 LC couples; 25 couples in each group). Thus, the proposed study will provide estimates of intervention feasibility, acceptability, and preliminary efficacy that will inform planning and provide power and sample size calculations for future larger trials. By taking a coordinated approach to symptom management in LC, teaching communication skills, and addressing the concerns of both partners, the proposed intervention may provide maximum benefit and greatly facilitate the symptom management and adaptation of both elderly LC patients and their spousal caregivers.

Products: Pilot data shows that TEAM-LC is feasible and acceptable to both patients and caregivers. It also provides preliminary support for the role of TEAM-LC and patient-caregiver relationship functioning on our outcomes. These pilot data were used to support an ACS
Research grant that was recently funded (RSG15-058-01 PCSM; 7/01/2015 to 12/31/2019). Based on the pilot data obtained, two changes were made to the intervention. First, to conserve resources and enhance relevance, only stage 3A-4 LC patients will now be eligible. The second change is that half the sessions will now be conducted with patients and caregivers together and the other half will be conducted with patients and caregivers separately. This will allow: 1) more in-depth coverage of the tailored materials; 2) more one-on-one time with the interventionist to address individual concerns; and, 3) more time to practice skills and receive feedback.


**Project 3: Palliation of Depression in Nursing Home Residents with Serious Illness: A Non-pharmacological Approach**

Principal investigator: Joann P. Reinhardt, PhD, Jewish Home Lifecare Institute on Aging
Co-Investigator: Amy Horowitz, DSW, Department of Social Work, Fordham University

**Background and specific aims.**
Geriatric patients residing in long-term care (LTC) facilities are typically characterized by serious illness, poor life expectancy, and high symptom burden, attributes which parallel those of palliative care patients across health care settings. Among the most distressing symptom clusters for both residents and their family is the experience of significant depressive symptomatology, a common mental health comorbid condition associated with serious chronic illness in later life. The consequences of untreated depression can be devastating and include both the amplification of pain and symptom distress, as well as increased difficulty in treating these symptoms, along with poor quality of life, and impaired capacity for pleasure, meaning, and connection with others. Yet, both palliative care interventions, in general, and treatments for depression, in particular, lack an evidence-base relevant to the nursing home population, and remain largely inadequate to the need in LTC. The treatment of first choice for depression in nursing homes is typically antidepressant medication. However, the complexity of managing multiple concurrent serious illnesses, along with problems associated with polypharmacy, call for greater consideration of non-pharmacological, psychotherapeutic interventions, and in particular cognitive therapeutic interventions appropriate for residents with no or mild cognitive impairments, who continue to comprise 25-30% of the nursing home population. Yet, randomized trials of psychotherapy in long term care are largely lacking. This proposed pilot is a feasibility study of Problem Solving Therapy (PST) among 40 nursing home patients to treat subsyndromal depression in patients with serious life-threatening conditions who reside in LTC facilities. The specific aims of this study are:

1) To demonstrate PST implementation fidelity (recruitment, acceptance, and adherence to the protocol) within a nursing home setting.
2) To identify the potential of PST for nursing home residents with serious chronic illness and subthreshold depression relative to: (a) Primary outcomes of depression remission and clinically significant reductions in depressive symptoms; and (b). Secondary outcomes of symptom distress (pain, fatigue).

3) To estimate the effect size of the PST intervention compared to Usual Care with Social Contact for primary and secondary outcomes.

Findings from this study will contribute to the knowledge base on treating emotional disorders in palliative care and provide the pilot data needed for the design of a larger scale, multi-site study of PST in LTC. This study is innovative in several ways. First, it targets older adults with subsyndromal and minor (rather than major) depression, for who non-pharmacological approaches may be more appropriate but for which limited effectiveness evidence is available. Second, while there is evidence supporting the effectiveness of PST with depressed elders among primary, acute, and home care patients, no prior research has tested the application of this manualized psychotherapeutic program with a nursing home population. Third, in addition to primary outcome measures of depression remission and symptom reduction, the team is also examining secondary effects of PST on reduction of pain and fatigue which are both key targets of palliative care and symptoms that can be exacerbated by depression. These data will inform the development of a larger study to test the effect of this nonpharmacological treatment for subthreshold depression and symptom distress in this complex, medically ill population.

Products: The experience of this pilot points to the benefits of an integrated mental health component into the rehabilitation setting and involving rehabilitation professionals who are already involved with the older adults. Overall, there is an excellent conceptual fit between PST and the rehabilitation process since both focus on counteracting deficits through learning skills and the application of problem solving abilities. Rehabilitation professionals in the subacute setting, including occupational and physical therapists, could incorporate some of the principles and techniques of problem solving therapy in their rehabilitation sessions, and address problems related to affect as well as function, which are inevitably interrelated. Future efforts will focus on ways to address and test these ideas. Potential funding sources for subsequent projects based on pilot project findings are being explored. The follow was published in 2014 - Reinhardt JP, Horowitz A, Cimarolli VR, Eimicke JP, Teresi JA. Addressing depression in a long-term care setting: a phase II pilot of problem-solving treatment. Clinical therapeutics. Nov 1 2014;36(11):1531-1537.

Project 4: A Descriptive Analysis of Hospice Care for Older Patients with Heart Failure -
Principal Investigator: Laura Gelfman, MD, Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai

Co-Investigators: 1) Nathan E. Goldstein, M.D., Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai, 2) Melissa Carlson, PhD, MBA, Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai

Background and Specific Aims: Heart failure (HF) is a leading cause of death in the United States. HF is the most common cause of hospitalization among adults over the age of 65 and admission rates for this disease have increased steadily over the last two decades. Even with
current therapies, HF patients experience high symptom burden and mortality over the course of a prolonged and unpredictable illness. Symptomatic HF confers a worse prognosis than most cancers, with one-year mortality of approximately 45 percent. Despite these numbers, less than 10% of HF patients receive any form of palliative care; as of 2009 less than 12% of hospice admissions were for HF patients. Unlike the growing evidence of the benefits of palliative care and hospice for patients with cancer, there is a paucity of data regarding the predictors for hospice enrollment for HF patients. Like palliative care, hospice has the potential to improve clinical outcomes for older patients facing HF by improving pain and other symptom control, clarifying goals of care, and guiding treatment decisions to meet those goals. Little is known about which HF patients are assessing hospice and how enrollment impacts utilization.

Specific Aim 1 – Describe the Population of HF Patients who Enroll with Hospice: Using an existing Medicare dataset of all Medicare beneficiaries with at least one home health claim from 2009 and 2010 who were hospitalized for HF in a one-year period (July 1, 2009 to June 30, 2010), we will describe the population of HF patients enrolled with hospice.

Aim 2 – Identify the Predictors of Hospice Enrollment for HF Patients: Using propensity score matching, we will perform a secondary data analysis of an existing Medicare data file to identify the patient-level, physician-level and county-level factors that are associated with hospice enrollment in this population.

Aim 3 – Healthcare Utilization of HF Patients Enrolled with Hospice: Using a propensity-matched cohort of HF patients who used hospice and those who did not, we will compare the 30-day hospital readmission rates.

Products: Dr. Gelfman presented results from this pilot study at the American Academy of Hospice and Palliative Medicine Annual Assembly, Philadelphia, PA in March 2015. The final analyses are being conducted with plan to submit for publication in the next 3 months. In addition, Dr. Gelfman was awarded a Hartford Foundation Collaborative Pilot Project to create a HF Communication Task Force. Through this award, Dr. Gelfman and her co-leader, Dr. Bakitas, have created a team of key stakeholders (geriatrics, palliative care and cardiology, as well as patients and caregivers) to determine research priorities for improving HF communication. This team will be fundamental in helping me create models to improve communication for advanced HF patients. We organized and enacted our three-day workshop: “Improving Palliative Care for Patients with Heart Failure and Family Caregivers: Creating an Agenda for Research and Clinical Priorities” on June 7-9, 2015 in Birmingham, Alabama with supplemental support from The John A. Hartford Foundation, the National Palliative Care Research Center, Mount Sinai’s Claude Pepper Older American Independence Center, as well as UAB Centers for Comprehensive Cardiovascular Care and Palliative and Supportive Care. Dr. Gelfman will be presenting the results from this workshop in a presentation entitled “Improving Palliative Care for Patients with Heart Failure and Family Caregivers: Results from a National Working Group Examining Clinical & Research Priorities for Heart Failure and Palliative Care” at the 2016 AAHPM Annual Assembly in Chicago, IL along with her colleagues Dr. Bakitas, Dr. Goldstein and Dr. Fendler. Finally, Dr. Gelfman submitted an application for a K23 Career Development Award in March of 2015 and received an impact score of 10.
Project 5: Reducing symptom burden for chronically ill homebound patients through home-based primary care intervention - Principal investigator: Katherine Ornstein PhD MPH – Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai

Background and specific aims:
The majority of homebound patients experience significant symptom burden related to chronic illnesses, many of which go unrecognized and untreated. Common symptoms include pain, nausea, shortness of breath, fatigue, and depression. As an increasing number of elderly and frail patients are homebound as a result of multiple medical conditions and functional and cognitive impairment, the need for accessible medical and palliative care and symptom management in the home continues to grow. Home-based primary care (HBPC) is designed to improve quality of life and promote function and independence for older adults living with serious and chronic illness. HBPC programs work to reduce symptom burden in patients including treating pain, depression and fatigue in order to address the medical and psychological needs of homebound patients. Little is known as to whether patients’ symptoms are appropriately managed in such settings.

Primary research questions and hypotheses
What interventions are successfully used by HBPC programs to reduce pain, depression, anxiety, tiredness and loss of appetite in homebound patients?

Frequent visits, frequent phone encounters, medication changes, consultations, collaboration with nursing and social work will be used to reduce symptom burden.

Do homebound patients receiving HBPC with high symptom burden have different care needs than homebound patients without symptom burden?
Patients with high symptom burden at HBPC enrollment will require more follow up visits, higher call volume, and more social work involvement than patients without baseline burden

How will symptom burden change in homebound patients over time?
Patients with moderate-severe symptoms at baseline will have reduced burden by 2 months.

What are the formal and informal caregiver needs of homebound patients with high symptom burden?
Patients with high symptom burden will be highly reliant on formal and informal caregivers.

Methods: Patients will be recruited from Mount Sinai Visiting Doctors (MSVD), which provides HBPC for over 1000 homebound patients annually. All newly enrolled patients are administered a baseline Edmonton Symptom Assessment Scale as part of their routine clinical care on an initial visit. Patients with a completed ESAS assessment will be eligible for participation. After consent, a research assistant (RA) will assess depression via the Center for Epidemiologic Studies Depression scale. The RA will conduct follow up assessments via telephone every two months for up to 6 months. Each month the RA will review all medication changes/interventions made to address patient’s symptom burden. The RA will also collect treatment data for patients with previously documented symptom reduction (n=50) from a previous study.
Participation: Over one year, 104 new patients at MSVD were eligible to participate in the study (50% of newly enrolled patients). Of these, 78 (75%) consented to have follow-up phone calls. (An additional 7 consented to have their charts reviewed monthly). To date, 35 patients have completed the study (assessments completed through 6 months). 12 patients died before study completion and there has been 1 withdrawal. We are continuing to conduct bimonthly follow-up assessments on 30 patients at this time. Retrospective chart reviews of HBPC interventions have been completed on 22 patients.

Products: Hannah Major-Monfried, an MSSM medical student, completed further work on this project through the MSTAR program summer 2014. The results of this study were presented at the 2015 American Geriatrics Society Meeting. Dr. Ornstein received a K01 career development award in September, 2014.

Project 6: Elder Life program to prevent delirium in long-term care - Principal investigators: William Hung, MD, MPH and Kenneth Boockvar, MD, MS. – Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai, and Jewish Home Lifecare

Co-Investigators: Sharon Inouye, MD, Harvard University; Jeanne Teresi, PhD, Hebrew Home at Riverdale

Background and specific aims: Delirium is an acute cognitive disorder with features of inattention, disorganized thinking, and disordered consciousness that occurs in approximately one third of hospitalized older adults. As compared to those without delirium, patients with delirium have 2-3 fold higher mortality at 1 year and increased risk of nursing home utilization. The overall objective of this study is to test the effectiveness of an intervention to prevent delirium in nursing home (NH) residents. The intervention is adapted from Hospital Elder Life Program (HELP), which delivers risk factor-targeted components via a specialized geriatric care. It has not been tested in the nursing home setting.

The specific aims are:

1. To adapt and implement a delirium-prevention intervention in the nursing home by providing at onset and during acute illness standardized assessment and treatment for delirium risk factors with a team of an advanced practice nurse (APN) and an Elder Life specialist
2. To determine, as compared to control, the effect of the intervention in preventing delirium, function decline, and hospitalization associated with acute illness
3. To examine intervention adherence and acceptance by key stakeholders

We hypothesize that the intervention will be effective in preventing delirium during brief acute illness in NH residents, improving their long-term cognitive and functional trajectories, and preventing hospital transfer.

Methods: With OAIC funding we will conduct a controlled evaluation of the intervention among long-term care residents of 2 buildings at Jewish Home Lifecare’s Bronx campus. New cases of brief acute illness will be identified each weekday by referral and case finding. Residents with
brief acute illness on intervention units will be seen by the APN and Elder Life Specialist team, who will implement intervention components and continue for up to 10 days. Residents with brief acute illness on control units will be cared for as usual by the primary unit nursing home nursing and medical staff. We will use the Confusion Assessment Method, a widely-used, validated measure, to ascertain incident delirium each weekday during the first 10 days of the acute illness. Cognitive and physical function will be ascertained using the nursing home Minimum Data Set Cognitive Performance and Activities of Daily Living scales, and the Brief Interview of Mental Status (BIMS) at illness onset, 10 days after illness onset, and 1 and 3 months after illness onset. Analyses will compare occurrence of delirium, cognitive and physical function decline, and hospitalization among intervention and control groups, using generalized models that take into account multiple episodes per patient if they occur. We will perform interviews with intervention recipients, unit-based staff, and other providers to ascertain integration of the intervention with unit-based services, barriers and facilitators.

Projects: Adherence/feasibility findings were reported at the 2014 annual HELP and 2014 and 2015 American Geriatrics Society meetings. A paper was invited for revision at Journal of the American Geriatrics Society. Other project dissemination is occurring through a white paper for the American Medical Directors Association and a July 2015 feature in "Nursing Assistant Monthly." Using findings as pilot data, an NIA R21 application was submitted to test the efficacy of the intervention in a randomized, single-blinded, single-site controlled trial. It was scored at the 11th percentile but not funded. A grant proposal to extend follow-up of participants is under review at the Donaghue Foundation with a decision expected October 2015. A possible NIA R01 submission is being planned.

Project 8: The effect of palliative care on quality of life, function, and independence in older adults with serious chronic illness—Principal Investigator: Jay Horton, PhD, MPH—Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai

Co-Investigators: Eric Lee, Sean Morrison, Amy Kelley

Background and specific aims: As the population of older adults in the United States continues to grow, the number of Medicare beneficiaries with one or more serious chronic illnesses grows with it (Manini, 2011). The health care for these older adults, particularly at the end of life, is costly and is responsible for a disproportionately large percentage of the annual health care budget in the United States (Downey, Au, Curtis, & Engelberg, 2013). There has been ample evidence accruing for more than a decade indicating that the health care that older adults receive at the end of life is often of inappropriately high intensity and is associated with poor quality of life, incongruence with patient preferences, and poor pain and symptom management (Downey et al., 2013; Fu & Wang, 2008; Mittler, Landon, Fisher, Cleary, & Zaslavsky, 2010; Morden et al., 2012; Skinner & Wennberg, 2000). Additionally, older adults with more intensive hospital use at the end of life have been shown to have a greater degree of functional decline (Kelley, Ettner, Morrison, Du, & Sarkisian, 2012; Kelley et al., 2011).

Palliative care has been offered as a possible solution to this state of affairs by various national organizations (Institute of Medicine, 2003; National Cancer Institute, 2004; National Consensus
Project for Quality Palliative Care, 2013). Interdisciplinary, hospital-based palliative care teams offer an extra layer of care to patients with serious illness and their families beginning as early as diagnosis and continuing along with appropriate life-prolonging therapies if desired (Eti, 2011; National Consensus Project for Quality Palliative Care, 2013). Palliative care provides relief from pain and other symptoms, emotional and spiritual support, and coordination of care (Eti, 2011; Meier, 2006). Importantly, one of the key functions of palliative care is to work with patients and their family members to make sure that the treatment plan is guided by and in agreement with the patient’s and family’s values and goals of care (Litrivis & Smith, 2011; Meier, Casarett, von Gunten, Smith, & Storey, 2010).

Despite rapid expansion of the availability of palliative care, older adults continue to receive care that is high intensity, has many quality deficits, and accounts for an increasingly large percentage of our national health care spending (Downey et al., 2013; Kelley, Morrison, Wenger, Ettner, & Sarkisian, 2010; Morden et al., 2012). Although the majority of hospitals with greater than 50 beds now report having a palliative care program, there is a great deal of variation by state and hospital type (Goldsmith, Dietrich, Du, & Morrison, 2008; Morrison, Augustin, Souvanna, & Meier, 2011). While we know much about the epidemiology of treatment intensity and the factors associated with it, we know relatively little about whether programs aimed at reducing unwarranted treatment intensity are effective. Although there has been an increase in publication of palliative care clinical trials (Tieman, Sladek, & Currow, 2008), there remains limited evidence linking palliative care interventions to reductions in health care intensity for seriously ill patients. Studies to date have been small and therefore there is a need for population-based research to demonstrate both clinical and utilization outcomes of such programs.

The specific aims are: 1. Show whether hospitals with palliative care programs are more likely than those without palliative care programs to show better quality of life during the last six months of life for older adults who die with serious chronic illness as evidenced by decreased total hospital days, days in an intensive care unit (ICU), physician visits, percent of deaths occurring in the hospital, percent of deaths including an ICU visit, percent of patients seeing 10 or more physicians, and number of different physicians seen; and by increased percent enrolled in hospice and number of days enrolled in hospice.

2. Show whether hospitals with palliative care programs are more likely than those without palliative care programs to show better quality of life during the last month of life for the subset of older adults who die with cancer as evidenced by decreased total hospital days, days in an intensive care unit (ICU), percent of deaths occurring in the hospital, percent of deaths including an ICU visit, percent admitted to the hospital, and percent receiving life-sustaining treatment; and by increased percent enrolled in hospice and number of days enrolled in hospice; by decreased percent receiving chemotherapy in the last 14 days of life; by decreased percent enrolled in hospice in the last 3 days of life; and by decreased percent seeing 10 or more physicians in the last 6 months of life.

3. Show whether those hospitals with a higher “dose” of palliative care (those operating for a greater number of years, and for the subset of hospitals with palliative care programs in the National Palliative Care Registry, those hospitals that have more clinical staff) will demonstrate greater effects on quality of life, function, and independence for older adults living with serious chronic illness.
Methods: Primary Data Sources: The Dartmouth Atlas project. The Dartmouth Atlas project data are derived from Medicare claims data on older beneficiaries with serious chronic illnesses at the end of life. Patients were included if they had one or more of nine severe chronic illnesses associated with a high probability of death coded on at least one hospital discharge claim (Wennberg, 2004). The nine illnesses were metastatic cancer or cancer with poor prognosis, congestive heart failure, chronic obstructive pulmonary disease, dementia, diabetes with end organ damage, peripheral vascular disease, chronic renal failure, severe chronic liver disease, and coronary artery disease (Goodman, Esty, Fisher, & Chang, 2011). The Dartmouth Atlas project investigators provide hospital-level data for a variety of outcomes related to treatment intensity, quality of life, function, and independence.

National Palliative Care Registry. The National Palliative Care Registry is a repository created by the Center to Advance Palliative Care (CAPC) and the National Palliative Care Research Center (NPCRC) to collect information about the operational features of hospital palliative care programs (Center to Advance Palliative Care, 2012). Hospitals voluntarily enter operational data on an annual basis including key program structures and processes of care, including members of the interdisciplinary team, hours of availability, and number of consultations made in the previous year.

AHA Annual Survey. This voluntary annual survey of U.S. hospitals contains hospital-specific data elements on hospitals and health care systems, including variables describing organizational structure, utilization, staffing, hospital facilities, and services (American Hospital Association, 2012).

Design: This is a retrospective, cross-sectional, quasi-experimental study using propensity score adjustment to reduce selection bias on observables. The study will examine the effect that having a palliative care program has on a hospital’s average intensity of treatment, quality, independence, and function for patients who are over age 65 and have one or more serious chronic illnesses during the last six months of life. Baseline data regarding the characteristics of hospitals with and without palliative care will be explored with descriptive statistics (mean and percent) and compared using t-tests or chi square tests as appropriate. Statistical significance will be considered an alpha level of 0.05 or less. This study will compare hospital outcomes for older patients with severe chronic illness in hospitals with a palliative care program versus those in hospitals without a palliative care program using propensity score adjustments to reduce the effects of selection bias on observables. Selected hospital characteristics that have been demonstrated to be or are likely to be associated with the outcomes or with the presence of a formal palliative care program will be used as covariates in the derivation of propensity scores as well as in the final regressions. Balance among the covariates between the treatment and control groups will be assessed based on predetermined parameters with the investigator blinded to the outcomes. Inverse probability of treatment weighting will be used to reduce selection bias due to observable characteristics.

Sites/Sample: Hospitals and hospital care in this study will be restricted to those in the US. This study will include approximately 2,000 hospitals for which there are enough data to determine the presence or absence of a clinical palliative care program. Approximately one half of these hospitals are expected to have a palliative care program.

Products: Currently drafting paper for publication covering specific aims 1 & 3.
### III. Career Development

<table>
<thead>
<tr>
<th>Name</th>
<th>Department/Rank</th>
<th>Subsequent Funding</th>
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<tbody>
<tr>
<td>Hoda Badr, PhD</td>
<td>Assistant Professor, Oncologic Sciences</td>
<td>American Cancer Society CDA; NCI R03</td>
</tr>
<tr>
<td><strong>Abraham A Brody, RN, PhD</strong></td>
<td>Assistant Adjunct Professor, Geriatrics</td>
<td>NPCRC CDA</td>
</tr>
<tr>
<td>Melissa Garrido, PhD</td>
<td>Assistant Professor, Geriatrics</td>
<td>VA Career Development Award</td>
</tr>
<tr>
<td>Laura Gelfman, MD, MPH</td>
<td>Assistant Professor, Geriatrics</td>
<td>NIA Career Development Award-pending</td>
</tr>
<tr>
<td>William Hung, MD, MPH</td>
<td>Assistant Professor, Geriatrics</td>
<td>AHRQ Career Development Award</td>
</tr>
<tr>
<td>Amy Kelley, MD, MSHS</td>
<td>Assistant Professor, Geriatrics</td>
<td>Beeson/NIA Career Development Award</td>
</tr>
<tr>
<td>Fred Ko, MD, MSCR</td>
<td>Assistant Professor, Geriatrics</td>
<td>NIA Career Development Award-pending</td>
</tr>
<tr>
<td>Katherine Ornstein, PhD</td>
<td>Assistant Professor, Geriatrics</td>
<td>NIA Career Development Award</td>
</tr>
<tr>
<td>Smith, Cardinale, MD, MSCR</td>
<td>Assistant Professor, Geriatrics</td>
<td>CTSA KL2 grant; American Cancer Society CDA</td>
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</tbody>
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IV. Publications

2014


Roza, KA, Lee EJ, Meier DE, Goldstein NE. A Survey of Bereaved Family Members to Assess Quality of Care on a Palliative Care Unit . J Palliat Med. (In review)

Nathaniel JD, Garrido MM, Chai E, Goldstein, NE. Cost-Savings Associated with an Inpatient Palliative Care Unit: Results from the First Two Years. JAMA Internal Medicine (In review)


Hung WW. Declining adverse-event rates among patients with cardiac conditions but not with pneumonia or surgical conditions. J Clin Outcomes Manage (in press)


Tschirhart EC, Du Q, Kelley AS. Factors Influencing the Use of Intensive Procedures in the Last 6 Months of Life. (manuscript revised & resubmitted under review).

Ornstein K, Aldridge MDC, Garrido MM, Kelley AS. Hospice Use at End of Life Decreases Depressive Symptoms in Surviving Spouses. (manuscript in preparation)

Cooper Z, Mitchell SL, Gorges RJ, Rosenthal RA, Kelley AS. The impact of major emergency abdominal surgery on functional status in older patients: Data from the Health and Retirement Study. (manuscript in preparation)


Nathaniel JA, Garrido MM, Chai EJ, Goldstein NE. Cost-Savings Associated with an Inpatient Palliative Care Unit: Results from the First Two Years. *JAMA Internal Medicine.* Under review.


Gelfman LP, Aldridge M, Moore S, Murtaugh CM, Goldstein NE. A Descriptive Analysis of Hospice Use for Older Patients with Heart Failure. In Preparation.


Gelfman LP, Aldridge M, Morrison RS, Goldstein NE. The Impact of Palliative Care on the Healthcare Utilization and Cost of Hospitalized Adults with Heart Failure. In Preparation.


Ornstein, K., Teresi, J., Ocepek-Welikson, K., Ramirez, M. Meier, D., Morrison, R.S., & Siu, A. Use of an item bank to develop two short-form FAMCARE scales to measure family satisfaction in the setting of serious illness. Journal of Pain and Symptom Management, under review.


Ornstein, K., Aldridge, M., Garrido, M., Gorges, R. & Kelley, A. Hospice use for patients with serious illness decreases depressive symptoms in surviving spouses, In preparation

Ornstein, K. Leff, B. Roberts, L., Covinsky, K., Federman, A., Ritchie, C. & Szanton, S. Determining the prevalence of the homebound elderly in the U.S. using the National Health and Aging Trends Study (NHATS), in preparation


Ornstein, K., Teresi, J., Yeh, V., Schnur, J. Morrison, RS., Meier, D, Siu, A. Measuring family satisfaction in the setting of advanced cancer. In Preparation

Ornstein, K., Teresi, J., Ocepek-Welikson , K., Ramirez, M. Meier, D., Morrison, R.S., & Siu, A. Use of an item bank to develop two short-form FAMCARE scales to measure family satisfaction in the setting of serious illness. Journal of Pain and Symptom Management, under review.


V. External Advisory Board

The EAB consists of the following individuals:

1. Christine Ritchie, MD, MSPH - Harris Fishbon Distinguished Professor in Clinical Translational Research and Aging in the Division of Geriatrics, Department of Medicine at the University of California San Francisco (UCSF). (4 years)

2. Vincent Mor, PhD - Florence Pirce Grant Professor of Community Health in the Public Health Program of the Brown University School of Medicine. (4 years)

3. Jay Magaziner, PhD - Department Chair and Professor of Epidemiology and Preventative Medicine and Director, Division of Gerontology at University of Maryland School of Medicine (4 years)

4. Arnold Potosky, PhD - Professor of Oncology, Director of Health Services Research, Cancer Control Program, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC (3 years)
Mount Sinai OAIC

Recognition and Awards 2014

• Nathan Goldstein, MD – Received the AΩA (Alpha Omega Alpha) Leadership Award: a $25,000, one-year award to recognize and support further development of outstanding physician leaders. May, 2014.

• Brookdale Department of Geriatrics and Palliative Medicine – Our Department, in collaboration with Visiting Doctors, under Albert L. Siu, MD’s direction, has been awarded the Health Care Innovation Award - with an estimated funding amount of $9,619,517 - for the project, "Bundled Payment for Mobile Acute Care Team Services."

• Katherine Ornstein, PhD, MPH – Junior Faculty Career Development Award for “Downstream Effects of End-of-Life Patient Treatment Intensity on Spouses.” National Palliative Care Research Center May 1, 2014.

• Sara Bradley, MD and Ula Hwang, MD – Winners of the 2014 Excellence in Teaching Awards from the Institute for Medical Education (IME), for “outstanding achievement in teaching, and meaningful contributions to the educational activities at Mount Sinai and its affiliate hospitals.” April 16, 2014 (announced) May 22, 2014 (ceremony)

• R. Sean Morrison, MD – Won the American Cancer Society’s 2014 Clinical Research Professor's Award. This Award goes to investigators who have made seminal contributions in the area of cancer control that have changed the direction of clinical, psychosocial, behavioral, health policy or epidemiologic cancer research. March, 2014

• Brookdale Department of Geriatrics and Palliative Medicine – We have retained our #1 position in U.S. World and News Report’s Best Medical School Rankings for the fourth year in a row.

• William Hung, MD, MPH (PI); Courtney Dunn, LMSW; Emmadame Onyeobia, RN; Kenneth Boockvar, MD – Received a $260,655 grant from the VA to continue implementation for adapting care transition intervention to primary care setting (Patient Aligned Care Teams). October, 2013 – September, 2014.

• Ula Hwang, MD, MPH (Co-PI); William Hung, MD, MPH (Co-PI); Kenneth Boockvar, MD – Received a $189,466 grant from the VA to implement clinical decision support tools to improve prescribing in ED for older adults. October, 2013 – September, 2014.

• William Hung, MD, MPH; Judith L. Howe, PhD; Kenneth S. Boockvar, MD; Albert L. Siu, MD, MSPH – Received a $1.04 million grant from the VA to expand GRECC Connect, a project to educate and provide clinical support to rural providers to improve geriatric care. Bronx/NY Harbor GRECC will lead as the coordinating center for the project. Participating sites include Madison, WI; Rochester, NY; Seattle/Puget Sound, WA and Pittsburgh, PA, with newly-added sites New Bedford/Boston, MA; Durham, NC and San Antonio TX.
• Katherine Ornstein, PhD, MPH- Received an NIA Career Development Award for “Downstream Effects of End-of-Life Patient Treatment Intensity on Family Members.” September 15, 2014.

• William Hung, MD, MPH- Received an AHRQ Career Development Award for “Hospital Adoption of Models of Care and Practices for Older Adults and Its Impact.” September 1, 2014.
I. Description of Center

The theme of the Arkansas OAIC at UAMS is “Translational research on cardiac and skeletal muscle dysfunction in aging and disease.”

The main goals of the Arkansas OAIC are 1) To promote research that will both provide a mechanistic understanding of the basis for declining skeletal muscle function and myocardial performance with advancing age and translate what is learned from those studies to intervention studies that will ultimately affect nutritional recommendations and standard of care in the elderly; 2) To introduce state-of-the-art methodologies for studying protein metabolism to better enable basic molecular-based studies to ultimately translate the findings to the performance of clinical trials aimed at improving outcomes in elderly individuals; 3) use novel nutritional interventions in the prevention and treatment of cardiac and skeletal muscle weakness; 4) To train a new generation of geriatricians and gerontologists in improving functional independence of older Americans through therapeutic nutritional interventions. These goals will be achieved via the following Specific Aims.

Specific Aim 1. Provide scientific, intellectual, and innovation leadership among UAMS investigators.

Specific Aim 2. Stimulate translation between basic and clinical research through collaboration and interaction among investigators to improve our understanding of mechanisms contributing to declining skeletal muscle function and myocardial performance with age. Interventions will include, but not be limited to, therapeutic nutrient supplementation.

Specific Aim 3. Stimulate incorporation of emerging technologies and novel methods and approaches in analyzing protein metabolism and nutritional interventions for cardiac and skeletal muscle weakness.

Specific Aim 4. Serve as a source of advice and collaboration to other institutions (especially OUHSC and other OAICs) regarding technology and expertise in the center theme of the proposal and facilitate multi- and interdisciplinary strategies.

Specific Aim 5. Provide career development for future research leaders by increasing the recruitment of young and established investigators in aging, while emphasizing recruitment of minorities to UAMS.

Specific Aim 6. Expand the research outreach to maximally include minority representation in all studies.

This research will broaden our understanding of weakness of the cardiac and skeletal muscles that occurs as a result of aging or age-related diseases. We will also design methods to prevent and treat this weakness with nutrient supplementation, therapeutic nutrition and/or other interventions and improve the cardiac and skeletal muscle health of seniors. This OAIC will be instrumental in training the next generation of researchers in translational aging research to improve the functional independence of older Americans.
II. Research, Resources and Activities

II.A. Leadership Administrative Core

Jeanne Y. Wei, M.D., Ph.D., Leader
501-603-1261 (phone) 501-686-5884 (fax) weijeanne@uams.edu

Robert R. Wolfe, Ph.D., Co Leader
501-526-5708 (phone) 501-686-8025 (fax) rwolfe2@uams.edu

The LAC provides overall organization of the Arkansas OAIC, administrative infrastructure, and fosters collaboration among scientific, technical, and administrative staff. The LAC aims are to continuously direct and support the OAIC via strong leadership that helps accomplish the Arkansas OAIC goals. This has been achieved by constant, collegial communication among scientists and staff. OAIC leaders have worked hard towards ensuring that the goals are met and the cores remain focused on the OAIC theme. The LAC has fulfilled these responsibilities by reviewing the OAIC’s allocation and use of resources, assessing scientific opportunities for new uses of resources and developing plans to utilize, assess and plan collaborative research activities, and support review of developmental projects and exploratory studies and salaries of junior faculty. Ensuring that emphasis is placed on translation of basic research findings into clinical research within each core and basic research project remains a major objective of the LAC.

Progress towards LAC Specific Aims:

Specific Aim 1: The LAC has provided administrative support and fiscal management, including oversight of resource use and reallocation as needed; it has encouraged scientists to realize the potential for translation from basic to clinical research and to coordinate OAIC activities, including training and other center grants. The LAC has organized and conducted all committee meetings and review groups, ensuring that at least one-third of advisory panel reviewers are external to UAMS, and invited ad hoc reviewers to maintain program excellence and innovation. The LAC attended and participated in the annual National Pepper Center Meeting in Bethesda in 2015.

Specific Aim 2: The LAC has reviewed OAIC scientific progress, monitored regulatory compliance by OAIC-sponsored projects, and ensured that OAIC PI’s submit the annual reviews. The LAC has reviewed resource use with core leaders and monitored the progress of all the pilot projects to date. The LAC has convened annual meetings of the External Advisory Board and the Data Safety Monitoring Board in Arkansas. The LAC also prepared the progress reports (i.e., NIA, External Advisory Committee, DSMB) and ensured that the OAIC advised the scientific community about technology, methodology, analysis, and research training.

Specific Aim 3: The LAC has helped develop internal and external collaborations by providing access to Arkansas OAIC cores, particularly the nationally unique Analytical Core (RC3). New collaborations have been developed with the University of Arkansas at Fayetteville. The Arkansas OAIC website features ongoing research projects, interests, break-through results, Pepper Center conferences and activities. The LAC also collaborates closely with the UAMS Translational Research Institute and the UAMS Clinical and Translational Science Award to ensure effective leveraging of NIH funds.

We assisted the UAMS TRI in submitting the 5-yr, competing NIH CTSA application, and Dr. C Beck, a senior faculty member of the Geriatrics Dept, served as the CTSA’s Co-PI; Our Dept submitted 21 extramural grant applications in 2014-15; We are a member in the NIH-funded GeroScience Network, which is comprised of 12
academic medical centers in the US & four medical centers from across Europe, to jointly facilitate translational aging research from basic to clinical, to promote human longevity. There are currently only six of the 141 US medical schools that have both an NIH-funded Pepper Center and membership in the NIH GeroScience Network: Johns Hopkins Med Center, University of Michigan Medical Center, UTMB, Wake Forest, Duke, and UAMS. We are members in the NIH-PCORI awarded grant to the national Pepper Centers consortium, on falls prevention in the elderly, the STRIDE study.

Specific Aim 4: The LAC has overseen career development activities of trainees in the RCDC and also ensured that the pilot/exploratory studies are relevant to the theme of OAIC and related to research on aging. LAC has organized a mentoring committee of UAMS faculty for students and junior faculty and facilitated training opportunities for PI’s across diverse disciplines. LAC also oversees training of investigators in the use of the database that has been developed, called the Clinical Trials Management Suite (CTMS), a clinical and translational research informatics infrastructure based on National Cancer Institute funded Biomedical Informatics Grid (caBIG) tools and standards. It is also partly supported by the UAMS Clinical and Translational Science Award (CTSA). UAMS is the leading institution in the nation for implementation of such tools/standards and received several awards.

Specific Aim 5: The LAC has overseen the development of an electronic OAIC subject registry to facilitate recruitment of study subjects into Institutional Review Board (IRB)-approved Arkansas OAIC studies. The LAC also facilitates the development of an electronic database for data management of the Pepper-supported studies. It oversees and coordinates weekly database management meetings among the investigators and study coordinators to ensure that the electronic forms are tested and validated and that the data are being uploaded and maintained properly.

The LAC also organized and coordinated a Community Advisory Board for the Pepper Center that has been meeting monthly and has provided outreach into the community for dissemination of research and provided assistance with subject recruitment and active participation.

LAC has also prioritized recruitment of subjects among protocols, facilitated subject screenings by study physicians for OAIC researchers and maximized subject retention. LAC ensures that at least one of the OAIC investigators also participates as needed as members of the UAMS IRB committees and also ensures strict IRB compliance by all OAIC investigators.

Our faculty serve as mentors for many trainees, both locally at UAMS and around Arkansas, and nationally. In the nationally competitive Association For Aging Research (AFAR) Medical Student in Aging Research (MSTAR) program, we are currently mentoring two COM student awardees (S Rogers and S Foster); We are also mentoring eight medical students (one M-4, five M-3s and two M-2s) in the UAMS COM Honors Research Program, and we are optimistic that some of them will pursue aging research in the future.

We hold monthly campus-wide Pepper Center Seminars where scientists present their aging research updates. We are also helping faculty at Harding U (Dr. Sipe) to submit a R15 proposal to use velocity training for maximizing strength & function in older persons.

With faculty in the COM Department of Bioinformatics (Dr. Topaloglu), we have established a total online database management system, the Comprehensive Research Informatics Suite (CRIS), for studies in our NIA-funded P30, “Arkansas OAIC at UAMS” and for others. We are collaborating with UAMS Department of Pediatrics and the USDA in Arkansas (Drs. Borsheim and Adams) to improve hepatic lipid metabolism in older pts with hyperglycemia or hypertriglyceridemia, and will submit a R01 proposal to NIA. We are collaborating
with Dr. Allen of the College of Pharmacy to study cardiovascular contributors to cognitive aging, and will submit a R01 to NIA.

II.B.  RC-1: Biostatistics Core

Paula K. Roberson, Ph.D., Core Leader  
501-296-1556 (phone)  501-526-6729 (fax)  robersonpaula@uams.edu

Umit Topaloglu, Ph. D., Co Leader  
501-686-5303 (phone)  501-686-5300 (fax)  UTopaloglu@uams.edu

Progress towards RC1 Specific Aims:

SA1: Dr. Roberson and Ms. Schrader continued to meet with new pilot investigators and other Pepper Center members to provide input into the development of pilot project protocols as well as other aging-related research projects. This input includes not only development of sample size and power calculations, but overall study design considerations, since the power/sample size calculations, data analysis plans, and study design are all integrally related. They worked extensively with pilot investigators to develop data analysis plans for their projects. They have been meeting regularly with Dr. Cody Sipe of Harding University and other senior Pepper Center Investigators (Wei, Ferrando, and Azhar), to plan and develop an R15 application titled “Effects of Very High Speed Training on Mobility-Limited Older Adults,” planned for submission in June 2015. Dr. Sipe is a former Pepper Pilot awardee. Dr. Roberson also participated in the review of pilot award applications.

Dr. Topaloglu and Ms. Rodgers have been working on utilizing Comprehensive Research Informatics Suite (CRIS) for studies led by Pepper Center members. There are currently 16 studies in the CRIS and 13 of 16 have been moved to production, with the remaining 3 are in test system and waiting user acceptance to be moved to production. There are additional 4 new studies in regulatory approval process that are being developed in CRIS to make them ready when approvals are obtained. In addition to creating studies in participant management tool (C3PR) and creating questionnaires in LimeSurvey and/or Case Report Forms (CRFs) in OpenClinica, the data management team has imported new data into CRIS for a study. The Arkansas Claude D. Pepper Older Americans Independence Center Participant Recruitment Registry (APRR) has been the first protocol started in CRIS and currently it has 112 people registered.

SA2: The statistical data analysis effort has increased this year as more projects complete data acquisition and move into the analysis phase. Analyses of several projects are nearing completion and manuscripts are being drafted. For example, analyses are complete for the pilot award made to Dr. Sipe, a manuscript is in preparation, and some of these results are included as preliminary data in Dr. Sipe’s upcoming R15 application. The Biostatistics Core also assisted with poster layout and data analysis for a medical student who presented data from this study, in which he participated, for the annual UAMS Student Research Day.

The Core has continued to support data management for existing studies as well as moving new studies into CRIS to allow data collection/study conduct in a secure and standard based system. The CRIS is currently interfaced with Epic (UAMS’ EMR system) and the patients’ demographics are imported and enrollment details for those who are in one of the 13 studies are sent to Epic from our participant registry. Furthermore, the lab results of those participants are also being imported to CRIS from Epic. The interface with Epic will continue to work in real time bases.

The following studies are currently in CRIS:

1. The Development of a Geriatric Data Registry
2. The South-Central Study of Aging: The Arkansas Centenarian Study (in test)
SA3: Most of the educational activities in biostatistics and data management have been informal in nature, occurring in discussions, either one-on-one, or in small groups, as a part of discussions regarding project planning, protocol development and review, grant application development, database development, and review of analytic results. Drs. Roberson and Topaloglu participated in the annual national Pepper Center meeting in April 2015 and presented a poster about the CRIS and its use among the Pepper Center researchers. Both Drs. Roberson and Topaloglu attend the monthly research seminars and presented a core update and information session in the January seminar. They also participate in the monthly administrative meetings of the center.

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Publications:

The following publications have received support from RC1:


4. Christine Rodgers, Umit Topaloglu Ph.D., Paula Roberson, Ph.D., Gohar Azhar, M.D., Arny Fernando, Ph.D., Robert Wolfe, Ph.D., Jeanne Y. Wei, M.D., Ph.D., Comprehensive Research Informatics Suite (CRIS) for Aging Research, Claude D. Pepper Older Americans Independence Centers (OAIC) 2015 annual meeting


II.C. RC-2: Nutrition, Metabolism, and Physiology Core

Arny Ferrando, Ph.D., Leader
501-526-5711 (phone) 501-686-8025 (fax) aferrando@uams.edu

Gohar Azhar, M.D., Co Leader
501-526-5821 (phone) 501-686-5884 (fax) azhargohar@uams.edu

Dennis Sullivan, M.D., Co Leader
501-257-2503 (phone) 501-257-2501 (fax) sullivandennish@uams.edu

The RC2 provides expertise, instrumentation, training, and evaluation in support of translational research.

Progress towards RC2 Specific Aims:

Specific Aim 1: There are currently 10 ongoing research protocols (designated by (A)) out of the 24 supported to date by this aim of RC2 (see table). Protocols require functional tests, as well as nutritional and metabolic evaluations. We have hired a dietician, Amanda Dawson, MS, RD who is able to provide close oversight and control of nutritional studies.
<table>
<thead>
<tr>
<th>Investigator</th>
<th>Project Title</th>
<th>Sponsor</th>
<th>Core Support Provided</th>
<th>RC2 Specific Aim(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrando, AA</td>
<td>Dairy Macronutrient Effects on the Metabolic Syndrome</td>
<td>Dairy Research Institute</td>
<td>Body composition, nutritional assessment, functional measures, glucose metabolism</td>
<td>1 and 2</td>
</tr>
<tr>
<td>Ferrando, AA (A)</td>
<td>Effect of Dietary Protein Intake Distribution on Protein Metabolism and Skeletal Muscle</td>
<td>Dairy Research Institute, Egg Nutrition Center, National Cattlemen’s Beef Association</td>
<td>Body composition, metabolic kitchen, functional measures, protein metabolism</td>
<td>1, 2, and 3</td>
</tr>
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<td>Ferrando, AA (A)</td>
<td>Effect of bimagrumab in older adults with sarcopenia</td>
<td>Novartis Institute for BioMedical Research</td>
<td>Body composition, functional measures, blood biomarkers, questionnaires</td>
<td>1, 2, and 3</td>
</tr>
<tr>
<td>Ferrando, AA (A)</td>
<td>Overcoming TWEAK signaling to Fully Restore Muscle Mass and Mobility Function after Total Joint Arthroplasty</td>
<td>NIH 1R01HD084124-01 (Co-I)</td>
<td>Protein metabolism</td>
<td>2 and 3</td>
</tr>
<tr>
<td>Ferrando, AA (A)</td>
<td>The Benefits of Egg for Breakfast</td>
<td>Egg Nutrition Center</td>
<td>Body composition, nutritional assessment, functional measures, protein metabolism</td>
<td>1, 2, and 3</td>
</tr>
<tr>
<td>Ferrando, AA (A)</td>
<td>Tolerance of Enteral Formulas</td>
<td>Nestle Healthcare Nutrition</td>
<td>nutritional assessment</td>
<td>1 and 3</td>
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<tr>
<td>Borsheim, E (A)</td>
<td>Effects of amino acids on regional lipid metabolism</td>
<td>NIH R01 AG033761</td>
<td>Body composition, blood biomarkers, fat, glucose, and protein metabolism</td>
<td>1, 2, and 3</td>
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<tr>
<td>Name</td>
<td>Title</td>
<td>Funding</td>
<td>Research Focus</td>
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<td>Lefler, LL</td>
<td>A Lifestyle Physical Activity Intervention for Older, Sedentary Women</td>
<td>NIH/National</td>
<td>Assessment of Activity</td>
<td>1</td>
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<td>Institute for</td>
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<td>Nursing Research</td>
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<td>Wolfe, RR (A)</td>
<td>Is there a maximal anabolic response to beef intake?</td>
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<td>metabolic kitchen, protein metabolism</td>
<td>1, 2, and 3</td>
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<td></td>
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<td>Cattlemen’s</td>
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<td>Beef Association</td>
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<tr>
<td>Wolfe, RR</td>
<td>Lysine Supplementation and Glucose Metabolism</td>
<td>TRI Pilot Grant</td>
<td>Stable Isotope Analysis, glucose metabolism</td>
<td>1, 2, and 3</td>
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<td>Baxter Laboratories</td>
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<td>Fram, R and Sipe, C</td>
<td>Relationship of BMI, musculoskeletal performance and functional capacity in older patients with CHF</td>
<td>OAIC Pilot</td>
<td>Body composition, functional measures, echocardiogram</td>
<td>1, 2, and 3</td>
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<tr>
<td>Baum, J</td>
<td>The role of leucine and ω-3 fatty acids in skeletal muscle function during aging</td>
<td>OAIC Pilot</td>
<td>Nutritional counseling, cellular metabolic studies, amino acid analyses</td>
<td>1, 2, and 3</td>
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<tr>
<td>Washington, T</td>
<td>The Effect of Leucine Supplementation on Aged Skeletal Muscle Regenerative Capacity</td>
<td>OAIC Pilot</td>
<td>Metabolism, Physiology counseling, amino acid analyses</td>
<td>1, 2, and 3</td>
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<tr>
<td>Csiszar, A</td>
<td>Improvement of cardiovascular function in rats by arginine supplementation</td>
<td>OAIC Pilot</td>
<td>Cardiac function by Doppler echocardiogram</td>
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<td>Singh, S</td>
<td>Modulation by 4-hydroxynonenal (4-HNE) of the phosphorylation status of acetyl-</td>
<td>OAIC Pilot</td>
<td>Harvest of mouse tissues; body composition, echo-</td>
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<tr>
<td>Name</td>
<td>Research Topic</td>
<td>Study Type</td>
<td>Notes</td>
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<td>CoA carboxylase (ACC)</td>
<td>CoA carboxylase (ACC) as a determinant of ectopic fat levels in mouse skeletal</td>
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<td>Hauer-Jensen, M</td>
<td>Arginine supplementation reverses muscle wasting due to deficient de novo</td>
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<td>Training in aging research</td>
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<td></td>
<td>arginine synthesis</td>
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<td>Functional Outcomes in CHF patients, with protein intake</td>
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<tr>
<td>George, M</td>
<td>Biologic Factors Influencing Cachexia in the Elderly</td>
<td>OAIC Pilot</td>
<td>Stable isotope determination of amino acid turnover</td>
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<tr>
<td>Ayyadevara, S</td>
<td>Role of amino-acid deficiency in aging-related muscle atrophy</td>
<td>OAIC Pilot</td>
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<tr>
<td>Todorova, V</td>
<td>Transcriptional analysis of anthracycline-induced cardiotoxicity in elderly</td>
<td>OAIC Pilot</td>
<td>Cardiac function by Doppler echo-cardiogram</td>
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<td></td>
<td>cancer patients</td>
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<tr>
<td>Kim, IL-Young</td>
<td>Effect of Citrulline Ingestion on Peripheral Vascular Function</td>
<td>OAIC Pilot</td>
<td>Training in clinical aging research, blood flow measures</td>
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</tr>
<tr>
<td>Nick Hurron (A)</td>
<td>The effects of essential amino acids on lipid and glucose metabolism in type 2</td>
<td>OAIC Pilot</td>
<td>Stable Isotope Analysis, glucose metabolism, lipid</td>
<td></td>
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<tr>
<td></td>
<td>diabetes</td>
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<td>metabolism, amino acid metabolism</td>
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<td>1, 2, and 3</td>
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<tr>
<td>Rtika, Abraham (A)</td>
<td>Nutritional therapy for autonomic dysfunction in the elderly HF patients</td>
<td>OAIC Pilot</td>
<td>Training in clinical aging research, Blood pressure and heart rate</td>
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</table>
Specific Aim 2: Five of the active studies employ skeletal muscle biopsies and/or stable isotopes to evaluate macronutrient metabolism. RC2 also assists with analysis of body composition and coordination with the metabolic kitchen for all the projects. Four projects are focusing on interventional effects on skeletal and/or cardiac functional outcomes.

Specific Aim 3: Training opportunities are available to investigators at all times for their specific protocols.

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Specific Aim</th>
<th>Methodology</th>
<th>Training</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foster, Stephen</td>
<td>Use of a capillaroscope to evaluate circulation and predict CAD in seniors</td>
<td>Capillaroscopy, functional evaluations, LIME data collection</td>
<td>MSTAR</td>
<td>1,2</td>
</tr>
<tr>
<td>Picetti, Dominic</td>
<td>Strength and cardiovascular stress assessment in transgenic mouse models of heart failure. Evaluation of nutrition &amp; hydration in seniors</td>
<td>Grip strength, treadmill testing mouse models, Nutritional assessment LIME data collection</td>
<td>Pepper junior scholar</td>
<td>1,2</td>
</tr>
<tr>
<td>Price, Elvin</td>
<td>Effect of gene polymorphisms on body composition and response to heart failure medications</td>
<td>Body composition, functional evaluations</td>
<td>KL2 scholar</td>
<td>1,2</td>
</tr>
<tr>
<td>Raza, Sakeena (A)</td>
<td>Improvement in functional capacity of obese elderly with heart failure</td>
<td>Training in clinical aging research, Functional Outcomes in Obese CHF patients, exercise and protein intake</td>
<td>OAIC Pilot</td>
<td>1,2 and 3</td>
</tr>
</tbody>
</table>
For example investigators new to functional assessments are being co-mentored by Drs. Ferrando, Azhar or Wei. Investigators new to nutritional evaluations and metabolism are being co-mentored by Drs. Ferrando or Wolfe. Translational research opportunities are available to all investigators conducting bench research. The monthly OAIC meetings have been successful in bringing together investigators with varied backgrounds, expertise and interests, and have encouraged new collaborations. For example, Dr. Cody Sipe, from nearby Harding University, and our Cardiology Fellow, Dr. Ricky Fram, have collaborated with Drs. Ferrando, Wolfe, and Azhar on pilot project investigating CHF patients’ performance on the CSPFP-10. In addition, young investigators from the University of Arkansas at Fayetteville (Drs. Baum and Washington) have been awarded pilot projects testing nutritional optimization in aging muscle cells and the rodent skeletal muscle. Dr. Elvin Price, a KL2 scholar from the Arkansas CTSA, is an investigator new to aging research, and has been working with Drs. Wei and Azhar to incorporate functional assessments in his research on pharmacogenomics in the elderly. Dr. Masil George and Sakeena Raza are junior level geriatricians who have pilot projects examining the effect of exercise and nutrition on cardiac and functional outcomes in patients. A number of our Pepper Scholars are conducting LIME surveys and collecting data on nutritional and functional health data in older adults. These data are being deposited in our state-of-the-art, computerized research informatics suite, CRIS and this will facilitate linkage to other studies. One of our junior Pepper scholars, Stephen Foster recently received a MSTAR award for a novel study using a capillaroscope for the prediction of coronary artery disease in an outpatient setting in seniors. Another Pepper scholar, Dominic Picetti is working in the laboratory for evaluation of physiological cardiovascular and skeletal muscle function in our cardiac-specific, transgenic mouse model of heart failure with preserved ejection fraction with mild over-expression of serum response factor, as well as other models. Finally, Dr. Elisabet Borsheim, from Arkansas Children’s Hospital and the USDA Children’s Nutrition Center has joined our group and is investigating lipid and amino acid metabolism in hyperlipidemic patients through her RO1 project.

**Major activities** include the ongoing support of the above active protocols and the concomitant mentorship and training inherent in studies conducted by junior faculty.

**Significant Results/Findings:** Within the last year, the following summarizes important findings resulting from work supported by RC2:

1. In a recent paper, one of our pilot awardees (Kim) recently demonstrated that contrary to a popular belief, the total protein intake, and not the intake pattern, was the primary determinant of anabolism in an older population (Kim, Il-Yong, Schutzler, S.E., Schrader, A., Spencer, H., Kortebein, P., Deutz, NEP, Wolfe, R.R., *Ferrando, A.A.* Quantity of dietary protein intake, but not pattern of intake, affects net protein balance primarily through differences in protein synthesis in older adults American Journal of Physiology: Endocrinology and Metabolism 308:E21-E28, 2015).

2. With a poster presentation at Experimental Biology 2014, Dr. Kim demonstrated that that aging reduces nitric oxide (NO) synthesis. However, the decrease in NO synthesis was not attributed to limited availability of citrulline but instead to the inability to synthesize NO via nitric oxide synthetase.

3. In another poster presentation at Experimental Biology 2015, Dr. Kim demonstrated that whole body net protein accretion was increased with a protein intake above the previously accepted “optimal” protein intake primarily through further reductions in protein breakdown.

4. At our UAMS Showcase of Medical Discoveries, we presented evidence that TPN infusion of amino acids in patients with head and neck cancer improves whole body net protein accretion through increases in protein synthesis. Further, it was demonstrated that concomitant infusion of insulin/glucose infusion resulted in no further improvement.
Other achievements:

The following publications have received support from RC2:


11. Volpi E, Campbell WW, Johnson MA, Jensen GL, Morley J, Wolfe RR. Is the Optimal Level of Protein Intake for Older Adults Greater Than the Recommended Dietary Allowance? PMCID: PMC3660117


13. Zivkovic AM, Bay C, Cree-Green M, Wolfe RR, Walzem RL. Acylcarnitines and flux through the β-oxidation pathway: fuel utilization and switching in response to an oral glucose tolerance test in young normoglycemic and elderly subjects with impaired vs. normal glucose tolerance (Submitted for publication).


17. Wolfe RR. Implications of the age-related loss of muscle mass, strength, and function. Aging Health [Review], IN PRESS.


40. Emmanuel D. Williams, Steven C. Rogers, Xiaomin Zhang, Gohar Azhar, Jeanne Y. Wei. Elevated Oxygen Consumption Rate in Response to Acute Low- Glucose Stress: Metformin Restores Rate to Normal Level (under review Experimental Gerontology, 2015).

41. Azhar, Gohar; Wei, Jeanne Y , Ashcraft, Kristine Neradilek, Moni B; Newman, Richard L; Pacleb, Chelsea; Moyer, Nicolas; Sass, Rachel. Differences in Medicare quality measures among nursing homes before and after initiation of routine referral of long-term care residents for pharmacogentic testing (Current Geriatrics and Gerontology Research, in review, 2015)

II.D. RC-3: Analytical Core

Robert Wolfe, Ph.D.
501-526-5708 (phone) 501-686-8025 (fax) rwolfe2@uams.edu

Elisabet Borsheim, Ph. D.
501-364-3053 (phone) 501-364-2818 (fax) eborsheim@uams.edu

Progress towards RC3 Specific Aims:
Specific Aim 1. Provide analytical support for RCDC investigators and pilot projects that utilize stable isotope tracers.

In this reporting period, the following peer-reviewed publications reporting results supported by analyses provided by the core, document our success in this area.


10. Morio B, Wolfe RR. Ketone Bodies. eLS 1-10, 2015. DOI: 10.1002/9780470015902.a0003819.pub2


Review articles and text chapters since previous report:


Articles Submitted or In Press since previous report:

1. Zivkovic AM, Bay C, Cree-Green M, Wolfe RR, Walzem RL. Acylcarnitines and flux through the β-oxidation pathway: fuel utilization and switching in response to an oral glucose tolerance test in young normoglycemic and elderly subjects with impaired vs. normal glucose tolerance. SUBMITTED.

2. Coker RH, Schutzler S, Deutz, NE, Miller S, Wei J, Wolfe RR, Nutritional formulation comprised of essential amino acids, protein and phytosterol reduces risk factors for metabolic disease in overweight individuals with mild hyperlipidemia, Nutr Med Card Disease, IN REVIEW.


Specific Aim 2. Support the development and execution of innovative pilot projects related to muscle metabolism.
In the past year, one new pilot project (Nicholas M. Hurren, PhD) has been initiated that will use stable isotope tracers to investigate muscle metabolism in humans. In addition, the projects of Il-Kim Young, PhD, Tyrone Washington, PhD and Jamie Baum, PhD are continuing. All these projects deal directly with muscle metabolism. In the current year, several of these projects will transition from cell culture and mice to human studies. Drs. Wolfe and Borsheim have been actively working with other potential young investigators to develop submissions for pilot projects that will study various aspects of muscle metabolism using stable isotope tracers.

Specific Aim 4. Develop young investigators in the field of muscle metabolism and aging.
Efforts have been successful to recruit young investigators within the institution, and to also expand our base of young investigators throughout the state of Arkansas. The Isotope Tracer Methodology course (see below) has provided a good pool of potential new investigators, and we have recently recruited Dr. II-Young (Neil) Kim via that route to be trained in the Geriatrics Department as an investigator in muscle protein metabolism in elderly. Dr. Cody Sipe is a recently appointed Assistant Professor at Harding University and is the recipient of a pilot project to test a new approach to quantifying functionality. As he develops skills in this area, stable isotope tracer studies of muscle metabolism will be incorporated into his project. As mentioned above, Drs. Tyrone Washington and Jamie Baum are young investigators in muscle metabolism who are both supported by pilot studies. As reported in previous progress report, Dr. Borsheim brought several young investigators to Little Rock, who are all working on projects relevant to aging. They are active participants in the Pepper Center. One of them, Nicholas Hurren, PhD, was awarded a Pepper Center pilot grant in this grant period, and two others (Eugenia Carvalho, PhD, and Leybi Ramirez, MD) have submitted projects for the next pilot grant cycle. They attend a weekly lab meeting of the Research Core, and meet individually with both Dr. Borsheim and Dr. Wolfe in addition.

**Specific Aim 5. Educate the scientific community regarding the *in vivo* applications of tracer methodology using stable isotopes in human subjects.**

Dr. Wolfe is the Course Director of the annual course on Isotope Tracer Methodology which we completed in Cleveland, Ohio in November 2014. Seventy six investigators attended the course, which consists of didactic lectures, workshops, and one-on-one sessions. The primary focus of the course is the performance of stable isotope tracer studies, including analysis of enrichment and calculations associated with relevant modeling.

**Specific Aim 6. Provide analytical support for externally funded research grants dealing with muscle metabolism and aging.**

A variety of studies have been supported that are either ongoing (listed in the table below) or completed (reflected by the list of publications above). Projects directly supported by this core are listed below.

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<tr>
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<td>Overcoming TWEAK signaling to fully restore muscle mass and mobility function after total joint arthroplasty</td>
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<td>Authors</td>
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<tr>
<td>Raastad, T &amp; Hamarsland, H</td>
<td>Effect of protein intake on muscle protein synthesis and breakdown after exercise</td>
<td>The Norwegian School of Sport Sciences</td>
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<tr>
<td>Ayyadevara, S</td>
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<td>Hurren, NM</td>
<td>Effects of essential amino acids on postprandial lipaemia</td>
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<td>Kim, IY</td>
<td>Effect of citrulline ingestion on peripheral vascular function</td>
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<td>Singh, S</td>
<td>Modulation by 4-hydroxynonenal (4-HNE) of the phosphorylation status of acetyl-CoA carboxylase (ACC) as a determinant of ectopic fat levels in mouse skeletal muscle</td>
<td>OAIC Pilot</td>
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<tr>
<td>Todorova, V</td>
<td>Transcriptional analysis of anthracycline-induced cardiotoxicity in elderly cancer patients</td>
<td>OAIC Pilot</td>
</tr>
<tr>
<td>Washington, T</td>
<td>The effect of leucine supplementation on aged skeletal muscle regenerative capacity</td>
<td>OAIC Pilot</td>
</tr>
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</table>

II.E. RCDC - Research Career Development Core

Gohar Azhar, M.D.  
501-526-5821 (phone)  501-686-5884 (fax)  azhargohar@uams.edu

Jeanne Y. Wei, M.D., Ph.D., Leader  
501-686-5303 (phone)  501-686-5884 (fax)  weijeanne@uams.edu

Specific Aim 1. Recruit postdoctoral fellows, junior faculty, and/or midlevel investigators who are interested in aging research within the OAIC theme to become independent investigators and future academic leaders.

We are very pleased to have recruited Il-Young Kim, Ph.D., as an RCDC trainee for year 4. Dr. Young is a junior researcher with an interest in muscle metabolism who has been working under the mentorship of Dr. Robert Wolfe. Dr. Young has been most productive during the past year and has 3 first author publications on protein and amino acid supplementation in the elderly and a number of other manuscripts in preparation.

Our second trainee for this year is Marquis Bryce Ph.D. Dr. Bryce is an analytical chemist who completed a post-doctoral training at the Bureau of Standards at Bethesda, Maryland. He also has a background in Nano-medicine and has used silver nanoparticle to study oxidative damage in Caenorhabditis elegans. We are fortunate and excited that Dr. Bryce has developed a strong interest in metabolomics and the field of aging science. He will be using
Dr. Raza’s pilot project entitled, “Improvement in Functional Capacity of Obese Elderly with Heart Failure” is still continuing with functional evaluations of subjects. The process has been a little slow because the class of heart failure with preserved ejection fraction (HFPEF) is a relatively new term, even for healthcare providers, but the project is expected to be completed by the end of the year. Dr. Raza’s educational booklet on heart failure is being used in the clinic and has received good reviews by patients and caregivers. Dr. Raza has a first author manuscript on anemia in the elderly in press and others in preparation. She is also collaborating with Dr. Abraham on the centenarian project. Dr. Todorova has been working on gene changes secondary to Adriamycin associated cardiomyopathy in elderly breast cancer patients. She also has a first author manuscript describing her results. Dr. Todorova has resubmitted an R21 on cardiomyopathy in elderly breast cancer patients. Dr. George has completed her project and is preparing the manuscript on the effect of protein intake and home-based exercise therapy for publication.

Specific Aim 2. Provide programmatic support for each trainee to develop research expertise on aging.

Dr. Il-Young Kim has an office adjacent to his mentor, Dr. Wolfe’s laboratory on the 7th floor. Dr. Price has his own laboratory space and office in the biomedical building within 200 yards of the Reynolds Institute. Dr. Abraham has an office on the 5th floor (the Pepper Center floor) of the Reynolds Institute on Aging, which is a designated space for OAIC researchers.

Drs. Raza, Todorova, George and Rogers have offices on the Pepper Center floor. In addition, the entire sixth floor houses over 14,000 square feet of new wet lab space devoted to Cardiovascular Aging Research. Drs. Todorova and Rogers have bench space in the laboratory on the 6th floor. Both offices are equipped with computers and printers. There are 2 tissue culture hoods available to the basic scientists, as well as a state of the art, fluorescent atomic force microscope with confocal imaging, laser capture microscope, Seahorse equipment for measuring mitochondrial respiration, real-time PCR equipment and other pertinent laboratory equipment for cellular and molecular biology.

In addition, the 3rd and 4th floors provide space for basic and translational research programs on aging, which includes nutrition, metabolism, and exercise laboratory, with research areas for investigators to measure the total amount of calories expended in a 24-hour period, body composition, and metabolism in humans. A research dietician, Amanda Dawson, is also available for the investigators 5 days a week. There is a large gym area, the Ottenheimer Fitness Center and the Rehabilitation Center as well as the Jackson Spine Center hydrotherapy facility for exercise training and a testing laboratory for measuring maximal and submaximal aerobic performance and muscle strength and function. Drs. Raza, George and Abraham are all utilizing the nutritional and gym facilities for their heart failure subjects. In addition, biochemistry laboratories are available for analyzing muscle, blood, and urine samples. The 3rd floor also has a cardiovascular physiology lab with Hokansen plethysmograph, a tilt table and echocardiographic equipment. The RCDC trainees conducting human studies have been trained in the use of all this equipment. A mass spectrometry laboratory is also available, manned by experienced technicians that permit investigators to use stable, nonradioactive tracers to examine metabolic responses to exercise and diet if needed. The state-of-the-art basic science laboratories are arranged in three clusters and the floors are interconnected, allowing scientists with common research interests to work closely together and to facilitate communication among trainees and other faculty members.

The second floor of the RIOA facility is devoted to outpatient services, cognitive impairment research, physical
fitness, rehabilitation therapy, occupational therapy and SeniorNet. Outpatient services include the Thomas and Lyon Longevity Center (TLLC), the Memory Research Clinic, and the Functional Independence Center. Patient evaluations and observations provide valuable insights into possible interventions to promote functional independence. The Heart Health Clinic is also housed on the 2nd floor and this facilitates recruitment, screening, education and functional evaluations of study subjects by the trainees under supervision of Drs. Azhar and Wei.

All RCDC trainees also have the support and back-up of research staff for IRB related issues, continuing reviews and/or audits. Two fully trained clinical trials coordinator, Amanda Pangle and Scott Schutzler assist new and junior faculty traverse the IRB regulatory requirements and ensure that all investigators are up-to-date and comply with the rules and regulations. In addition, the RCDC trainees also receive support from Dr. Umit Topaloglu and the bioinformatics team for seamless data entry into electronic databases such as CRIS and Open Clinical.

All our previous RCDC trainees have been progressing well. Dr. Masil George has completed testing the effect of nutritional supplementation and home-based exercise program on an OAIC funded pilot project and is writing the manuscript. Steven Rogers Ph.D. is working on his model of endothelial cell senescence in response to glucose stress. Dr. Mendiratta has continued to be productive but has changed her tenure to an educational track. Dr. Ricki Fram has completed her cardiology fellowship and is in private practice. Dr. Anna Csiszar has been promoted to Associate Professor at the University of Oklahoma, Reynolds Institute and continues to be extremely productive.

Specific Aim 3. Provide mentoring to foster career development with scheduled, structured evaluations.

Dr. Il-Young Kim meets with Dr. Wolfe’s and his group on weekly to discuss progress of the projects and more often as needed for guidance. He is also receiving support from Dr. Azhar for plethysmography, subject selection, and functional evaluations. In addition, he meets regularly with the biostatistics and informatics team led by Drs. Roberson and Topaloglu for data input and analysis. Dr. Young has presented twice at Pepper seminars, campus-wide aging seminars and also at a Pepper external review, which was well received.

Dr. Bryce’s primary mentor for his aging-related research on is Dr. Wolfe and secondary are Drs. Ferrando and Reis. He meets weekly with his mentors at the Reynolds Institute. He is provided support by the clinical coordinator for IRB by the Pepper Center as well as statistical and bioinformatics support.

Dr. Abraham’s primary mentor is Dr. Azhar and co-mentors are Drs. Wei and Robertson. There are structured research meetings with the primary mentor on a bi-weekly basis and with the other co-mentors on a monthly basis. Dr. Abraham also attends the research meetings at the endocrine division on campus related to aging. She will also meet with Dr. Roberson and their staff on an as-needed basis for assistance with statistical design and database development. She is acquiring expertise on the use of the tilt table for blood pressure hemodynamics and echocardiography under Dr. Azhar’s supervision. Dr. Abraham is currently in the process of choosing co-mentors from the department of endocrinology to augment the sphere of her research as geriatric endocrinologist.

Dr. Raza’s primary mentor is Dr. Azhar and co-mentors are Drs. Wei and Robertson. Her schedule is similar to Dr. Abraham’s and she attends biweekly research meetings with Drs. Azhar and Wei and is advised on biostatistics by Dr. Robertson and her staff. Dr. Raza also collaborates with RC2 investigators as their study physician and has acquired expertise in the technique of skeletal muscle and adipose tissue biopsies through RC2 core facilities. She has acquired training and expertise on the use of the Hokansen plethysmography. She is also acquiring training in 2-D doppler echocardiography. In addition, she has learned the methodology of nitric oxide western blotting. Dr. Raza has provided updates on the progress of her pilot study at the monthly Pepper Seminars.

Dr. Todorova’s primary mentor is Dr. Klimberg and co-mentors are Drs. Wei and Azhar. She meets with her mentor on a weekly basis and her co-mentors on a monthly basis. Dr. Todorova has presented her project updates at the Pepper seminars. Dr. Masil George’s primary mentor is Dr. Azhar and secondary mentors are Drs. Wei and Wolfe. Dr. George meets with Dr. Azhar on a weekly basis and her co-mentors on a monthly basis. She also recently gave an update on her research at a Pepper Center seminar.
Dr. Anna Csiszar primary mentor is Dr. William Sonntag and co-mentors are Dr. Rubenstein and Wei. She meets with her primary mentor on a weekly basis and co-mentors on a monthly basis. She also continues to attend the Pepper Center meetings via teleconferencing and provides project updates. She is also working on her Beeson award which provides her additional structured training under her primary mentors.

Dr. Rogers is being mentored by Dr. Wei and his co-mentors are Drs. Wolfe and Azhar. Dr. Rogers attends bi-weekly laboratory meetings as well as monthly structured meeting to discuss his progress with Dr. Wei. Dr. Rogers has completed working on his AFAR award and has another 2 manuscripts in preparation on the effect of glucose on endothelial cells and signaling. In addition Dr. Rogers has learned IRB regulations, clinical evaluation of study subjects with his collaboration with Dr. Raza on her heart failure subjects and learned arterial plethysmography techniques and functional evaluations.

Structured feedback is also provided to candidates face-to-face on a 6 monthly basis. Structured written evaluation of their work and overall performance is also provided to them on an annual basis. Features of evaluation include progress based on their performance, attendance and participation conferences, presentations, protocol development, developing expertise in new techniques, grant and manuscript writing skills and any acquisition of awards. In addition, the RCDC trainees also get to evaluate their mentors and provide feedback on the courses and training received and offer suggestions for improvement.

Drs. Raza, Todorova, Abraham, George and Rogers have manuscripts in preparation. Dr. Rogers and Dr. Mendiratta have manuscripts in review. All RCDC trainees attend the monthly OAIC meetings and present regularly at these meetings. They also participate in interdisciplinary journal clubs hosted by the Pepper Center.

**Specific Aim 4. Provide advice and guidance for planning individually tailored educational and research experiences, as well as career development opportunities most appropriate for each person's background.**

Dr. Il-Young aims to continue aging research with a focus of metabolism. Dr. Bryce is also enthusiastic about building his career in skeletal muscle aging metabolomics.

Dr. Ritika Abraham is in her 2nd year in endocrinology and plans to rejoin the Reynolds Institute on Aging as a geriatric endocrinologist on completion of her training. Dr. Sakeena Raza is a junior geriatric faculty at the Reynolds Institute on Aging. She is interested in cardiovascular aging and will be mentored by Dr. Azhar and Dr. Wei. Dr. Todorova is being supported in her efforts to transition from oncology to aging research by Drs. Wei and Azhar. She will be investigating the molecular mechanisms of Adriamycin-induced cardiomyopathy in geriatric patients with cancer. She also plans to study the effect of Adriamycin on the skeletal muscles of subjects with cardiomyopathy. Dr. Masil George continues to work on her pilot project but has selected palliative care her main area for further development. She is being supported in her efforts by all her mentors and also the palliative care attendings in the division of oncology. Her long-term objective is to study nutritional and exercise interventions in end-stage heart failure patients.

Dr. Steven Rogers has remained active in aging research and was a recipient of the AFAR award. He continues to refine his vascular model of aging with the ultimate goal of devoting himself to translational aging research. Since his long-term interest is cardiology and cardiovascular research, he is being mentored by Drs. Wei, Azhar and Zhang, with different aspects of clinical, translational and basic research training pertinent to his project. Dr. Mendiratta has decided to change her focus to educational research but will continue to attend Pepper Center seminars and develop interest groups to recruit students and fellows into aging translational research.

Our medical students working with our physician-scientists have expressed interest in aging and are eager to learn research during their summer breaks and elective rotations. Another M2 student, Stephen Foster received an MSTAR award this year to investigate the usefulness of a capillaroscope in imaging peripheral blood vessels in the elderly. The students plan to choose geriatrics and pursue an academic path in basic and translational aging research.
Specific Aim 5. Provide access to equipment and facilities available in the IOA at UAMS, the Arkansas OAIC, and other facilities on campus, including the NIH-supported CCTR.

All equipment and facilities are available to the OAIC trainees, including the newly completed laboratory and office spaces on the four new floors of the Reynolds Institute on Aging building. Dr. Young uses the metabolic equipment on the 7th floor and also cardiovascular physiological equipment and patient screening rooms on the 3rd floor. Dr. Bryce has laboratory space on the 7th floor which he shares with Dr. Young. Dr. Young has acquired expertise in the use of the forearm plethysmography equipment and has published the results in peer reviewed journals. Metabolomic training and support with mass spectroscopy is available on the 7th floor. Dr. Abraham will use the cardiovascular physiology laboratory on the 3rd floor of the Reynolds Center, which includes a fully equipped tilt table with portable 2-D Doppler echocardiography. Dr. Raza is currently using the Ottenheimer Fitness Center and the Rehabilitation Center as well as the Jackson Spine Center hydrotherapy facility. Dr. Raza is also using the RC2 exercise equipment for evaluating skeletal muscle strength. In addition, Dr. Raza is using the forearm plethysmography and other exercise equipment of RC2 located in the physiological laboratories on the second floor of the Reynolds Institute on Aging. Dr. Todorova is working in the basic-science cardiovascular laboratories on the 6th floor of the Reynolds Institute and has access to all equipment. Dr. George used the exercise physiology equipment of RC2 for evaluating the subjects' skeletal muscle strength. Dr. Steven Rogers has dedicated bench space and his own office with computer and printer and access to all research facilities at the Reynolds Institute on Aging and UAMS. State-of-the-art atomic force confocal microscopy is also available and Dr. Rogers has received training on it. DNA sequencing equipment is available on the 6th floor of the Reynolds Institute as well as the Rockefeller Cancer center on campus.

In brief, opportunities are available for cross training of basic molecular and cellular scientists in clinical physiological research in rodents and humans and vice-versa, for clinical researchers in basic techniques. Joint laboratory meetings are held in which clinical and basic trainees interact and get updates on a variety of different projects. This ensures opportunities for collaboration among junior researchers and mutual learning. Professional development is also available in the form of graduate courses leading to a Ph.D. degree in the biology of aging. A graduate student, Emmanuel Williams is currently pursuing his Ph.D. in the biology of aging and a previous one, Scott Helms, has already graduated. There is also an opportunity to acquire a master's of public health degree or take biostatistical courses offered through collaboration with the CTSA. An extensive annual course of metabolomics is offered by Dr. Wolfe’s group which is widely attended by researchers all over the country. For example, this course assisted Dr. Young build his basic knowledge in metabolomics techniques and start his research in muscle metabolism. One of our junior scholars, Stephen Foster, is learning to use the capillaroscope to evaluate circulation and predict coronary artery disease (CAD) in seniors. Stephen Foster is being mentored by Drs. Wei, Azhar and Roberson. For all the studies, bioinformatics support, integration of data and projects is being provided by Dr. Topaloglu and his team who are also active in training the investigators in the use of the Computerized Research Informatics Suite (CRIS).

Our trainees have developed educational products for seniors which include; a) home-based exercise DVD for seniors and b) an educational module for heart failure recognition and self-management of chronic disease for seniors and their caregivers. These products were developed with input from the Pepper and APECC board members.

We also have a number of novel transgenic mouse models which include cardiac-specific serum response factor (SRF)-over-expressing and under-expressing model and a p49/STRAP over-expressing model. The SRF models are pertinent to the aging cardiovascular system. We are still in the process of defining the function of p49/STRAP.

We will share our educational models with the community and other investigators. We will also share transgenic mouse models of aging.
<table>
<thead>
<tr>
<th>Trainee and research focus</th>
<th>Mentors and Core support</th>
<th>Presentations/meetings</th>
<th>Publications/abstracts/awards</th>
</tr>
</thead>
</table>
3. Red Sash Teaching Award 2013 and 2014  
4. Best Physician award 2013  
5. Accepted as a fellow of AGS 2014 |
| Cardiopulmonary resuscitation in elderly | Anna Czisar Ph.D | Sonntag/Wei RCDC, RC2, RC3 | GSA, AGS, monthly Pepper and Beeson meetings, journal club, IRB training and updates |
2. AFAR award 2014. |
| Glucose stress in endothelial cells | Masil George M.D. | Coker/Azhar/Wei RCDC, RC2,RC1 | OAIC pilot: Biologic factors influencing cardiac cachexia in the elderly. |
| Cardiac cachexia           | Coker/Azhar/Wei RCDC, RC2,RC1 | GSA, monthly Pepper seminars, interdisciplinary geriatric seminars’ Palliative care conference, IRB training and updates | 1. OAIC pilot: Biologic factors influencing cardiac cachexia in the elderly.  
<table>
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<tr>
<th>Name</th>
<th>Title</th>
<th>Authors</th>
<th>Events and Trainings</th>
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<tr>
<td>Sakeena Raza M.D.</td>
<td>Functional changes in obese elderly subjects with HFPEF</td>
<td>Azhar/Wei/Wolfe/Coker RCDC,RC2, RC1</td>
<td>AGS, Annual OAIC meeting at Bethesda, monthly Pepper meetings, interdisciplinary geriatric seminars, journal club, IRB training</td>
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<td></td>
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<td>42. OAIC pilot: Improvement in Functional Capacity of Obese Elderly with Heart Failure.</td>
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<td>Todorova, VK Ph.D.</td>
<td>Aging, cancer and effects on cardiac and skeletal muscle</td>
<td>Klimberg/Wei/Azhar/Zhang RCDC, RC2</td>
<td>Monthly Pepper meetings, Weekly Oncology meetings, weekly lab meetings, journal club, IRB training and updates.</td>
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<td></td>
<td></td>
<td></td>
<td>2. I. Rubio et al. Published online 6 February 2013 J PEN J Parenter Enteral Nutr DOI: 10.1177/0148607112474994</td>
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<td>Rtika Abraham M.D</td>
<td>Nutritional therapy for autonomic dysfunction in the elderly HF patients.</td>
<td>Wei/Azhar/Roberson RCDC, RC2, RC1</td>
<td>AGS, monthly Pepper meetings, weekly endocrine seminars, weekly lab meetings, interdisciplinary geriatric seminars, journal club, IRB training and updates.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1. Is short-term PEG-tube placement beneficial in acutely ill elderly patients? A proposed decision making algorithm. Abraham RR, Girotra M, Wei JY, Azhar G. Geriatrics and Gerontology International (Accepted April 2014)</td>
</tr>
<tr>
<td>II Kim Young</td>
<td>Wolfe/Ferrando/Roberson RC1, RC2, RC3, RCDC</td>
<td>Monthly Pepper meetings, Weekly metabolomics lab meetings, weekly journal club, interdisciplinary geriatric seminars, IRB training and updates.</td>
<td>TRI pilot award full application (2015): Selected for full TRI Pilot award application. Title: Role of Dietary Protein Intake on Whole Body Protein Accretion in Elderly Individuals (IL Kim: PI).</td>
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**Recent Publications of RCDC trainees:**


14. Azhar, Gohar; Wei, Jeanne Y, Ashcraft, Kristine Neradilek, Moni B; Newman, Richard L; Pacleb, Chelsea; Moyer, Nicolas; Sass, Rachel. Differences in Medicare quality measures among nursing homes before and after initiation of routine referral of long-term care residents for pharmacogenic testing (Current Geriatrics and Gerontology Research, in review, 2015)


Submitted/pending review:

Emmanuel D. Williams, Steven C. Rogers, Xiaomin Zhang, Gohar Azhar, Jeanne Y. Wei. Elevated Oxygen Consumption Rate in Response to Acute Low- Glucose Stress: Metformin Restores Rate to Normal Level (under review, Experimental Gerontology, 2015).

In preparation (RCDC trainees):


5. Masil **George** et al. “Estimating the cost savings by incorporating Palliative Medicine in Long-term Care: A growing need for Arkansas Older Adults” (in preparation).


**II.F. Pilot/Exploratory Studies Core**

Robert Reis, D.Phil., Leader  
501-257-5560 (phone) 501-257-5578 (fax) reisrobertj@uams.edu

Arny Ferrando, Ph.D., Co Leader  
501-526-5711 (phone) 501-686-8025 (fax) aferrando@uams.edu

**Goal 1. Increase funding available for translational research in muscle dysfunction and aging by partnering with other UAMS/OUHSC funding sources.**

Pilot-study funds at UAMS and OUHSC have been quite limited, especially relative to rising demand. These pilot funds have been particularly helpful in allowing a number of talented young investigators to generate preliminary data to support their applications for funding by NIH, VA, or other major extramural agencies. In the last year, 7 new extramural grants were awarded to pilot recipients, at least partially based on preliminary data generated with the pilot support. Of these, 3 involved UAMS/OUHSC intramural or university-administered resources.

**Goal 2. Encourage UAMS investigators proposing clinical studies to fully utilize the services of the UAMS Center for Clinical and translational Research (CCTR), funded by a CTSA that includes pilot support.**

Many PESC pilot recipients conducting human studies, especially junior ones, have also benefited from CTSA core facilities — including Drs. Raza, George, Abraham, Todorova, Hurren, Hauer-Jensen, Aykin-Burns, and Kim.

**Goal 3. Expand the network of investigators working in related areas in order to increase translational research collaborations and cross-linking among basic-science, clinical, and health-services researchers.**

Both full and partial PES proposals have been accepted. These collaborations are occurring in almost all pilot projects, especially as the basic researchers seek assistance of translational or clinical investigators for clinical aspects of their projects, and conversely, clinical researchers have sought out basic-science expertise to explore mechanistic aspects of their projects. As an example, Sakeena Raza, M.D., has been working with Steven Rogers Ph.D. to learn about vascular reactivity in heart-failure patients.

**Goal 4. Give priority to studies that forge new links between disparate research groups, foster interdisciplinary collaborations (leading to better, more tightly coordinated approaches to problem solving), and/or incorporate new technologies into aging research.**

Two notable examples are a year-3 pilot award to Vladimir Zharov, a world leader in nanotechnology and developer of novel instrumentation for photothermal microscopy, both of which he has applied to analysis of
aging muscle; and year-4 awards to Bryce Marquis for metabolite analyses by mass spectroscopy, and to Alexei Basnakian for development of his innovative assay methods to evaluate DNA damage in aging, and to assess key enzymes involved in its repair.

**Goal 5. Actively encourage and recruit faculty from underrepresented minority groups.**

We have been fortunate to recruit a very talented minority junior-faculty member at OUHSC, Tyrone Washington Ph.D., into basic aging research.

**Goal 6. Support OAIC PESCs with core resources in addition to pilot funds.**

OAIC leadership have been proactive in stimulating proposals focused on translational aging research. Investigators who receive pilot funding also are offered support from the OAIC cores and assistance in identifying collaborators to help in adding appropriate analytical tools to their investigations. Core utilization by pilot recipients is summarized in tables accompanying the cores’ progress reports.

For the fifth round of pilot support, we received meritorious applications from ten investigators, including 3 senior investigators new to the field of muscle aging, and 7 junior investigators (6 from UAMS, 1 from OUHSC). These have completed the initial review process, and reviewer critiques were compiled to guide investigators in their proposal revisions. The second review will take place in July for grants to begin by Sept., 2015.

<table>
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<tr>
<th>Pepper Center Pilot Awardees</th>
<th>Papers</th>
<th>Grants</th>
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<td>Support dates</td>
<td>Publication s since award (citing P01)</td>
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<tr>
<td><strong>Pilot P.I.</strong></td>
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<tr>
<td>Anna Csiszar</td>
<td>02/12 -01/13</td>
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<td>Martin Hauer-Jensen</td>
<td>12/11 - 11/12</td>
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<td>Sharda P. Singh</td>
<td>03/12 - 03/13</td>
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<td>Jamie Baum</td>
<td>01/12 - 12/12</td>
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<td>Cody Sipe</td>
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<td>Nukhet Aykin-Burns</td>
<td>04/12 - 03/13</td>
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<td>Masil George</td>
<td>06/12 - 05/13</td>
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<td>Sakeena Raza</td>
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<tr>
<td>Srinivas Ayyadevara</td>
<td>6/12 - 5/13</td>
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<tr>
<td>Tyrone Washington</td>
<td>03/13 - 02/14</td>
<td>7 (2)</td>
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<td>Valentina Todorova (2 pilots funded)</td>
<td>08/12 - 07/13, 09/14 – 08/15</td>
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<td>Neil II Young Kim</td>
<td>09/13 - 08/15</td>
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</table>
Grants awarded within the last year to pilot recipients:
1. Todorova, V. (P.I.) FDA Chief Scientist’s Challenge Grant (E0756201), Todorova (Co-PI); 07/01/2014—07/30/2015.

Grants submitted within the last year by pilot recipients:
1. (pending) Todorova, V. (P.I.), NIH R21 grant 2015–2017

Partial listing of citations benefiting from PESC grants
*Cites Pepper Center pilot support; pilot recipient in bold.


Zhou, D. “Pharmacological clearance of senescent cells by ABT263 mitigates total body irradiation-induced premature aging of the hematopoietic system in mice” (submitted to Nature Medicine)


Abstracts

**Jamie I. Baum**, Stephanie A. Shouse, Jeanne Wei, Robert R. Wolfe. Leucine (leu) and w-3 fatty acids (FA) act synergistically through mTOR to activate translation initiation in young and aged C2C12 myotubes. Abstract published; presented as a poster, Exp. Biol. 2014.

**George M., Curseen K., Balamurugan A.** 2015 American Medical Directors Association Long Term Care Medicine conference, February 27-March 2, Nashville, TN. “Estimating the cost savings by incorporating Palliative Medicine in Long-term Care: A growing need for Arkansas Older Adults”. (in preparation)
I. DESCRIPTION OF CENTER

The UCLA Claude Pepper Older Americans Independence Center (OAIC) is designed to maintain and restore the independence of older persons. The UCLA Center’s theme is “Preventing Disease and Disability in Vulnerable Populations: a Translational Approach”.

We define vulnerable populations as 1) underserved (i.e., low income, uninsured, and minorities) or 2) at increased risk of losing independence because of chronic diseases or conditions, advanced age, or functional impairment. We define translational as overcoming two barriers to effective research. The first is the inability to transfer new understandings of disease mechanisms gained in the laboratory into new diagnostic, therapeutic, and preventive care. The second is the inability to get results from clinical studies into everyday clinical practice and health decision making. In studying vulnerable populations, the UCLA OAIC emphasizes research that extends across the full spectrum of translational research. Within this theme, an important focus of the UCLA OAIC is on understanding the role of inflammation in disease and disability.

The UCLA OAIC addresses health disparities that vulnerable older persons face because of 1) inadequate understanding of contributors (e.g., socioeconomic status, inflammation) to health and specific illnesses (e.g., HIV, sleep disorders, depression), 2) lack of effective preventive or therapeutic approaches (biomedical and behavioral), or 3) inadequate ability to get needed treatment to vulnerable older populations (e.g., cultural barriers, ineffective health systems). It also helps overcome the barriers between the promise of basic science research and the delivery of better health.

The Center stimulates scientific discovery through 4 Resource Cores:

- Recruitment and Retention Core
- Research Operations Core
- Analysis and Cost-effectiveness Core
- Inflammatory Biology Core
Resource Cores provide 4 levels of support:

- Consulting (e.g., few hours of advice, reading a paper or proposal)
- Ongoing or long term partnership (e.g., via purchasing their services)
- Partnership on new proposals
- Additional research support for CDA’s to be decided on a case-by-case basis

The UCLA OAIC specific aims are:

1) To provide intellectual leadership for research on the Center’s theme, *Preventing Disease and Disability in Vulnerable Populations*

2) To stimulate T1 and T2 translational research addressing the Center’s theme by consultation, provision of services, and collaboration through 4 resource cores

3) To engage the Los Angeles community in the conduct of OAIC research

4) To foster career development of future research leaders through Career Development Awards

5) To nurture novel ideas by funding rapid pilot awards

6) To collaborate with other NIH-funded (e.g., CTSI, RCMAR, L.A. CAPRA, Demography Center) and foundation-funded (e.g., Hartford Center of Excellence) efforts that support the UCLA OAIC’s mission

II. RESEARCH, RESOURCES AND ACTIVITIES

A. CORES

A1. Leadership/Administrative Core
A2. Research Career Development Core
A3. Pilot and Exploratory Studies Core

A1. Leadership/Administrative Core (LAC)

Core leader:
David B. Reuben, MD
Archstone Foundation Chair and Professor of Medicine
David Geffen School of Medicine at UCLA
10945 Le Conte Avenue, Suite 2339
Los Angeles, CA 90095-1687
Ph: 310-825-8253
Fax: 310-794-2199
Email: dreuben@mednet.ucla.edu

Core Co-leaders:
Cathy Alessi, MD
Director, VA Greater Los Angeles Geriatric Research, Education and Clinical Center (GRECC)
Email: cathy.alessi@va.gov
The LAC provides support for planning, organizational, evaluation, and administrative activities related to the other Cores and to the OAIC as a whole. It monitors, stimulates, sustains, evaluates, and reports progress towards the Center’s overall goals. To do so, the LAC has established eight specific aims:

1) to provide day-to-day management of the UCLA OAIC
2) to provide fiscal management for the UCLA OAIC
3) to provide administrative oversight for internal quality control of ongoing research and training
4) to review and optimize use of UCLA OAIC resources by internal and external projects
5) to create linkages between UCLA OAIC Cores/investigators and other UCLA, VA, and RAND researchers whose work relates to the theme and mission of the Center, especially the new UCLA CTSI and the UCLA Research Center for Minority Aging Research (RCMAR)
6) to solicit applications for new Career Development Awards (CDAs) and pilots and coordinate the review process for new CDA, pilots, and Developmental Projects (DPs)
7) to ensure communication, coordination, and collaboration among the UCLA OAIC cores, (intra-OAIC) and between the UCLA OAIC and other OAICs (inter-OAIC)
8) to maintain contact with NIA staff, the national OAIC Coordinating Center, the External Advisory Board, and External Selection Panel

A2. Research Career Development Core (RCDC)

Core leader:
Alison A. Moore, MD, MPH
Professor of Medicine/Geriatrics
David Geffen School of Medicine at UCLA
10945 Le Conte Avenue, Suite 2339
Box 951687
Los Angeles, CA 90095-1687
Ph: 310-825-8253
Fax: 310-794-2199
Email: aamoore@mednet.ucla.edu

Core co-leader:
Theodore J. Hahn, MD
Deputy Director, Geriatric Research Education and Clinical Center (GRECC)
VA Greater Los Angeles Healthcare System
Email: theodore.hahn@va.gov
The overarching mission of the RCDC is to develop future leaders in aging research, focused in the area of UCLA’s theme, *Preventing Disease and Disability in Vulnerable Populations: a Translational Approach*. The RCDC promotes the development of future research leaders who address this theme, particularly leaders who can integrate clinical insights regarding health, disease, independence, and disability in older adults with knowledge of advances in the basic sciences, including gerontology, to develop better interventions to maintain health and independence.

The goals of the RCDC are to:

1) identify junior faculty who have the greatest potential as future leaders in aging research to receive three year career development awards (CDAs), focused on our OAIC theme;
2) foster the research training and careers of these junior scientists;
3) provide a supportive environment for CDA awardees that maximizes the likelihood of successful training, research progress and ultimate career success;
4) emphasize training for most CDAs that will integrate translational science in addressing research questions; and
5) serve as a resource in aging-related research mentorship for UCLA junior faculty.

**A3. Pilot and Exploratory Studies Core (PESC)**

**Core leader:**

Gail Greendale, MD  
Professor of Medicine and Obstetrics & Gynecology  
David Geffen School of Medicine at UCLA  
10945 Le Conte Avenue, Suite 2339  
Box 951687  
Los Angeles, CA 90095-1687  
Ph: 310-825-8253  
Fax: 310-794-2199  
Email: ggreenda@mednet.ucla.edu

The overarching purpose of the UCLA Pilot and Exploratory Studies Core (PESC) is to promote innovative basic, clinical and translational research, conducted by collaborating teams of junior and senior investigators, that falls within the UCLA’s research theme and carries out the Center’s goals. Each pilot study will meet at least one of the following goals:

a) To provide preliminary studies on which subsequent, larger basic or clinical investigations will be based;
b) To develop new basic or clinical methodologies that surmount critical barriers to progress in a given discipline, thus opening new research avenues;
c) To develop novel multi-disciplinary research approaches to complex geriatrics research questions;
d) To accomplish bi-directional basic and clinical sciences translation; or
e) To identify diagnostic and/or treatment strategies that bring discoveries to the bedside in order to improve health and optimize function of geriatric patients.
Specific Aims

1. To administer a rapid pilot program, fast-turn-around awards of $1,000 to $10,000 each, targeted at junior faculty, advanced trainees whose research will be advanced by a small infusion of support quickly and to senior faculty who wish to add a specific aging focus to their ongoing work.

2. To closely monitor progress of rapid pilots and to promptly identify and remediate obstacles to each pilot’s successful completion.

3. To provide mentoring and infrastructural support that will foster development of rapid pilot projects into presentations at national meetings, peer-reviewed manuscripts and independent grant awards.

B. RESOURCE CORES

B1. Analysis/Cost-Effectiveness Core (ACEC)
B2. Inflammatory Biology Core (IBC)
B3. Recruitment Core (RC)
B4. Research Operations Core (ROC)

B1. Analysis/Cost-Effectiveness Core (ACEC)

Core leader:
Arun S. Karlamangla, MD, PhD
Professor of Medicine/Geriatrics
David Geffen School of Medicine at UCLA
10945 Le Conte Avenue, Suite 2339
Box 951687
Los Angeles, CA 90095-1687
Ph: 310-825-8253
Fax: 310-794-2199
Email: akarlamangla@mednet.ucla.edu

The Analysis and Cost Effectiveness resource core (ACEC) provides broad, technical, analytic support in biostatistical methods, comparative effectiveness methods, and cost effectiveness analysis to UCLA aging researchers to help identify modifiable causes and pathways to morbidity and disability in vulnerable populations, and develop interventions that address these causes and pathways.

The Specific Aims of the Analysis/Cost-Effectiveness Core are:

1. To provide analytic support in research study design (selection of analytic strategy, and sample size/power issues), statistical data analysis, and interpretation and accurate description of findings, for:
   • OAIC Career Development Awardees,
   • OAIC supported pilots and development projects,
   • UCLA junior researchers conducting research that meets UCLA OAIC mission, theme, and goals,
• Externally funded UCLA research projects that meet the UCLA OAIC mission, theme, and goals (See below for list of external projects that will purchase core support in the first year).

2. To provide training workshops / tutorial seminars to UCLA aging researchers on state-of-the-art methods for statistical data analysis, comparative effectiveness studies, and cost effectiveness analysis, specifically tailored to data from older adults.

**B2. Inflammatory Biology Core (IBC)**

**Core leader:**
Michael Irwin, MD, PhD  
Professor of Psychiatry and Biobehavioral Sciences  
David Geffen School of Medicine at UCLA  
300 Medical Plaza, Suite 3109  
BOX 957076  
Los Angeles, CA 90095-7076  
Ph: 310-825-8281  
Fax: 310-794-9247  
Email: mirwin1@ucla.edu

**Core co-leader:**
Elizabeth Breen, PhD  
Associate Professor of Psychiatry and Biobehavioral Sciences  
David Geffen School of Medicine at UCLA  
ebreen@mednet.ucla.edu

The OAIC Inflammatory Biology Core (IBC) provides a mechanism by which OAIC research programs at UCLA and other institutions can incorporate comprehensive protein and molecular analyses of inflammatory biology into both internally funded and external projects. Consistent with the OAIC Center’s theme *Prevention of Disability in Vulnerable Populations: A Translational Approach*, the IBC aims to: a) stimulate translational links between basic and clinical research in inflammatory biology, b) develop effective preventive or therapeutic interventions that target inflammation or biobehavioral risk profiles associated with inflammation, and c) bring new knowledge about inflammatory biology biomarkers and mechanisms underlying successful clinical intervention into clinical practice and decision-making. The IBC focuses on the linkages between basic and clinical sciences, and provides opportunities for OAIC research projects to examine inflammatory mechanisms, underlying molecular genetics, and role of inflammation on biobehavioral, systemic, and cellular processes. Together, the IBC provides strategic focus on the translation of such inflammatory biology mechanisms into the identification of chronic disease risk in older adults and prediction of response to treatment. A single, comprehensive core in inflammatory biology yields substantial gains in efficiency and quality for the individual external projects supported by the IBC.
The OAIC Inflammatory Biology Core aims to:

1. Expand and support the analysis of inflammatory biology in existing UCLA OAIC research programs and in new OAIC pilot projects and developing research programs. This includes both intellectual support and assay services.
2. Develop new analytic approaches to facilitate in vivo analysis of inflammatory dynamics and their functional genomic impact on elderly individuals.
3. Provide training in behavioral, immunologic, and molecular aspects of inflammatory biology in general, and specifically, as they pertain to the unique issues in aging. This training emphasizes biological knowledge about the sources and targets of inflammatory signals (including genetic and epigenetic influences and gene expression consequences), with a particular focus on behavioral and functional impacts.

B3. Recruitment and Retention Core (RRC)

Core leader:
Catherine A. Sarkisian, MD, MS
Associate Professor of Medicine/Geriatrics
David Geffen School of Medicine at UCLA
10945 Le Conte Avenue, Suite 2339
Box 951687
Los Angeles, CA 90095-1687
Ph: 310-825-8253
Fax: 310-794-2199
Email: csarkisian@mednet.ucla.edu

With the UCLA OAIC’s theme of “Preventing Disease and Disability in Vulnerable Populations: a Translational Approach,” our Recruitment and Retention Core (RRC) provides a critical piece of our OAIC’s mission by facilitating recruitment and retention of the most vulnerable seniors – specifically lower income and minority seniors who have been historically and continue to be underrepresented in research studies. To successfully enroll these seniors into research protocols, scientists need to build trusting mutually beneficial relationships with community leaders. This is a process that takes many years and is not generally accomplished within the confines of a typical RO1 (or equivalent type of grant) timeline or budget. For over 15 years, our academic scientists have worked in close partnership with many community leaders in aging on community-based projects aimed at improving the health and quality of life of lower income older adults. With appreciation of our complementary expertise, our academic-community partnerships are based on deep mutual respect and a shared vision for implementing and testing practical evidence-based interventions to empower older adults to stay active and healthy. Capitalizing upon these relationships, the UCLA OAIC RRC has provided invaluable assistance and leadership to academic investigators seeking to enhance the reach and impact of their funded science.
Specific Aims:

1. Collaborate with UCLA, Charles Drew University (Drew) and affiliated academic investigators to accelerate and facilitate recruitment and retention of lower income and minority seniors.

2. Facilitate new partnerships between community partners and affiliated scientists directed at conducting community research focused on preventing disease and disability in vulnerable older adults.

**B4. Research Operations Core (ROC)**

Core leader:
Teresa E. Seeman, PhD
Professor of Medicine/Geriatrics
David Geffen School of Medicine at UCLA
10945 Le Conte Avenue, Suite 2339
Box 951687
Los Angeles, CA  90095-1687
Ph: 310-825-8253
Fax: 310-794-2199
Email: tseeman@mednet.ucla.edu

Core co-leader:
Heather McCreath, PhD
Researcher
Department of Medicine/Division of Geriatrics
David Geffen School of Medicine at UCLA
Email: hmccreath@mednet.ucla.edu

The Research Operations Core (ROC) provides state-of-the-art data collection and data management services to support the successful implementation of OAIC-funded and externally-funded projects addressing questions relevant to the UCLA OAIC’s theme *Prevention of Disability in Vulnerable Populations: A Translational Approach* – a focus that flows from the substantive interests and expertise of UCLA OAIC-affiliated researchers. ROC faculty and staff expertise, and our ability to field data collection modalities suited to a variety of community settings, are key to our success in implementing projects in such populations. Since its inception in 2000, the ROC has developed a reputation for excellence in data collection and data management services, having successfully supported close to 120 observational and intervention projects to date. The ROC maintained its status as a premier research resource through on-going efforts to leverage developing technologies and available expertise to enhance the services offered in support of successful implementation of studies in diverse, vulnerable populations. The ROC’s overarching goal is to optimally support the full spectrum of research operations services needed for the successful design and implementation of projects ranging from basic science to population-based studies and thereby contribute to the success of the UCLA OAIC in supporting translational research to maintain older adults’ independence, especially among vulnerable populations.
ROC Specific Aims include:

1. Research Operations Services – Provide consulting for:
   (a) Data collection – provide assistance in development of data collection procedures, manuals of operations and instruments as well as training and oversight of research staff;
   (b) Data management – provide on-going monitoring/tracking of subject recruitment and study progress; quality control monitoring; double-pass data entry, data cleaning and documentation; and data security procedures to ensure confidentiality/privacy; and
   (c) Proposal preparation - provide consulting and assistance with scientific and operational aspects as proposals are prepared;

2. Innovation/New Initiatives – Expand and enhance ROC services through:
   (a) developing interoperability between ACCESS and Web versions of the Pepper Informatics (Pi) data management systems and between Pi and REDCap, the data entry system supported by the national CTSI program, to allow seamless exchange of data between all modalities of Pi and REDCap;
   (b) deepening our collaborations with the UCLA CTSI, including joint efforts to enhance community-based data collection protocols, to evaluate and enhance data management systems, and efforts to encourage and facilitate participation in research by vulnerable populations;

3. Training – Provide workshops on research methods and operations for research faculty (through participation in OAIC Seminar Series) and for staff, often through collaboration with other cores;

C. PILOTS
YEAR 9 (JULY 2014 – JUNE 2015)

**Rapid Pilots:**

<table>
<thead>
<tr>
<th>Principal Investigator (Mentor if Junior PI)</th>
<th>Title of Pilot</th>
<th>Research Aims</th>
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</thead>
<tbody>
<tr>
<td>Sangeeta Dhawan, PhD</td>
<td>Promoting Beta Cell Regeneration In Aging with Growth Factor Gdf11</td>
<td>Can treatment with Gdf11 increase beta cell proliferation in islets isolated from aged mice? Can treatment of aged mice with Gdf11 restore the capacity for endogenous beta cell replication?</td>
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<tr>
<td>(Peter Butler, MD, Professor of Medicine)</td>
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<tr>
<td>Pritha Gupta, MD Cardiovascular Disease Fellow</td>
<td>Soluble Cd200* May Positively Correlate with Age and CAD Severity</td>
<td>Soluble CD200 in human serum will increase with age. Higher levels of soluble CD200 will protect against incidence and progression of coronary artery disease (CAD). Higher levels of soluble CD200 receptor will protect against incidence and progression of CAD.</td>
</tr>
<tr>
<td>(Aldons J. Lusis, PhD, Professor of Human Genetics and Medicine)</td>
<td>*Cd200 is a candidate gene that may protect against heart failure; a soluble form is measurable in human serum</td>
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<tr>
<td>Vera Chesnokova, PhD Associate Professor of Neurology</td>
<td>Gro1* Promotes Senescence Of Hippocampal Neuronal Progenitors In Ageing Brain</td>
<td>Cytokine-induced Gro1 will suppress hippocampal neuronal proliferation and promote premature senescence of hippocampal neuronal progenitor cells.</td>
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<tr>
<td></td>
<td>*Gro1 is a ligand for G-protein coupled receptor CXCR2, which is expressed in neural progenitors</td>
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<tr>
<td>Miklos Peterfy, PhD Associate Professor of Medicine</td>
<td>Hematopoietic Rejuvenation As A Therapeutic Approach In Aging-Associated Inflammation And Metabolic Dysfunction</td>
<td>“Rejuvenation” of the hematopoietic compartment through bone marrow transplantation will reduce inflammation (assessed by multiple cytokines and chemokines) and provide metabolic benefits (improved glucose tolerance) in aged mice.</td>
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<tr>
<td>Homero Del Pino, PhD, Adjunct Assistant Professor of Medicine, (Alison A. Moore, MD, Professor of Medicine)</td>
<td>Evaluating the Usability of an Alcohol Screening and Brief Intervention for Older Adults With HIV</td>
<td>Evaluate the usability of the Comorbidity-Alcohol Risk Evaluation Tool [CARET]) adapted for HIV and an accompanying brief intervention in HIV-positive African-American, Latinos, and Whites aged 50 years and older.</td>
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Rapid pilots awarded July 1, 2014 through April 3, 2015

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<thead>
<tr>
<th>Principal Investigator (Mentor if Junior PI)</th>
<th>Title of Pilot</th>
<th>Research Aims</th>
</tr>
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<tbody>
<tr>
<td>Ram Singh, MD Professor of Medicine and Pathology</td>
<td>Changes In Non-Conventional T-Cells That React Against Lipids With Aging: Role In Inflammation And Immune Suppression</td>
<td>Do phospholipid-reactive T cells expand with age, and display an activated phenotype with increased production of pro-inflammatory cytokines, as compared to these cells in younger mice? Will the in vivo activation of phospholipid-reactive T cells impair responses to a foreign antigen, such as influenza matrix protein?</td>
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<tr>
<td>Theodore Robles, PhD Associate Professor of Psychology</td>
<td>Social Engagement And Health In Assisted Living Facilities (ALFs)</td>
<td>Identify whether perceptions of aging relate to older adults’ social engagement in ALFs. Evaluate whether ALF residents’ social engagement is linked to their concurrent and subsequent health outcomes. Examine inflammation, indexed through circulating inflammatory markers and inflammatory gene expression, as a mechanism linking social engagement to health.</td>
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III. CAREER DEVELOPMENT AWARDS

Joseph Dzierzewski PhD (2013 – 2016)
Assistant Researcher, UCLA Department of Medicine

Cognitive response to improved sleep in late-life: the role of inflammation
Sleep disordered breathing (SDB) and insomnia are the most common sleep disorders in late-life, and recent evidence suggests that these two disorders co-occur in nearly half of patients. SDB and insomnia have been independently associated with cognitive complaints cross-sectionally in younger and middle-aged samples; however, there is a relative dearth of information concerning the combined impact of these disorders on cognitive functioning, especially in older adults. Little is known about potential pathways through which disturbed sleep may impact cognitive functioning in late-life, though alterations in inflammatory factors are a promising candidate. Both SDB and insomnia have known inflammatory consequences, which also have known associations with late-life cognitive functioning.

Aim 1: Examine the cross-sectional relationships between sleep and neurocognitive functioning, and explore the role of inflammatory factors.
**Aim 2:** Determine whether a novel Cognitive Behavioral Treatment for Insomnia + Positive Airway Pressure treatment improves neurocognitive functioning and inflammation in older adults with comorbid SBD and insomnia.

**Aim 2.1:** Examine the effects of improved sleep on neurocognitive functioning and inflammatory factors in older adults with comorbid SBD and insomnia.

**Lee Jennings, MD (2013 – 2016)**
Assistant Professor of Medicine/Geriatrics

**Evaluation of a comprehensive dementia care program: quality, health outcomes, cost and utilization**

Dementia is a chronic disease that requires well-integrated medical and social services to provide high quality care and prevent complications, including ED visits and hospitalizations for ambulatory sensitive conditions. In July 2012, UCLA launched the Alzheimer’s and Dementia Care (ADC) program, a quality improvement program that uses a co-management model with nurse practitioner Dementia Care Managers partnering with primary care physicians and five community-based organizations to provide comprehensive dementia care.

The program has enrolled over 1100 patients in 2 ½ years. Based on the Centers for Medicare and Medicaid Services triple aim (better quality, better health, and lower cost), we propose a rigorous evaluation of this new model of care for dementia disease management.

Specifically, we aim to evaluate how well the UCLA Alzheimer’s and Dementia Care Program:

1. Provides better quality of dementia care
   Hypothesis: The quality of care as measured by adherence to the Assessing Care of Vulnerable Elders (ACOVE)-3 and Physician Consortium for Performance Improvement (PCPI) quality indicators for dementia will be better for program enrollees as compared to literature benchmarks for similar populations of community-dwelling adults with dementia.

2. Improves patient and caregiver health outcomes
   Hypotheses:
   2a: Neuropsychiatric complications for ADC enrollees, as measured by the Neuropsychiatric Inventory Questionnaire (NPI-Q), will worsen at a slower rate as compared to a national cohort of dementia patients. The ADC program is designed to improve management of dementia-related behaviors, leading to fewer neuropsychiatric complications and less caregiver distress despite progression of cognitive and functional impairment.
   2b: Caregiver strain, depressive symptoms, and self-efficacy for managing dementia-related problems and accessing help as measured by the Modified Caregiver Strain Index, Patient Health Questionnaire (PHQ-9), and a new 9-item caregiver survey assessing caregivers’ experience with dementia care and perceived needs, respectively, will improve as compared to baseline measures.
3. Decreases hospital, emergency department (ED), and nursing home utilization; increases hospice utilization; and is cost-effective for enrollees as measured by Medicare claims data

Hypotheses: ADC program enrollees will have a slower rate of increase in costs and acute care utilization as compared to a cohort of UCLA dementia patients not in the ADC program. Although, patients with dementia are likely to have increased healthcare use as their disease progresses, ADC program interventions, including better management of neuropsychiatric complications, caregiver education and support, and better advance care planning, will reduce unnecessary ED visits and hospitalizations and increase hospice use, thus slowing the rate of cost increase as patients’ dementia progresses.

Joanna Schaenman, MD, PhD (2014-2016)
Assistant Professor of Medicine/Infectious Diseases

Evaluation of T Cell Immune Function Impairment in Elderly Solid Organ Transplant Recipients

Project Goals

Kidney transplant recipients older than 65 years old are at increased risk of death compared with younger transplant recipients, hypothesized to be due to alterations in T cell immunity leading to vulnerability to infection. However, although evaluation of the immunologic changes associated with aging is a growing field, this topic has yet to be examined in transplantation. As the incidence of chronic kidney disease rises in the aging population, the number of elderly patients requiring transplantation will continue to increase. Kidney transplant recipients are an ideal group to study due to the high volume of transplant recipients available for clinical trial enrollment at our center.

The current approach to immune suppression after transplantation targets goal drug levels regardless of patient age. By studying alterations in T cell function found in the peripheral circulation in elderly and younger renal transplant recipients in Aim 1, we will reach an improved understanding of the mechanism of immune dysfunction in terms of senescence, exhaustion, and antiviral immunity. To unravel the mechanisms behind these changes, Aim 2 will explore differences in peripheral blood T cell gene expression profiles in elderly versus younger transplant recipients. Aim 3 will apply novel computational bioinformatics to integrate the large immunophenotyping and gene expression datasets generated from these analyses to generate a composite phenotype of the immune compromised elderly renal transplant recipient. The deliverables from this project will be mechanistic analyses of immunosenescence in elderly transplant recipients and the development of biomarkers for noninvasive testing that can be applied to optimize post-transplant immune suppression and monitoring. Hypothesis: Elderly kidney transplant recipients will demonstrate increased frequency of T cells characterized by immunosenescence, terminal differentiation, and deficiencies in antiviral immunity, as compared with younger transplant recipients.
Specific Aims:

**Aim 1:** Characterize the T cell immune phenotype and function of elderly kidney transplant recipients as compared with younger transplant recipients longitudinally post-transplant.

1A: Determine the peripheral T cell immunophenotype using markers of immunosenescence and terminal differentiation via multiparameter flow cytometry.

1B: Characterize the quality and quantity of the T cells mediating immune response to CMV by measuring intracellular cytokine secretion after *in vitro* stimulation with CMV.

**Aim 2:** Determine the mechanism(s) of development of age-related T cell impairment after transplantation by analysis of changes in gene expression.

2A: Assess changes in gene expression in RNA isolated from total peripheral blood mononuclear cells from elderly versus younger kidney transplant recipients.

2B: Determine changes in gene expression in the T cell immune phenotype of the renal transplant recipient most strongly associated with age.

**Aim 3:** Modeling the immunophenotype and gene expression networks to provide new insights into mechanisms underlying aging of the immune system.

3A: Bioanalytic evaluation using a multivariate statistical approach to analyze immune phenotype and gene expression data to identify data attributes most strongly associated with patient age.

3B: Combination of most strongly associated immune phenotype and gene expression characteristics using principal component analysis to generate a model that captures important relationships in the data.

The successful execution of this project will advance the understanding of aging-related science in the field transplant medicine and infectious disease, and facilitate my transition into the field of aging research. This proposal addresses an important unmet need in the field of transplant medicine regarding outcomes in elderly transplant recipients and will be the first to formally address immune dysfunction and vulnerability to infectious complications from a geriatrics perspective. This work will therefore also provide new insights into the field of biologic investigations of mechanisms of aging by examining these mechanisms in the setting of immunosuppression, and from the perspective of infection predisposition and prevention.
## UCLA OAIC CDA Awardees (Current Cycle 2011 – Present)

<table>
<thead>
<tr>
<th>Name</th>
<th>Current Status</th>
<th>OAIC CDA Award/ Year of Award</th>
<th>Subsequent Grants, Career Development Awards</th>
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<tbody>
<tr>
<td><strong>FORMER AWARDEES</strong></td>
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</table>
| **Jordan E. Lake, MD**                              | Assistant Professor Medicine/Infectious Diseases | 7/11 – 6/14                          | 1. The Campbell Foundation. “Telmisartan and Flow-Mediated Dilatation in Older HIV-Infected Patients at Risk for Cardiovascular Disease.” Role on project: PI. February 2012 – February 2014. Total direct costs: $76,500  
3. NIH K23. “Inflammation, Fibrosis and End-Organ Disease in HIV-Infected Adults.” Role on project: PI. June 2014 – May 2019. $875,000  
4. NIH R21: “CBT and Exercise to Reduce Pain and Substance Abuse in Older Adults with HIV.” Role on project: PI. August 2014 – July 2016. $275,000. |
| **David Merrill, MD, PhD**                          | Assistant Professor Psychiatry                  | 7/11 – 6/13                          | 1. UCLA CTSI Institutional KL2 Translational Science Award. “Relationship of physical activity to hippocampal structure and memory in MCI.” Role on project: PI. July 2013 – June 2016. Total direct costs: $374,250. |
IV. PUBLICATIONS (2014 – 2015)


29. Inagaki TK, KA Muscatell, MR Irwin, M Moieni, JM Dutcher, I Jevtic, EC Breen, NI Eisenberger. The role of the ventral striatum in inflammatory-induced approach toward support figures. *Brain, Behavior, and Immunity* 44:247-52. PMCID: PMC4275369


V. EXTERNAL ADVISORY BOARD MEMBERS

James S. Goodwin, MD
Professor, Division of Geriatric Medicine
George and Cynthia Mitchell Distinguished Chair of Geriatric Medicine
Director, Sealy Center on Aging
The University of Texas, Medical Branch
(2013 – Present)

James S. Jackson, PhD
Director
Institute for Social Research
University of Michigan
Ann Arbor, MI
(2006 – Present)

Stephanie A. Studenski, MD, MPH
Medical Officer;
Chief, Longitudinal Studies Section
Director, Baltimore Longitudinal Study of Aging
National Institute on Aging
(2013 – Present)
Alison A. Moore, MD, MPH

- 2014 Outstanding Mentor Award, UCLA Medical Student Training in Aging Research (MSTAR) Program

Catherine A. Sarkisian, MD, MS

- 2014 Society of General Internal Medicine Distinguished Professor in Geriatrics

Teresa E. Seeman, PhD

- 2015 Arthur Cherkin Award, UCLA Multicampus Program in Geriatric Medicine and Gerontology and the VA-UCLA Geriatric Medicine Fellowship Program
General Brief Description of Minority Activities:

RCMAR Initiative:
The UCLA OAIC provides ongoing operational assistance to the new UCLA Resource Center for Minority Aging Research (RCMAR), one of seven centers funded for the 2002-2017 cycle of this NIH initiative. Carol M. Mangione, MD, MSPH, co-leader of the UCLA OAIC Recruitment and Retention Core, is also the principal investigator of the UCLA RCMAR program, called the Center for Health Improvement for Minority Elders (CHIME). Alison A. Moore, MD, MPH, leader of the UCLA OAIC Research Career Development Core, is the leader of the RCMAR CHIME Investigator Development Core. Catherine A. Sarkisian, MD, MS, leader of the UCLA OAIC Recruitment and Retention Core, is the leader of the RCMAR CHIME Community Liaison Core. The RCMAR Coordinating Center is based at UCLA.

CHIME is a collaborative research and mentoring program with faculty at UCLA and Charles R. Drew University that addresses health disparities for African American and Latino elders through training and mentorship of minority faculty. CHIME also provides the research infrastructure needed to improve the health of minority elders through participatory research within local communities. The center is active in the recruitment, retention, and promotion of minority junior faculty through mentorship and support of research efforts on the health of minority elders.

OAIC Diversity Supplement - Adapting an Alcohol SBI (CARET) for Older Adults with HIV Infection:
The UCLA OAIC received a two-year diversity supplement (07/01/14 – 06/30/16) to fund Homero del Pino, PhD.

Dr. del Pino is committed to becoming an independent investigator focused on alcohol misuse and HIV in aging populations. He completed a PhD in philosophy, with a focus on action theory. During and after graduate school, Dr. del Pino worked for six years at AIDS Project Los Angeles and trained state health departments and community-based organizations in evidence-based substance abuse and HIV-prevention interventions. His experience managing health-related programs led him to join Charles R. Drew University (CDU) as a full-time administrator in the NIMHD-funded U54 program, AXIS, that houses clinical and translational, community, and technology resources and provides consultation services for researchers.

Dr. del Pino now holds a dual faculty appointment at CDU and UCLA. The goal of Dr. del Pino’s project is to adapt and pilot test the Comorbidity-Alcohol Risk Evaluation Tool (CARET), a screening tool for at-risk drinking in older adults and an accompanying brief intervention (BI) to meet the needs of an ethnically diverse group of HIV-positive adults aged 50 years
and older. The ultimate aim of this work is to reduce at-risk drinking and associated negative health outcomes for this population. The results of this pilot study will provide Dr. del Pino with the foundation to prepare an NIA OAIC Career Development Award and/or K01 proposal to further develop his career and research skills. Preparation for a career development award application will begin during Year 2 of the award period. The specific aims of this project are to partner with AIDS Project Los Angeles (APLA) and to:

1) Adapt the CARET and BI for HIV-positive African-Americans, Latinos and Whites aged 50 years and older.
2) Test the acceptability of the adapted CARET-HIV and BI with HIV-positive African-American, Latinos, and Whites aged 50 years and older (n=12, 4 in each racial/ethnic group) and healthcare providers (n≥5).
3) Pilot test the adapted CARET-HIV and BI among HIV-positive African-Americans, Latinos and Whites aged 50 years and older to assess the initial efficacy and feasibility of the adapted SBI during a home health visit (n=12, 4 in each racial/ethnic group).

Research projects dealing with minority health that received research support from UCLA OAIC Resource Cores 2014-2015:

- **Trial to increase walking sedentary older Latinos** (PI: Sarkisian, C)
  OAIC IBC provided analysis of metabolic (insulin) and inflammatory (CRP) markers. Findings indicate that in sedentary older Latinos, increasing physical activity was associated with improvements in these metabolic and inflammatory markers of health. The IBC assisted with manuscript preparation.

- **Family care of older Latinos with Diabetes** (PI: Mendez-Luck, C)
  OAIC Recruitment and Retention Core (RRC) facilitated recruitment and enrollment of dyads of seniors with diabetes and their adult caregivers in the Phase 3 pilot intervention.

- **African Americans with congestive heart failure** (PI: Briggs-Malonson, M)
  OAIC RRC facilitated connections with community partners to help recruit and enroll focus group participants. Collaborated with manuscript preparation.

- **Effectiveness of an intensive dietary sodium intervention in elderly Latinos** (PI: Macabasco, A)
  OAIC RRC is actively assisting with participant recruitment for Phase II of this study.

- **Exploring the Social Support of Gay Men in Sobriety** (PI: Del Pino, H)
  OAIC RRC facilitated recruitment by connecting with LA Gay and Lesbian Center.

- **Focus Groups of older, low-income Latino adults about retirement saving** (PI: Blanco).
  OAIC RRC facilitated recruitment through the Mexican American Opportunity Foundation.


Section I. Description of Center

The UCSF Claude D. Pepper Older Americans Independence Center

Established in 2013, the UCSF Claude D. Pepper Older Americans Independence Center focuses on addressing predictors, characteristics, and outcomes of late-life disability in vulnerable populations at increased risk for disability or death. Late-life disability, defined as needing help with daily activities, is common, burdensome, and costly to patients, families, and society. Late-life disability is influenced by medical vulnerabilities (including comorbid illnesses, aspects of medical care, medicines, procedures, neuropsychiatric conditions, and behaviors), social vulnerabilities (social supports, financial resources, communication and literacy, and ethnicity), and their interaction. The overriding goal of the UCSF OAIC is to improve the health care and quality of life of vulnerable older adults with or at risk for disability through the following aims:

1) Catalyze research on disability in vulnerable older persons at UCSF by serving as a hub that brings together scholars and leverages resources;  
2) Provide tangible, high-value support to funded projects at UCSF that stimulate new research on disability, and lead to new research opportunities for senior and junior investigators;  
3) Support pilot studies that accelerate science and lead to research funding in late life disability;  
4) Identify the future leaders of geriatrics research and support them with career development funding and exceptional mentoring; and  
5) Develop a leadership and administrative structure that spurs interdisciplinary collaboration, making the OAIC greater than the sum of its parts.

Our Center supports researchers who share our passion for improving the well-being of older persons. We view our resources as venture capital that will catalyze the careers and research paths of investigators who will do cutting edge research that advances the care, health, and wellbeing of older persons, both within the UCSF community and nationally.

Principal Investigator
Kenneth Covinsky MD, MPH  
University of California, San Francisco, Division of Geriatrics  
SFVAMC Section of Geriatrics and Palliative Medicine  
4150 Clement (181G)  
San Francisco, CA 94121  
415-221-4810, ext 4363  
Ken.Covinsky@ucsf.edu
Section II. Research, Resources and Activities

A. Cores:

The Leadership Administrative Core (LAC) plays the central role in coordinating the five UCSF OAIC cores, in maintaining communication across programs, and identifying new opportunities, both within and outside the OAIC. The LAC monitors the success of each core based on tangible metrics of productivity: Research leading to publications in the highest impact journals and new NIH grant funding. The LAC monitors, stimulates, evaluates, remediates, and reports progress toward the goals of the OAIC. The LAC also maintains the substantial collaborations with other UCSF research centers, including the UCSF CTSI and RCMAR, and seeks to establish new collaborations which will leverage OAIC resources and develop new and established investigators in aging research. The overall goal of the LAC is to provide the leadership and administration to support the activities of the entire UCSF OAIC.

Core Leader:
Kenneth Covinsky, MD, MPH
University of California, San Francisco, Division of Geriatrics
SFVAMC Section of Geriatrics and Palliative Medicine
4150 Clement (181G)
San Francisco, CA 94121
415-221-4810, ext 4363
Ken.Covinsky@ucsf.edu

The Research Career Development Core (RCDC) identifies, supports, and nurtures talented junior investigators who will become national leaders in aging research through the RCDC Scholars Program and Advanced Scholars Program. The RCDC Scholars Program targets early career faculty and seeks to accelerate their path towards NIA K awards. The Advanced Scholars Program targets current K award recipients and accelerates the path towards their first R01. Both programs provide extensive mentoring and opportunities to participate in an innovative series of seminars designed to develop skills essential to success in aging research, facilitate interdisciplinary communication, build knowledge and relationships that will stimulate translation between basic and clinical research, and accelerate their productivity. The RCDC leadership also works with leaders of the Resource Cores to provide scholars access to additional support. These mentorship and curricular programs help junior investigators progress along the pathways that lead to high impact publications and grant funding that develops the scholar’s national reputation as a leader in their area. Mentoring services, seminar series, resource core services, and programmatic support are also available to Associate Scholars whose goals are to develop careers in aging research. A particular focus of the Associate Scholars Program is junior faculty who have trained outside of geriatric medicine, but seek to incorporate Geriatric principles into their developing research program. The Research Career Development Core also sponsors a diversity supplement program to increase the number of faculty members from underrepresented and diverse backgrounds conducting aging research at UCSF.
Current Career Development Scholars:

Rebecca Brown, MD, Assistant Professor, Division of Geriatrics
Dr. Brown’s research program focuses on how socio-economic disadvantage contributes to the early development of Geriatric problems, including ADL and IADL disability, cognitive impairment, and falls. She is using the Health and Retirement Study (HRS) to conduct a nationally representative study of the impact of poverty (as assessed by multiple SES measures) on the early development of these usually “Geriatric” problems. She plans a career that will consider the impact of a comprehensive model of social vulnerability. This model will extend her previous work on homelessness, extend her RCDC work on poverty, and also consider factors such as substance abuse, social isolation, and mental illness. Following receipt of her K23 award, Dr. Brown transitioned from a Research Career Development Junior Scholar to a Research Career Development Advanced Scholar.

Ryan Greysen, MD, Assistant Professor, Division of Hospital Medicine
Dr. Greysen’s background in sociology and quality of care has convinced him that the disease focused approach to post-discharge care in hospital medicine needs to be complemented by a more patient-centered approach grounded in principles of Geriatrics. His central hypothesis is that poor post-discharge outcomes, like readmission, are highly driven by social vulnerability (such as limited social support and low SES) as well as the common failure to recognize common consequences of hospitalization, such as progressive disability and cognitive decline. Following receipt of his K23 award, Dr. Greysen transitioned from a Research Career Development Junior Scholar to a Research Career Development Advanced Scholar.

Sei Lee, MD, MAS, Associate Professor, Division of Geriatrics
Dr. Lee is a Geriatrician with an innovative focus on improving care of frail elders with diabetes. He has developed the hypothesis that frail elders, especially in nursing homes, are a vulnerable population at risk from overtreatment and the unintended consequences of disease guidelines. His focus is on identifying the risks and benefits of glycemic control in this vulnerable population.

Alex Smith, MD, MPH, Assistant Professor, Division of Geriatrics
Dr. Smith is a Palliative Medicine physician and UCSF His research interest is to improve quality of life in elders with disability. RCDC program support and mentoring are directed at obtaining data and training that will lead to a R01 intervention study to improve quality of life in vulnerable disabled elders. His career plan will focus on further developing his understanding of disability and its measurement, and the principles underlying the design of successful Geriatric interventions.

Brie Williams, MD, MS, Associate Professor, Division of Geriatrics
Dr. Williams is a Geriatrician and NIA K23 awardee. Her work has examined health outcomes and the provision of health care in older prisoners. Her research has determined that cognitive impairment may be a crucial determinant of poor health outcomes in older prisoners. As an advanced scholar, she will collect preliminary data that proves she can administer cognitive instruments in the jail setting.
**Eleni Linos, MD,** Assistant Professor, Department of Dermatology
Dr. Linos is a Dermatologist and Epidemiologist interested in improving the quality of life of older adults with skin cancer. Her work focuses on the development of a decision-tool for elderly patients and those with limited life expectancy who have non-melanoma skin cancer. The purpose of this tool is to inform a patient of the potential benefits and risks of the various treatment options, thus improving near-end-of-life care for these patients.

**Jennifer Lai, MD, MBA,** Assistant Professor, Division of Gastroenterology
Dr. Lai is a Hepatologist and NIA K23 awardee. Her work examines frailty, a validated geriatric construct of increased vulnerability to physiologic stressors, in liver transplant candidates. This study measures functional status, frailty, and health outcomes of patients on the liver transplant waitlist. Preliminary results indicate that frailty strongly predicts wait-list mortality, even after adjustment for liver disease severity demonstrating the applicability and importance of the frailty construct in this population.

**Raquel Gardner, MD,** Assistant Professor, Department of Neurology
Dr. Gardner is a Neurologist whose research program is dedicated to describing the long-term neurobehavioral sequelae of both recent and remote traumatic brain injury (TBI) in older adults and also to discovering predictors of neurobehavioral decline versus resilience following TBI. The goals of this research are to inform prognostication, risk-stratification, and ultimately treatment and prevention of post-TBI neurobehavioral decline and neurodegeneration in older adults.

**Core Leaders:**
Louise C. Walter, MD
Professor of Medicine
Chief, Division of Geriatrics
University of California, San Francisco
San Francisco VA Medical Center
4150 Clement (181G)
San Francisco, CA 94121
415-221-4810, ext 3052
Louise.Walter@ucsf.edu

Kristine Yaffe, MD
Professor of Medicine
University of California, San Francisco
San Francisco VA Medical Center
4150 Clement (181)
San Francisco, CA 94121
415-221-4810, ext 3985
Kristine.Yaffe@ucsf.edu
The Research Design and Analysis Core (RDAC) provides OAIC investigators access to statistical services at all stages of the research lifecycle. Through the establishment of a central hub of statistical expertise, the RDAC ensures smooth delivery of statistical knowledge and rigor across the spectrum of scientific research at the OAIC. This improves the quality of OAIC research studies, helps nurture trainees, facilitates interdisciplinary research groups, and ultimately enhances research on prediction, characterization, and outcomes of late-life disability, especially in vulnerable populations. The RDAC promotes wider use of state of the art statistical practice, lowers barriers of access to basic statistical services to all research groups including trainees, provides access to specialized statistical resources (such as state of the art prognostic model development, complex longitudinal and latent class analysis, and causal inference methods), and develops statistical procedures targeted to solving problems in aging research, and more specifically to challenges that commonly arise in research on disability and function.

In addition to supporting OAIC investigators with these services, the RDAC has identified a substantial number of UCSF investigators holding extramurally funded grants that support a broad range of interdisciplinary translational research on age-related impairment and disability. Three of these have been selected as providing special opportunities to pursue translational research in the OAIC theme area, and will each be allocated substantial RDAC effort in Year 1 as OAIC affiliated External Projects. For the first External Project, the RDAC provided assistance with developing risk-stratification models to predict thromboembolism recurrence and major hemorrhage and helping the investigators account for missing data, competing outcome events, and complex longitudinal predictor measures in Dr. Margaret Fang’s R01. For the second External Project, the RDAC provided vital assistance for statistical analysis of disability trajectories, accounting for the complex survey-weighted design in the data set, and proper handling of the competing risk of death in the disability analyses in a study by Ken Covinsky, MD on hip fracture in older adults. For the third External Project, the RDAC provided guidance on a range of causal analysis methods including propensity score adjustment, instrumental variables modeling, and local instrumental variables to address essential heterogeneity in a study by Louise Walter, MD on prostate-specific antigen practices and outcomes in the elderly.

Core Leader:
John Boscardin, PhD
Professor of Medicine, Division of Geriatrics
University of California, San Francisco
San Francisco VA Medical Center
4150 Clement (181G)
San Francisco, CA 94121
415.221.4810 x3621
John.Boscardin@ucsf.edu
The Data, Measures, and Accrual Core (DMAC) serves to help investigators leverage existing data to conduct high-value research on late-life disability in vulnerable older adults by 1) aiding the design of research studies using existing data; 2) facilitating the inclusion of measures of function and disability into primary data collection studies and the recruitment of vulnerable older patients for these studies; and 3) developing new tools for capturing functional status data from large datasets. To accomplish these activities, the DMAC provides several types of services.

First, the DMAC provides consultation and data management support for research using existing data sources, with a particular focus on three high-value national datasets: the Health and Retirement Study, national VA data, and the Minimum Data Set, a national registry of data from nursing homes. These services include (a) consultations with experts to help design studies of late-life disability using existing data sources; (b) an online resource library of information about use of the 3 supported datasets for research on late-life disability; and (c) data management support to access and prepare data files for research.

Second, the DMAC consults with investigators to add measures of function and disability to primary data collection studies, and to provide guidance on recruitment and retention of vulnerable older adults in research.

Third, the DMAC supports a development project that investigates the usability and validity of national VA data for measuring functional status in older veterans.

In addition to supporting OAIC investigators with these services, the DMAC supports two External Projects. For the first External Project, the DMAC provided consultation on adding functional status measures and improving recruitment in a study by Christine Miaskowski, PhD on chemotherapy-induced neuropathy in older adults. For the second External Project, the DMAC provided consultation on functional and quality of life measures and data management support for a trial by Dr. Leah Karliner on the impact of bedside interpretation services for older hospitalized adults.

Core Leaders:
Michael Steinman, MD
Associate Professor of Medicine, Division of Geriatrics
University of California, San Francisco
San Francisco VA Medical Center
4150 Clement (181G)
San Francisco, CA 94121
415.221.4810 x3677
Mike.Steinman@ucsf.edu

Christine S Ritchie, MD, MSPH
Professor of Medicine
Harris Fishbon Distinguished Professor
University of California San Francisco
Department of Medicine, Division of Geriatrics
3333 California Street, Suite 380
San Francisco, CA 94143-1265
415.502.0951
Christine.Ritchie@ucsf.edu
The Pilot and Exploratory Studies Core (PESC) facilitates the development and progress of innovative research relating to the Pepper Center focus on the predictors, characteristics, and outcomes of late-life disability, especially in vulnerable older populations. We are especially interested in the interaction of serious clinical conditions, disability, and social disadvantage. The goals of the PESC include: 1) Solicit and select innovative proposals from highly qualified applicants; 2) Provide investigators of PESC studies with the support and infrastructure of the OAIC Cores; 3) Integrate PESC studies and investigators with resources from the UCSF Clinical and Translational Science Institute (CTSI) and other relevant resources at UCSF; 4) Monitor the progress of PESC studies; and 5) Provide mentorship and resources to transform PESC funded studies into successful independently-funded projects. The PESC focuses on identifying projects from outstanding investigators who are conducting aging research that is likely to lead to external funding and is aligned with the OAIC theme.

Current Pilot Studies:

**Andy Auerbach, MD**: Characterizing Post-Acute Care Costs for Older Patients Discharged from an Academic Medical Center

**Emily Finlayson, MD, MS**: Functional Outcomes after Breast Cancer Surgery in Older Nursing Home Residents

**Salomeh Keyhani, MD**: Improving 30-day Readmission Risk Prediction for Hospitalized Older Adults Using Measures of Social Risk and Functional Status from Electronic Medical Records

**Rebecca Sudore, MD**: Piloting a Guide to Prepare Older Adults to Make Informed Decisions for Disability and Serious Illness

**Wolf Mehling, MD**: Paired Integrative Home Exercise for Seniors With Dementia And Their Caregivers: A Pilot Study

**Elena Portacolone, PhD, MBA, MPH**: The Social Isolation of Older Americans Living in High-Crime Neighborhoods: Root Causes and Possible Solutions

**Caroline Stephens, RN, PhD, GNP**: Improving Palliative Care Access Through Technology (ImPacT): A Pilot Study

**Joaquin Anguera, PhD**: Self-Guided Internet and Mobile Health Technologies for the Delivery of Behavioral Interventions in Hispanic/Latino Populations

Core Leaders:

Christine S Ritchie, MD, MSPH
Professor of Medicine, Harris Fishbon Distinguished Professor
University of California San Francisco
Department of Medicine, Division of Geriatrics
3333 California Street, Suite 380
San Francisco, CA 94143-1265
415.502.0951
Christine.Ritchie@ucsf.edu

Brie Williams, MD, MS
Associate Professor of Medicine
University of California, San Francisco
3333 California Street, Suite 380
San Francisco, CA 94143-1265
415.514.0720
B. Research:

Pepper Development Projects:

Development Project 1: Statistical Methods and Software for Validating the Prognostic Model Building Process

A common goal in aging research is to develop accurate prognostic models for functional outcomes. The OAIC faculty have been leaders in the development of methods for prognostic modeling and their translational use in clinical medicine in settings such as cancer screening, diabetes, and in broader aging populations. Validation of the prognostic model is critically important to guarantee that its predictive accuracy will not degrade when applied in external data sources. By far the most common approach in the literature is split-sample validation; the model is developed in just one portion of the data and then validated in the remaining portion. Any discrepancy between the predictive accuracy in the development and validation sets is regarded as evidence of overfitting or optimism. The statistical literature is in strong agreement that split-sample assessment of model optimism is extremely inefficient for two reasons: (i) there is a substantial loss of estimation precision from developing the model in a portion of the data, and (ii) unless sample sizes are extremely large, little can be learned about the model optimism from a single split-sample.

Alternative approaches to assessing model optimism that make full use of the data include cross-validation and bootstrapping. These methods have much in common in that they (i) replicate the development and validation cycle many times and (ii) use a full or nearly full version of the dataset for each cycle. One difficulty in routinely implementing either cross-validation or bootstrapping has been a lack of user-friendly software to implement the computationally intensive calculations. Furthermore, the algorithms in the literature focus on optimism due to estimating the model coefficients in the development sample (i.e. maximum likelihood estimation means that the model coefficients are optimally chosen for the development sample) but for the most part ignore optimism due to overfitting in the model building process (e.g. selection of predictors; categorization of continuous predictors; choices related to functional form for continuous predictors).

This development project aims to develop cross-validation and bootstrapping algorithms to assess model optimism that consider all of the steps that investigators use in the prognostic model-building process including: (i) explicitly acknowledging that predictor construction is not usually pre-specified, e.g. continuous predictors are often categorized using their observed distributions in the data; (ii) reflecting that variable selection is often a mix of pre-specification, inclusion of bivariately significant predictors, and stepwise or best subsets selection. The algorithms were developed in both SAS and Stata to allow researchers to routinely obtain an honest and efficient assessment of this full process model optimism.

Our software is novel for several reasons. First, analysts using SAS or Stata were not previously able to routinely assess optimism in the prognostic model building process. With the exception of Harrell’s rms library, software implementations of even simplistic bootstrapping or cross-validation algorithms for assessing model optimism are not widely or routinely used by analysts. Second, we partitioned the optimism into that due to coefficient estimation and that due to the details of the model building process.
Development Project 2: Measurement and Validation of Functional Measures in National VA Databases

Large clinical and administrative databases have been the source of extensive research. However, because data on functional status and disability are often not systematically collected during clinical care, studies of late-life disability have been unable to take advantage of these large-scale data sources.

Recent developments in VA provide a potential breakthrough in this area. Over the past 3 years, VA’s central office has been encouraging medical centers to collect annual data on functional status for all patients age 75 years and older, including information on Katz Activities of Daily Living (ADLs) and Lawton Instrumental Activities of Daily Living (IADLs). It is estimated that over half of VA facilities are routinely collecting functional status data, with data collection typically done by clinic nurses during patient triage and entered into checkbox formatted templates in the electronic medical record. In most facilities, data from these checkboxes are captured as a “health factor,” a discrete and searchable data field. These data can potentially be merged with information from other VA databases to answer novel questions about the epidemiology, predictors, and outcomes of disability in the millions of older veterans who receive care through VA.

Despite this tremendous potential, we know of no attempts to use these data for research or to develop strategies for reliably extracting these data from VA information systems and/or validate their accuracy. Validating the accuracy of these data is of critical importance, as it is unclear how accurately functional status data are being assessed and recorded in routine clinical care.

Thus, our second development project is a validation study that compares information recorded on ADL and IADL status during routine clinical care with the same data evaluated in a structured research setting.

**Specific Aim 1:** To identify how functional status data are encoded across VA health care systems, and to develop automated tools to extract these data from national VA data sources.

**Specific Aim 2:** To assess the validity of functional status data recorded in 3 VA health systems compared with a gold standard of structured self-report.

For Aim 1, we have started to work with VA’s Informatics and Computing Infrastructure (VINCI) to identify and extract health factor data on functional status from VA’s Corporate Data Warehouse (CDW). Because templates for coding and storing health factor information are not fully consistent across local VA health systems, we will use specific keywords (such as “ADL” and “bathing”) to identify and extract relevant health factor data fields in an iterative process. Extraction of such data is simpler and more reliable than natural language processing, since functional status data are entered into a set template rather than as free text notations.

For Aim 2, we will validate chart-recorded functional status against structured self-report data collected from patients at 3 VA sites. Twice per week, we will extract Corporate Data Warehouse data from each site to identify patients age 75 and older who had new functional status data entered within the past week (source databases are updated nightly). We will stratify these patients into functional strata (independent in all ADLs vs dependent in 1 or more ADLs) and contact a random sample of patients within each stratum by phone within 2 weeks of their clinic visit. After obtaining verbal consent (see end of this section for more information on human subjects protections), we will use the 6-item Short Blessed Test to assess cognitive status. For subjects with no to minimal cognitive impairment (test score ≤8), we will use standardized research questionnaires to ask patients about their need for assistance with the 6 Katz ADLs and 7 Lawton IADLs, and whether any of these have changed since their last clinic visit. (Previous
studies have found that the Katz and other ADL scales are reliable when administered by telephone.) Because self-report is the criterion standard for these functional status measures, we will compare these standardized self-reports against functional status measures recorded for the same patients in VA health factor data. Our primary analysis will evaluate the sensitivity and specificity of ADL assessment in VA, dichotomized into any versus no ADL dependencies, and assess Spearman correlation between the chart-based and research-based ADL scores (with scores from 0-6). Given an estimated sensitivity and specificity of 0.85-0.90 and Spearman correlation coefficient of 0.80, a sample size of 300 will produce 95% confidence intervals of approximately +/- 0.05 around our point estimates.

We will share our data extraction algorithms with VA’s VINCI research program and Office of Geriatrics and Extended Care. If our study confirms the validity of VA functional status data, next steps would include investigating the predictive validity of these measures on health services utilization and outcomes. Similarly, we will work with UCSF Medical Center and other groups to promote collection of functional status data in their clinical information systems. Because functional status data predict hospital admission (or re-admission), they are likely to be of interest to health system administrators.

**Pepper Supported External Projects:**

We have identified a substantial number of UCSF investigators holding extramurally funded grants that support a broad range of interdisciplinary translational research on age-related impairment and disability. Five of these have been selected as providing special opportunities to pursue translational research in the OAIC theme area, and have each be allocated substantial RDAC and DMAC effort as OAIC affiliated External Projects.

**External Project 1: Anticoagulation Treatment and Long-Term Outcomes after Venous Thromboembolism** – Margaret Fang (PI). Recurrent venous thromboembolism (VTE) and bleeding complications of its treatment often cause functional impairment and late-life disability, or accelerate their course. This project focuses on predicting long-term outcomes of venous thromboembolism and how best to balance the risks and benefits of anticoagulant therapy, including in vulnerable older patients. The RDAC provided assistance with developing risk-stratification models to predict thromboembolism recurrence and major hemorrhage and helped the investigators account for missing data, competing outcome events, and complex longitudinal predictor measures.

**External Project 2: Needs and Outcomes of Elders with Hip Fracture: Supportive, Functional, Palliative** – Kenneth Covinsky (PI). Hip fracture is a leading cause of late-life disability in the elderly. This research aims to describe trajectories of disability in the two years before and the two years after hip fracture and to determine which elders are at highest risk for death and disability following hip fracture. The RDAC has provided vital assistance for statistical analysis of disability trajectories, accounting for the complex survey-weighted design in the data set, and proper handling of the competing risk of death in the disability analyses.

**External Project 3: Prostate-Specific Antigen Practices and Outcomes in the Elderly** – Louise Walter (PI). Prostate-specific antigen screening in elderly men can potentially lead to harmful downstream consequences and may increase late-life disability. This research project looks at differences in downstream outcomes between prostate-specific antigen screened and non-screened groups. The RDAC has provided guidance on a range of causal analysis methods.
including propensity score adjustment, instrumental variables modeling, and local instrumental variables to address essential heterogeneity.

External Project 4: Characterization Of and Treatment for Chemotherapy Neuropathy – Christine Miaskowski (PI). This study seeks to characterize chemotherapy-induced peripheral neuropathy (CIN) by studying a sample of patients with (n=400) and without (n=200) CIN who have chemotherapy, and evaluating differences in phenotypic (i.e., sensory and motor characteristics, mood, symptoms, quality of life) and genotypic characteristics (i.e., candidate gene studies). The DMAC provided support for integration of functional status and disability measures into the data collection procedures. DMAC consultants helped the investigators think through, select, and understand the most high-yield measures in this area that are applicable to the study, allowing the team to better evaluate the impact of CIN (and potential treatments thereof) on function and disability. Second, patients with extensive non-cancer medical conditions and/or disadvantaged social standing can be difficult to recruit into studies. The DMAC worked with the study team to identify ways in which the team could increase inclusion and retention of these patient populations. This included identifying and making connections with clinical sites rich in these types of patients, and guidance on increasing recruitment and retention for this population that has many reasons to decline or withdraw from participation in a study such as this one.

External Project 5: Bedside Interpreter Intervention, Hospital Outcomes of Older LEP Patients – Leah Karliner (PI). This study is evaluating the impact of an interpreter intervention for older, hospitalized patients with limited English proficiency (LEP) on healthcare utilization and patient/provider satisfaction. The DMAC assisted Dr. Karliner to integrate optimal measures of function and disability into her study, thus better understanding how improving communication in this vulnerable group may improve functioning within the hospital and after discharge. In particular, the DMAC provided guidance on conceptualizing which types of outcome measures would be most valuable in this study setting, selecting specific measures, and helping her develop the protocols to implement these measures. Once data have been collected, Dr. Karliner will work with the DMAC again to help interpret the meaning of findings related to disability-related outcome measures, and to publish these findings in the peer-reviewed literature. In addition, the DMAC is assisting with data management of the project, providing assistance with quality assurance and ensuring the integrity of the data.

In addition to the External Projects above, which represent close ongoing involvement, Drs. Steinman, Ritchie, Covinsky, Walter, and other Pepper faculty have met with and supported a number of other investigators in targeted consultations. To provide a representative, but in, sample, these include: supporting Dr. Beth Cohen to learn about and access the Health and Retirement study to evaluate the association between lifetime trauma exposure and late-life outcomes; advising Dr. Margot Kushel on methods for measuring functional impairment in a cohort of older homeless adults she is developing; helping Dr. Leah Karliner interpret measures of functional status for an R01-supported interpreter intervention for hospitalized older adults; advising Dr. Christine Miaskowski on methods to improve recruitment of vulnerable older adults for a study of chemotherapy-induced neuropathy; providing guidance to colleagues at the UCSF Memory and Aging Center on research design; and several others.
C. Pilots:

**Andy Auerbach, MD**, Professor, Division of Hospital Medicine  
Pilot: **Characterizing Post-Acute Care Costs for Older Patients Discharged from an Academic Medical Center**  
The goal of this study is to generate estimates of post-discharge utilization patterns among adult Medicare beneficiaries discharged from UCSF Medical Center between 1/1/2012 and 12/31/2012. Dr. Auerbach will link CMS data to rich administrative data already available at UCSF. These estimates will in turn be used to develop clinical research grants to support inpatient transitions of care programs (e.g. use of discharge coordinators), consultative services such as palliative care services, and to potentially support novel demonstration projects where post-acute care costs are bundled or shared among key stakeholders.

**Emily Finlayson, MD, MS**, Associate Professor, UCSF Department of Surgery  
Pilot: **Functional Outcomes after Breast Cancer Surgery in Older Nursing Home Residents**  
The goals of this pilot project are to determine the functional trajectories of older women who undergo breast cancer surgery while living in a nursing home, and to provide preliminary data for an R01 application for a broader study of the downstream consequences of mammography and surgical treatment of breast cancer among nursing home residents.

**Salomeh Keyhani, MD**, Associate Professor, UCSF Division of General Internal Medicine and the San Francisco VA Medical Center  
Pilot: **Improving 30-day Readmission Risk Prediction for Hospitalized Older Adults Using Measures of Social Risk and Functional Status from Electronic Medical Records**  
The goal of this pilot is to develop natural language processing algorithms to extract data on social risk and function from electronic health records in order to improve 30-day readmission risk prediction for hospitalized older adults. This pilot will also provide preliminary data for an R01 application that will compare the performance of current readmission models, which include demographics and health status, to a model that also includes social risk and function extracted using automated natural language processing algorithms for two conditions: congestive heart failure and stroke.

**Rebecca Sudore, MD**, Assistant Professor, Division of Geriatrics  
UCSF Pepper Center Co-Director of Diversity  
Pilot: **Piloting a Guide to Prepare Older Adults to Make Informed Decisions for Disability and Serious Illness**  
The goal of this pilot study is to obtain preliminary data about the efficacy of an interactive, multimedia web-based intervention, called PREPARE, designed to improve decision making for diverse, older adults over the course of disability and serious illness (www.inetsite1.com). This pilot will generate data to support an R01 application to test the efficacy of PREPARE among diverse older adults with disability (≥ 1 dependence in an instrumental activity of daily living(IADL)) and < 2 years life expectancy (determined by physicians) in a county healthcare system.
Elena Portacolone, PhD, MBA, MPH, Assistant Professor of Nursing
Pilot: The Social Isolation of Older Americans Living in High-Crime Neighborhoods: Root Causes and Possible Solutions
Despite the fact that living in high crime neighborhoods is likely to increase isolation and therefore have poor health outcomes, very little is known about the subjective experience of isolated older adults living in these areas. Furthermore, only partial knowledge is available on the formal and informal support available to isolated older residents of high-crime neighborhoods and any gaps in services they may perceive. This study aims to address these knowledge gaps by examining the experience of older adults living in high-crime neighborhoods and understanding the relationships between these individuals and their support networks.

Wolf Mehling, MD, Associate Professor of Medicine
Pilot: Paired Integrative Home Exercise for Seniors With Dementia And Their Caregivers: A Pilot Study
Alzheimer’s dementia is a major public health challenge, and with the absence of disease-altering medications, it is critically important to study alternative strategies. There is also a huge need for innovative programs that assist both individuals with dementia and their caregivers in the community. In an effort to address both of these needs, Dr. Wolf Mehling is conducting a pilot study that consists of a brief series of progressive interactive exercises from sit to stand to be practiced in dyads. The paired exercise intervention shows the potential to ameliorate the impact of dementia for patients and caregivers and has the potential to be widely implemented, thereby addressing the impending dementia epidemic.

Caroline Stephens, RN, PhD, GNP, Assistant Professor of Nursing
Pilot: Improving Palliative Care Access Through Technology (ImPacTT): A Pilot Study
Nursing homes are increasingly becoming the place of care and site of death for frail older adults dying from multiple chronic illnesses. Unfortunately, little is known about nursing home residents and family experiences with symptom management and advanced care planning, particularly in an ethnically and racially diverse, palliative care-eligible population. This pilot study builds on focus group data and hospital/nursing home partnerships to assess the feasibility, cost and resident/family outcomes of a technology-enhanced hospital-based palliative care team. The goal of this project is to evaluate how telehealth can extend the reach of palliative care consult service and improve access to palliative care through technology.
Section III. Career Development: Provide names and funding subsequent to Pepper pilot funding.

Research Career Development Advanced Scholars

Sei Lee, MD, MAS, Associate Professor, Division of Geriatrics
Dr. Lee received a VA HSR&D Locally Initiated Project grant.
(No grant #) Understanding and Improving Diabetes Care in VA Community Living Centers

Alex Smith, MD, MPH, Assistant Professor, Division of Geriatrics
Dr. Smith received a K23 Beeson Career Development Award.
K23AG040772  Late Life Disability: Epidemiology, Symptoms, Quality of Life

Brie Williams, MD, MS, Associate Professor, Division of Geriatrics
Hartford Geriatrics Health Outcomes Research Program Mini-Grant - 2013
National Palliative Care Research Center Pilot Award: The Relationship between Distressing Symptoms, Functional Decline and Emergency Services Use in Older Jail Inmates - 2013
UCSF University Community Partnerships Grant funded - 2013
Diversity Supplement from the National Institute on Aging - 2014
Pilot grant to the Robert Wood Johnson Foundation - 2014
University of California Office of the President Research Catalyst Award: The UC Consortium on Criminal Justice Healthcare - 2014

Rebecca Brown, MD, Assistant Professor, Division of Geriatrics
Dr. Brown received a NIH/NIA K23 grant and KL2 from the National Center for Advancing Translational Sciences.
KL2
K23 AG045290  Epidemiology and Outcomes of Premature Geriatric Syndromes
Following receipt of the K23 award, Dr. Brown transitioned from a Research Career Development Junior Scholar to a Research Career Development Advanced Scholar.

Ryan Greysen, MD, Assistant Clinical Professor, Division of Hospital Medicine
Dr. Greysen received a NIH/NIA K23 grant and KL2 from the National Center for Advancing Translational Sciences.
KL2
K23AG045338  Functional, Cognitive, and Social Vulnerabilities and Hospital Readmission
Following receipt of the K23 award, Dr. Greysen transitioned from a Research Career Development Junior Scholar to a Research Career Development Advanced Scholar.

Jennifer Lai, MD, Assistant Professor of Medicine
Dr. Lai received a K23 Beeson Career Development Award in Aging Research
K23AG048337  Frailty and Functional Status in Older Liver Transplant Patients
Section IV. Publications: Provide only those that are a direct result of Pepper Center resources and list publications published in the 2014-2015 years only.


Section V. External Advisory Board Members Names, Institutions and Years of service

The UCSF Pepper Center’s External Advisory Committee was selected in 2013 and perform their next site visit in September 2015.

**Committee Members:**
Jean Kutner, MD, MSPH, University of Colorado School of Medicine (2013-present)
Mark Lachs, MD, Weill Medical College of Cornell University (2013-present)
Seth Landefeld, MD, University of Alabama at Birmingham (2013-present)
Minority Research

General Brief Description of Minority Activities:
The UCSF OAIC developed an active collaboration with the UCSF RCMAR, led by Dr. Perez-Stable. Dr. Covinsky presented the mission and work of the UCSF OAIC to the RCMAR faculty and trainees, and we developed a process to make OAIC core resources available to the RCMAR. We collaborated with the RCMAR on their pilot studies RFA in 2014 and awarded a joint award to Dr. Joaquin Anguera.

Minority Trainees:
The RCDC seeks to encourage diversity among investigators by outreach programs that encourage applications from women and minority investigators. Two of the RCDC funded investigators are women. One of our investigators is from a group included in the NIH definition of persons underrepresented in biomedical research. (Dr. Smith-native Hawaiian.) Another of our investigators, Dr. Williams, meets the recently expanded NIH definition of diverse investigators, which includes investigators who grew up in circumstances of severe socio-economic deprivation (defined as most of childhood in a household with income below the poverty line).

Minority-Related Research Projects:
PESC Awardee, Joaquin Anguera, PhD, was awarded a joint award between the UCSF Pepper Center and the UCSF Center for Aging in Diverse Communities in 2014. Dr. Anguera is a neuroscientist who specializes in developing & implementing cognitive training interventions. Currently, he works to translate the BRIGHTEN study’s cognitive assessment tool into Spanish to deploy it into Spanish-speaking communities.

RCDC Advanced Scholar, Alex Smith MD, MPH has a strong interest in understanding how cultural factors influence the perspectives and experiences of patients with serious illness or disability and their families. For example, in a recent study, Dr. Smith found that two-thirds of Chinese American, African American, Latino, and white elders with disability would want to be told their prognosis if they had less than 5 years left to live. He therefore argues that clinicians should offer to discuss prognosis with their very elderly patients, both because it allows for more informed medical decision making and because many patients want to know so they can prepare for the future.
Dr. Smith’s recent work has examined cultural differences in how informal caregivers view their role in caring for older adults aging in the community, and how this role affects caregivers’ quality of life. Another study explored preferences for communication about prognosis, which may vary depending on one’s unique cultural history.

Pilot Awardee Rebecca Sudore, MD’s primary research focus is on improving advance care planning and medical decision making for vulnerable older adults with limited health literacy. She published the first prospective study demonstrating the effect of limited literacy on mortality in the elderly and has shown that elders with limited literacy have greater difficulty making
medical decisions for informed consent and advance care planning. She has also designed and tested an informed consent process for patients with limited literacy and an advance directive that is both literacy and culturally appropriate. The goal of her pilot study is to obtain preliminary data about the efficacy of an interactive, multimedia web-based intervention, called PREPARE, designed to improve decision making for these diverse, older adults. Dr. Sudore recently received a three-year PCORI grant to develop PREPARE in Spanish and test with Hispanic users. The Hispanic and Latino population is increasing in the US, with an estimated 3 million Latinos aged 65 years and older. This population is expected to increase six-fold by 2030.

In addition to the specific projects listed above, all 7 RCDC awardees are conducting research using populations or datasets that include large proportions of women and ethnic minority subjects.

Publications Pertaining to Minority Research:


The University of California, San Francisco
Claude D. Pepper Older Americans Independence Center

2014-2015 Recognition and Awards

Ken Covinsky, MD, MPH
Visiting Professor, University of Haifa, Haifa, Israel – 2014
Associate Editor, JAMA Internal Medicine
Hal Luft Award for Mentoring in Health Services and Policy Research (UCSF)
Mentee recognition: Ryan Greysen, Best Oral Abstract, Society of Hospital Medicine

Louise Walter, MD
American Geriatrics Society Outstanding Service on the Research Committee – 2014

Kristine Yaffe, MD
UCSF Academic Senate Clinical Science Faculty Research Lecturer Award – Clinical Science Award – 2013

Mike Steinman, MD
Awarded the Faculty Advising in the Master’s Degree in Clinical Research program
Completed CTSI Mentor Training Program
Awarded the UCSF Academic Senate Distinction in Mentoring Award
Recognition as Exceptional Reviewer, Annals of Internal Medicine and Pharmacoepidemiology and Drug Safety
Mentees won awards for best poster in class at the Society of General Internal Medicine (Meera Sheffrin, MD), and best poster at the 2014 OAIC meeting (Kasia Lipska, MD)

Christine Ritchie, MD, MSPH
Selected as a distinguished panelist for the 2014 UCSF Department of Medicine Quality and Safety Symposium – 2014

Brie Williams, MD, MS
Editor-in-Chief of Current Geriatrics Diagnosis and Treatment
Invited workshop member (1 of 15) for the IOM and National Academy of Sciences “Workshop on Incarceration and Health”
Outstanding Teacher of the Year Award, UCSF Division of Geriatrics - 2014
President’s Research Catalyst Award, University of California Office of the President - 2014
Nominee, The Distinction in Mentoring Award, UCSF – 2015

Alex Smith, MD, MPH
American Academy of Hospice and Palliative Medicine PDIA National Leadership Award-2014.
UCSF Department of Medicine Voice “TED-like” Talk winner - 2014
Sei Lee, MD, MAS
American Geriatrics Society Outstanding Community Service from the Quality Performance and Measurement Committee –2014

Rebecca Brown, MD
Best Research Mentor, Medical Student Training in Aging Research (MSTAR) program, UCSF-2014
Benjamin Lieberman Scholar Award, Division of Geriatrics, UCSF

Ryan Greysen, MD
American Geriatrics Society New Investigator Award—2014
American Geriatrics Society Outstanding Junior Research Manuscript Award—2014
UCSF Department of Medicine Voice “TED-like” Talk winner - 2014

Rebecca Sudore, MD
Mentee won AAHPM Investigator Paper Award in the Junior Faculty category – 2014
AGS Outstanding Scientific Achievement for Clinical Investigation Award – 2015

Salomeh Keyhani, MD
Dr. Keyhani serves as the Policy Lead for the VA Stroke QUERI and is responsible for setting the strategic aims for the Stroke QUERI's policy portfolio.

Jennifer Lai, MD
American Geriatrics Society New Investigator Award – 2015
San Francisco Business Times “Top 40 under 40” Leadership Award
American Geriatrics Society Presidential Poster Awards for 2 abstracts

Raquel Gardner, MD
Harvard Medical School Loan Repayment Assistance Program Awardee - 2015

Elena Portacolone, PhD, MBA, MPH
Invited to attend the Butler-Williams Scholar Program at the National Institute on Aging (NIA) for promising early-stage investigators in the field of aging.- 2014
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.

The research objectives:
- 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

The educational objectives:
- 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.
Phone: 352-294-5800    Fax: 352-294-5836   Email: mpahor@ufl.edu

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:

Natalie Ebner, Ph.D.  natalie.ebner@ufl.edu
Assistant Professor, Department of Psychology

Yenisel Cruz-Almeida, Ph.D.  cryeni@ufl.edu
Assistant Professor, Departments of Aging & Geriatric Research and Neuroscience

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.
Phone: 352-294-5800   Fax: 352-294-5836   Email: mpahor@ufl.edu

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 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.
Phone: 352-273-6796   Fax: 352-273-5920   Email: cleeuwen@ufl.edu

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 (Northern, Western blot and Quantitative-PCR, enzyme-linked immunosorbent assays), genome-wide gene expression analysis using a novel microarray technology, analytical chemistry (liquid chromatography-mass spectrometry-mass spectrometry and gas chromatography mass spectrometry using stable isotope dilution techniques) 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, Emotion, Motor, Sensation/Pain. 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.

**Biostatistics and Data Management Core (RC 3)**
Leader: Samuel Wu, Ph.D.
Phone: 352-392-1941   Fax: 352-273-5365   Email: samuw@biostat.ufl.edu

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 The UF & Shands Academic Health Center’s new electronic medical record system (EPIC) 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.
Phone: 352-273-5914    Fax: 352-294-5836    Email: tmanini@ufl.edu sanjayranka@gmail.com

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.
Phone: 352-294-5800       Fax: 352-294-5836       Email: mpahor@ufl.edu
Co-Leader: Christy Carter, Ph.D.
Phone: 352-273-5727       Fax: 352-294-5836       Email: ccarter@ufl.edu

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

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 (Table 1a). The UF OAIC has also supported 100 grants that have 
been completed (Table 1b).

<table>
<thead>
<tr>
<th>Title of Grant</th>
<th>PI</th>
<th>Award Date</th>
<th>Proposed End Date</th>
<th>Source</th>
<th>OAIC Core support</th>
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<td>Aspirin in reducing events in the elderly</td>
<td>Anton, S</td>
<td>7/1/2010</td>
<td>1/31/2017</td>
<td>NIH U01AG029824</td>
<td>RC 1, 2</td>
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<td>Efficacy of Fermented Papaya Preparation (FPP) on Markers of Systemic Inflammation</td>
<td>Anton, S</td>
<td>7/1/2013</td>
<td>6/30/2015</td>
<td>Osato Research Institute, Japan</td>
<td>RC 1</td>
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<td>REVIVE-Resveratrol to enhance vitality and vigor in elders</td>
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<td>5/31/2017</td>
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<td>End Date</td>
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<td>Net tools for the characterization of gene prediction in prokaryote genomes; application to pseudomonas aeruginosa genomes</td>
<td>Brocchieri, L</td>
<td>8/5/2010</td>
<td>7/31/2015</td>
<td>NIH</td>
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<td>Working memory: a critical factor underlying alcohol reduction intervention response</td>
<td>Bryant, V (Woods)</td>
<td>5/1/2015</td>
<td>4/30/2018</td>
<td>NIAAA</td>
<td>F31AA024060</td>
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<td>Daily consumption of an electro-kinetically modified water beverage and its effects on physical fitness and well-being for an older adult population</td>
<td>Buford, T (Borsa)</td>
<td>9/1/2014</td>
<td>8/31/2015</td>
<td>Revalesio Corp.</td>
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<td>KAATSU training to enhance physical function of older adults with osteoarthritis</td>
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<td>4/1/2014</td>
<td>3/31/2016</td>
<td>NIH</td>
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<td>Multi-modal intervention to reduce cardiovascular risk among hypertensive older adults</td>
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<td>7/1/2013</td>
<td>6/30/2015</td>
<td>AHA</td>
<td>13SDG17080033</td>
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<td>Development of a clinical assessment tool for the measurement of walking adaptability post-stroke</td>
<td>Clark, D</td>
<td>4/1/2014</td>
<td>3/30/2015</td>
<td>UNF</td>
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<td>Rehabilitation of corticospinal control of walking following stroke</td>
<td>Clark, D</td>
<td>6/1/2014</td>
<td>5/30/2018</td>
<td>VA B1149R</td>
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<td>Alcohol and HIV: Biobehavioral interactions and intervention</td>
<td>Cohen, R</td>
<td>9/30/2010</td>
<td>8/31/2015</td>
<td>NIH</td>
<td>P01AA019072-04</td>
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<td>Cognitive aging and memory clinical translational research program</td>
<td>Cohen, R</td>
<td>6/1/2009</td>
<td>6/30/2016</td>
<td>McKnight Brain Research Foundation</td>
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<td>ENIGMA Center for Worldwide Medicine, Imaging, and Genomics</td>
<td>Cohen, R (Thompson)</td>
<td>7/1/2014</td>
<td>6/30/2018</td>
<td>NIH</td>
<td>1U54EB020403</td>
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<td>Obesity and type-2 diabetes: Bariatric surgery effects on brain function (WISE Brain)</td>
<td>Cohen, R</td>
<td>7/1/2014</td>
<td>3/31/2019</td>
<td>NIH</td>
<td>1R01DK099334</td>
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<td>McKnight Inter-Institute Neuroimaging Initiative</td>
<td>Cohen, R</td>
<td>4/1/2015</td>
<td>3/30/2017</td>
<td>McKnight Brain Research Foundation</td>
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<td>Predicting brain changes in HIV/AIDS</td>
<td>Cohen, R (Thompson)</td>
<td>8/1/2012</td>
<td>7/31/2016</td>
<td>NIH</td>
<td>R01 1NS080655</td>
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<td>Southern HIV Alcohol Research Consortium (SHARC) Admin and Research support core</td>
<td>Cohen, R (Cook)</td>
<td>9/1/2012</td>
<td>8/31/2017</td>
<td>NIH</td>
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<td>Corticostriatal connectivity in OA pain</td>
<td>Cruz-Almeida, Y</td>
<td>6/1/2014</td>
<td>12/31/2015</td>
<td>UF CTSI pilot funding</td>
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<td>Project Description</td>
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<td>Start Date</td>
<td>End Date</td>
<td>Funding Agency</td>
<td>Co-funding Agency</td>
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<td>Neuroimaging age-related changes in pain modulation</td>
<td>Cruz-Almeida, Y</td>
<td>4/1/2015</td>
<td>3/31/2020</td>
<td>NIH 1K01AG048259</td>
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<td>The role of oxytocin in prosocial decision making in aging across humans and monkeys</td>
<td>Ebner (Chang)</td>
<td>9/1/2014</td>
<td>3/31/2015</td>
<td>NIH R24 AG039350</td>
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<td>Age-Targeted Automated Security Cueing Against Web-Based Social Engineering Attacks</td>
<td>Ebner (Oliveira)</td>
<td>9/1/2014</td>
<td>8/31/2016</td>
<td>NSF/SES0-1450624</td>
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<td>Effect of COMT Genetic Polymorphisms on response to propranolol Therapy in TMD</td>
<td>Fillingim, R</td>
<td>9/12/2014</td>
<td>8/31/2017</td>
<td>NIH 1U01DE024169</td>
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<td>Ethnic differences in responses to painful stimuli</td>
<td>Fillingim, R</td>
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<td>4/30/2019</td>
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<td>Pain and Aging Research Translational Initiative</td>
<td>Fillingim, R</td>
<td>9/1/2014</td>
<td>8/31/2019</td>
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<td>Basal Forebrain and Cognitive Aging: Novel Experimental and Therapeutic Avenues</td>
<td>Foster, T (Bizon)</td>
<td>4/1/2014</td>
<td>3/31/2019</td>
<td>NIH 2R01AG029421</td>
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<td>Estrogen and cognition over the lifespan</td>
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<td>Autophagy in liver injury</td>
<td>Leeuwenburgh, C (Kim)</td>
<td>7/1/2014</td>
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<td>Mitophagy: a novel target to improve liver function after ischemia/reperfusion injury</td>
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<td>RESveratrol To Improve Outcomes in older People with PAD (the RESTORE Trial)</td>
<td>Leeuwenburgh, C (McDermott)</td>
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<td>Cohort identification and natural history of sarcopenia in the Health, Aging and Body Composition study</td>
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<td>Novel Functionally-Selective Serotonin 5HT2 Drugs for Amphetamines Abuse/Disorder</td>
<td>Morgan, D</td>
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<td>A randomized double blind placebo controlled parallel group, multicenter study of the effects of repeated doses of subcutaneous REGN1033 treatment with and without exercise in safety, body composition muscle strength and stair climb power</td>
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<td>Randomized Trial of a Multifactorial Fall injury prevention strategy (STRIDE)</td>
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<td>The Effects of Aging on Experimental Models of Pain Inhibition and Facilitation</td>
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<td>Biological Markers of System Burden in Symptomatic Knee OA: A Prospective Study</td>
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<td>Optimizing chronic pain treatment with enhanced neuroplastic responsiveness</td>
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<td>Mitochondrial thioredoxin, caloric restriction, and age-related hearing loss</td>
<td>Someya, S</td>
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<td>Utilizing the RESCUE stroke caregivers website to enhance discharge planning</td>
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<td>Internet and telephone support for stroke caregivers</td>
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<td>Neuromodulation of Working Memory Function in Older Adults</td>
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Table 1b. OAIC support and contributions to completed external grants (completed 4/1/11 - 12/31/14)
The Core support indicated in the table is as follows: RCDC: Research Career Development Core; PESC: Pilot Exploratory Studies Core; LAC: Leadership and Administration Core; RC1: Clinical Translational Research Core; RC2: Metabolism and Biomarkers Core; RC3: Biostatistics and Data Management Core; RC4: Recruitment and Retention Core; RC 6: Data Science Core.
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<td>Role of skeletal muscle blood flow in regeneration and sarcopenia</td>
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<td>Saliva as an alternative to plasma to measure biomarkers in pain</td>
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<td>Evidence based decision making in geriatric genitourinary oncology</td>
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<td>Applying GRADE to health policy decision-making</td>
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<td>Bayesian methods for (Incomplete) longitudinal cancer data</td>
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<td>Effect of exercise on memory in geriatric depression: an fMRI pilot study</td>
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<td>Positron emission tomography with F-18 fluordeoxyglucose to identify early events in latent infection with mycobacterium tuberculosis</td>
<td>Fennelly, K (Ghesani)</td>
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<td>Biopsychosocial influence on shoulder pain</td>
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<td><strong>Ventilator-induced diaphragmatic atrophy: role of FoxO Signaling</strong></td>
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<td>9/15/2009</td>
<td>8/31/2012</td>
<td>NIH R21AG031974</td>
<td>RCDC, RC 1, 2, 3, 4 PESC</td>
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<td><strong>ACTIVE Phase III: UF/WSU Field Site</strong></td>
<td>Marsiske, M</td>
<td>5/1/2006</td>
<td>4/30/2013</td>
<td>NIH U01AG014276</td>
<td>RC 4</td>
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<td><strong>Physical, cognitive and mental health in social context</strong></td>
<td>Marsiske, M</td>
<td>7/1/2002</td>
<td>4/30/2013</td>
<td>NIH T32AG020499</td>
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<td><strong>Platform for multi-modal cognitive enhancement in the elderly (the wellness study)</strong></td>
<td>Marsiske, M (Bowers, D)</td>
<td>7/2/2010</td>
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<td>Novel 5HT2C agonist drugs with 5HT2A antagonist activity for cocaine addiction</td>
<td>Morgan (Booth)</td>
<td>9/30/2007</td>
<td>8/31/2012</td>
<td>NIH R01DA023928</td>
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<td>Novel Functionality-Selective Serotonin 5HT2 Drugs for Amphetamines</td>
<td>Morgan, D</td>
<td>9/16/2012</td>
<td>8/31/2014</td>
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<td>Serotonin 5HT2C Agonist drugs with 5HT2A/2B Antagonist Activity</td>
<td>Booth (Morgan Co-I)</td>
<td>9/16/2012</td>
<td>2/28/2014</td>
<td>Northwestern Univ. #500264</td>
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<td>Aerobic exercise to improve executive language function in older adults</td>
<td>Nocera, J</td>
<td>10/1/2009</td>
<td>9/30/2011</td>
<td>Veterans Affairs E6860M</td>
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<td>AMPS unrestricted educational grant</td>
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<td>11/1/2011</td>
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<td>ASSO Midi Pyrenees Sante France</td>
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<td>Biomarkers Symposium</td>
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<td>Exercise training and inflammatory risk factors for disability</td>
<td>Pahor, M (Nicklas)</td>
<td>9/15/2006</td>
<td>8/31/2011</td>
<td>NIH R01AG027529</td>
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<td>International Conference on Sarcopenia Research</td>
<td>Pahor, M</td>
<td>12/1/2012</td>
<td>5/13/2013</td>
<td>University of Toulouse</td>
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<td>Latent mobility abnormalities and frailty</td>
<td>Pahor, M (Verghese)</td>
<td>8/1/2005</td>
<td>6/30/2011</td>
<td>NIH R01AG025119</td>
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<td>LIFE Biomarkers training conference for young investigators</td>
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<td>3/31/2012</td>
<td>NIH P30AG028740-05S1</td>
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<td>The LIFE Study- biorepository supplement</td>
<td>Pahor, M</td>
<td>9/1/2012</td>
<td>11/30/2012</td>
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<td>Oxidative damage, disability and mortality in elders</td>
<td>Pahor, M</td>
<td>7/1/2007</td>
<td>6/30/2012</td>
<td>NIH R01AG026556</td>
<td>RC 1, RC 2</td>
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<td>Physical activity and depressive symptoms in LIFE-P: effects of genetic polymorphisms and symptom dimensions of depression</td>
<td>Pahor, P / Dotson, V</td>
<td>2/1/2012</td>
<td>11/30/2014</td>
<td>NIH U01 AG022376-07S1</td>
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<td>Testosterone Study-PK Supplement</td>
<td>Pahor, M (Snyder)</td>
<td>6/1/2012</td>
<td>4/30/2013</td>
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<td>Extension family lifestyle intervention project</td>
<td>Perri, M (Janicke)</td>
<td>8/1/2009</td>
<td>7/31/2014</td>
<td>NIH R18DK082374</td>
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<td>Promoting healthy weight with &quot;stability first&quot;</td>
<td>Perri, M (Kieman)</td>
<td>7/11/2007</td>
<td>5/31/2012</td>
<td>NIH R01CA112594</td>
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<td>Rural lifestyle intervention treatment effectiveness trial (rural LITE)</td>
<td>Perri, M</td>
<td>6/1/2008</td>
<td>5/31/2013</td>
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<td>Smart home-based health platform for behavioral monitoring diabetes and obesity</td>
<td>Perri, M (Helal)</td>
<td>9/26/2007</td>
<td>7/31/2012</td>
<td>NIH R21DA024294</td>
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<td>Mechanisms of diet-induced leptin resistance in ARC and VTA</td>
<td>Scarpace, P</td>
<td>7/15/2012</td>
<td>6/30/2013</td>
<td>NIH R01DK091710-01A1</td>
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<td>Training in the neurobiology of aging</td>
<td>Scarpace, P</td>
<td>5/1/2007</td>
<td>4/30/2013</td>
<td>NIH T32AG000196</td>
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**Notes:**
- **RCDC:** Interdisciplinary Research Coordination Center
- **RC:** Research Consortium
- **LAC:** Louisiana Action Coalition
- **PESC:** Pennington Biomedical Res Found./Coca-Cola
- **AMPS:** Aerobic Exercise and Physical Activity Study
- **R01:** National Institute of Health (NIH) R01 Grant
- **U01:** NIH U01 Grant
- **R21:** NIH R21 Grant
- **R24:** NIH R24 Grant
- **T32:** NIH T32 Grant
- **P30:** NIH P30 Grant
- **R18:** NIH R18 Grant
- **R15:** NIH R15 Grant
- **AG:** Ellison Medical Foundation
- **NS:** Pennington Biomedical Research Found.
- **Coca-Cola:** Coca-Cola Foundation
- **RCDC:** Northwestern University
- **RC:** American Heart Association
- **NIH:** National Institutes of Health
- **VA:** Veterans Affairs
- **LAC:** Louisiana Action Coalition
- **PESC:** Pennington Biomedical Res Found./Coca-Cola
- **R15:** NIH R15 Grant
- **R18:** NIH R18 Grant
- **R24:** NIH R24 Grant
- **T32:** NIH T32 Grant
- **P30:** NIH P30 Grant
- **R18:** NIH R18 Grant
- **R15:** NIH R15 Grant
- **AG:** Ellison Medical Foundation
- **NS:** Pennington Biomedical Research Found.
- **Coca-Cola:** Coca-Cola Foundation
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<th>Project Title</th>
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<td>CMS nonpayment for nosocomial injury and the risk of falls in hospitals</td>
<td>Shorr, R</td>
<td>9/30/2009</td>
<td>8/31/2013</td>
<td>NIH R01AG033005</td>
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<td>Gait and balance assessment with live video from the computerized patient record system (CPRS) interface with vista imaging</td>
<td>Shorr, R (Waters)</td>
<td>7/1/2009</td>
<td>6/30/2011</td>
<td>VA (Greenfield Innovators Award)</td>
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<td>Responses to Medicare's nonpayment for preventable hospital complications</td>
<td>Shorr, R</td>
<td>8/1/2011</td>
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<td>Systolic blood pressure intervention trial (SPRINT) clinical center networks</td>
<td>Shorr, R</td>
<td>9/1/2010</td>
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<td>Assessing the impact of chronic pain on biological measures of system burden and cellular aging</td>
<td>Sibille, K</td>
<td>6/30/2012</td>
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<td>Biological Markers of System Burden in Symptomatic Osteoarthritis</td>
<td>Sibille, K (Nelson KL2)</td>
<td>4/1/2012</td>
<td>3/31/2013</td>
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<td>Effects of chronic pain on psychosocial stress</td>
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<td>1/1/2011</td>
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<td>Mitochondrial isocitrate dehydrogenase and age-related hearing loss</td>
<td>Someya, S</td>
<td>7/1/2012</td>
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<td>The role of glutathione reductase in age-related hearing loss</td>
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<td>Web-based informational materials for caregivers of veterans post-stroke</td>
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<td>5/1/2008</td>
<td>1/31/2013</td>
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<td>Interdisciplinary training in rehabilitation and neuromuscular plasticity</td>
<td>Vandenborne, K</td>
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<td>4/30/2013</td>
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<td>Rehabilitation research career development program</td>
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<td>9/25/2007</td>
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<td>Developing a computer adaptive test for assessing safety after traumatic brain injury</td>
<td>Velozo, C (Seel)</td>
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<td>9/30/2011</td>
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<td>Development and validation of a self-efficacy item bank</td>
<td>Velozo, C (Shulman)</td>
<td>9/30/2009</td>
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<td>Comparative resistance exercise effects on knee osteoarthritis pain, functional impairment and cartilage turnover</td>
<td>Vincent, K</td>
<td>7/9/2010</td>
<td>5/31/2013</td>
<td>NIH R03AR059786</td>
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<td>Comparative resistance exercise effects on knee osteoarthritis pain, functional impairment</td>
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<td>12/1/2012</td>
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<td>Study of energy and aging</td>
<td>Wohlgemuth, S (Cummings)</td>
<td>9/30/2009</td>
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<td>Biostatistical Research Support Services for National Parkinson Foundation</td>
<td>Wu, S</td>
<td>4/1/2012</td>
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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.

**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 myocyte. 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 diacylglycerol 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.

The past research development projects are:

**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 evo
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 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 obesity and improved metabolich parameters. The mechanism appears to involve a restoration in the age and obesity impaired decline in leptin signaling. In the third year, we discovered 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 tagnmental area or hypothalamus was effective at detersing 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: A Pilot Study to Evaluate the Role of Brain Integrity on Post-Hospital Sarcopenia**
**Project Leader: Adam Woods, 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 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.

**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.

PRE-CLINICAL

**Project Title:** Effect of Aging on Chronic Heart Failure-Induced Dysfunction in Skeletal Muscle  
**Project Leader:** Peter Adhihetty, Ph.D.

Although CHF originates in the heart, peripheral abnormalities are observed within skeletal muscle leading to muscle atrophy and significant decreases in overall body weight. Clearly, skeletal muscle dysfunction and the extent of its severity, contributes significantly to the clinical phenotype and overall prognosis of CHF patients. Thus, understanding the molecular and cellular mechanisms associated with CHF-induced muscle impairments and loss represents an important and underdeveloped area of research that could lead to clinical therapeutic interventions. However, the detailed mechanisms underlying the pathogenesis of this muscle decline is yet to be determined. Hence, this proposal for the first time, will determine the effect of aging on CHF-induced muscle deterioration, and assess whether gene targeting (gene overexpression) impacting mitochondrial biogenesis may be potential therapeutic interventions for CHF. CHF will be induced (16 weeks following coronary artery ligation) in young and old Fischer 344 x Brown Norway rats (initial ages 6 and 26 months). Additionally, muscle-specific overexpression of the master mitochondrial regulator PGC-1 alpha will be performed in aged CHF animals. We will isolate mitochondria and use a wide spectrum of highly innovative and specialized techniques to assess mitochondrial and overall muscle function including respiration, intravital multiphoton excitation laser-scanning microscopy, and single fiber analysis. Thus, the overall goal of this study is to investigate the underlying mitochondrial-associated mechanisms responsible for skeletal muscle impairments in CHF when combined with aging, and to determine whether mitochondrial function via physiological and/or gene targeting can attenuate these decrements.

**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.

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 nuclear-encoded 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 344×Brown 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.

The completed pilot/exploratory projects are:
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 performance. 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] 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 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 myocytes. 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, myeloperoxidase), 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 regeneration and improved function in aged 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 years. 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
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 walking 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.

Table 1. EXPLORATORY AND PILOT STUDIES SUPPORTED BY THE OAIC 2007-2013

<table>
<thead>
<tr>
<th>PILOT AND EXPLORATORY STUDIES</th>
<th>Grants awarded or progress</th>
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<tbody>
<tr>
<td>1. A network based analysis of systematic inflammation (Borsa)</td>
<td>NIH RO1AR055899, George PI</td>
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<tr>
<td>2. ACE inhibition and muscle quality (Carter)</td>
<td>NIH RO1AG024526 supplement and VA contract, Carter PI</td>
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<tr>
<td>3. Feasibility of computer adaptive testing in elders (Velozo)</td>
<td>Shepherd Center, Seel PI, NIH U01AR057967, Shulman PI</td>
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<tr>
<td>4. Leptin inhibition, blood flow and sarcopenia (Tumer)</td>
<td>American Heart, Erdos PI, VA Tumer PI</td>
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<td>5. Autophagy and sarcopenia in a transgenic mouse model (Wohlgemuth)</td>
<td>NIH RC2AG036594, Cummings PI</td>
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<tr>
<td>6. Acute responses to blood flow restricted exercise (Manini)</td>
<td>State of Florida (LBR), resubmitting NIH R03AG032470, Manini PI, NFL Charities Manini PI, KAATSU Buford PI, Manini CoPI</td>
</tr>
<tr>
<td>7. Resveratrol for reduced muscle lipid content in older adults (Anton/Manini)</td>
<td>Development of MRI P31 spectroscopy methods complete, study in progress, 50% recruitment complete</td>
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<tr>
<td>8. Dose-Response Effects of Weight Loss on Systemic Levels of Inflammation and Oxidative Stress (Anton)</td>
<td>Study in progress, IRB approved, data collection completed, analyses in progress</td>
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<tr>
<td>9. The role of heat shock protein 70 overexpression on the recovery of muscle mass and function following cast immobilization in old rats (Judge)</td>
<td>James and Esther King Biomedical Research Program, Judge PI</td>
</tr>
<tr>
<td>10. Biological effects of weight loss and exercise in elders (Perri/Anton)</td>
<td>NIH K23AT004251 Award, Anton PI</td>
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<td>11. Physical exercise to prevent disability pilot study (Pahor)</td>
<td>NIH R01AG027529, Nicklas PI</td>
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<tr>
<td>12. and 13. Testosterone trial interactive voice response (IVR) pilot #1 and #2 (Pahor)</td>
<td>NIH Supplement U01AG022376-05A2, Pahor PI Funded NIH R21AG031974, Manini PI</td>
</tr>
<tr>
<td>14. Chemotherapy, weakness, fatigue and functional limitation in older breast cancer survivors (Manini)</td>
<td>Study in progress, IRB approved, data collection is in process</td>
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<tr>
<td>15. Resveratrol for improved memory: the RIPE trial (Anton/Manini)</td>
<td>McKnight Brain Research Foundation, Anton, Manini PI Thomas Maren Junior Investigator Award, Anton PI</td>
</tr>
<tr>
<td>16. Myogenic and proteolytic regulators in blood flow restricted Exercise (Manini)</td>
<td>Enrollment is complete, assays and data analyses are in progress, Grant funded: KAATSU Buford PI, Manini CoPI Grants submitted: NIH R03AG032470, Manini PI, NFL Charities Manini PI, NIH R13 Cook PI (Manini, Col)</td>
</tr>
<tr>
<td>17. The influence of resistance exercise on physical function, depression, quality of life, muscle morphology and bone metabolism in stroke patients (Vincent)</td>
<td>NIH R03AR059786, State of Florida, Foundation for Physical Medicine and Rehabilitation, Vincent PI</td>
</tr>
<tr>
<td>18. Reversal of age-related obesity by synergy of leptin and negligible wheel running (Shapiro)</td>
<td>Paper published, study complete, Mechanisms of diet-induced leptin resistance in ARC and VTA Scarpace, PI. Awarded 7/15/2012 to 7/14/2016</td>
</tr>
<tr>
<td>19. Molecular mechanisms of skeletal muscle loss in HIV-infected older persons (Manini)</td>
<td>Enrollment 100% complete, tissue analysis ongoing, manuscript is in preparation. Grant submission in September 2011</td>
</tr>
<tr>
<td>20. Locomotor reserve: a novel approach for detecting mobility deficits with aging (Clark)</td>
<td>NIH R01AG045218-01 National Institutes of Health Determinants of weakness and emerging mobility deficits in healthy older adults $1,000,000 Role: Principal Investigator Reviewed February 2013 (42nd percentile); resubmitted</td>
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<tr>
<td>Project Title</td>
<td>Abstract / Details</td>
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<tr>
<td>21. Epigenetic model of accelerated late life obesity and decline in muscle quality (Scarpace)</td>
<td>Mechanisms of diet-induced leptin resistance in ARC and VTA. Scarpace, PI. Awarded 7/15/2012 7/14/2016 NIH R01DK091710-01A1</td>
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<tr>
<td>23. Aging induced pluripotent stem cell (iPSC) study (Joseph)</td>
<td>Progress on characterizing these iPSC lines should be completed in the next 2 months with manuscript preparation pending. Additionally, we have established a collaboration with the NMR core of the South East Center of Integrated Metabolomics at the CTSI at UF (Directors: Drs. Edison and Walters) to characterize the global metabolic profiles of these cells. The Material Transfer Agreement to transfer iPSCs to our collaborator at the University of Minnesota to establish muscle cells has finally been approved following approx. 10 months from date of submission. We are revising IRB protocol to include additional NMR analyses by the CTSI and this has been approved pending revisions. Once approved we will transfer cells to the University of Minnesota.</td>
</tr>
<tr>
<td>24. Role of mitochondrial DNA repair in sarcopenia (Tornaletti)</td>
<td>Nuclear extracts and mitochondrial (mt) extracts prepared from EDL or soleus rat muscle tissue are utilized as source of repair proteins for activity assays. mt AP endonuclease activity was robust in all age groups analyzed. mt 8-oxoguanine DNA glycosylase activity significantly decreased with age. Current focus: We are developing a quantitative PCR-based method to directly measure the extent and type of DNA damage (AP sites, 8-oxoguanine) accumulating in mitochondria from aging muscle.</td>
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<tr>
<td>25. MALDI Imaging for co-localizing oxidative damage and lipids in skeletal muscle (Carter, Hsuan)</td>
<td>Project complete Data analyses near completion and now includes an intervention: Rapamycin and Intermittent Feeding (IF)</td>
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<td><strong>26. Cortical control of walking: assessment, mechanisms and functional implications</strong> <em>(Clark)</em></td>
<td>Project complete</td>
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<td>2 RO1a not funded</td>
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<td>1 VA Merit not funded</td>
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<td>1 RO3 not funded</td>
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<td>NIH R01</td>
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<td>National Institutes of Health</td>
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<td>Enhancing the automaticity of locomotor control using textured shoe insoles</td>
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<td></td>
<td>Role: Principal Investigator</td>
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<td>Submitted October 2014; under review</td>
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<td></td>
<td>VA Merit Review</td>
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<td>Department of Veterans Affairs, Rehabilitation Research and Development Service</td>
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<td></td>
<td>Enhancing the motor control of community ambulation using textured shoe insoles</td>
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<td>Role: Principal Investigator</td>
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<td>Submitted December 2014; under review.</td>
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<td>7 papers</td>
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<td>18 presentations</td>
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<tr>
<td><strong>27. Age-related iron accumulation and its role in mitochondrial dysfunction</strong> <em>(Xu)</em></td>
<td>Project complete</td>
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<tr>
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<td>RO1 resubmitted</td>
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<tr>
<td><strong>28. Effects of vitamin D supplementation on fall risk and functional outcomes in older adults with insufficient vitamin D levels: A pilot study</strong> <em>(Anton)</em></td>
<td>17 participants enrolled as of 1/13/15</td>
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<td>110 have been set for V1 to date.</td>
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<td>824 people have been telephone screened for the study to date.</td>
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<td><strong>29. Role of curcumin and methotrexate in improving physical function in older adults with elevated levels of inflammation</strong> <em>(Anton)</em></td>
<td>Project complete</td>
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<td>The pilot study was stopped because this anti-inflammatory agent was not accepted by frail elders for improving mobility and thus recruitment was not feasible.</td>
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<tr>
<td><strong>30. ACE inhibitors combined with Exercise for Seniors – Mechanisms (ACES-M)</strong> <em>(Buford)</em></td>
<td>IRB approved, several participants enrolled and randomized</td>
</tr>
<tr>
<td><strong>31. Effects of oxytocin on physical and cognitive functioning in the elders</strong> <em>(Ebner)</em></td>
<td>Since award notice, NIH, UF IRB, and FDA (for IND use) approval and extensive revisions have been obtained to improve the study design. First wave of participants is planned for early March 2015. Two theoretical papers have been submitted and published in the meantime and one empirical paper has been submitted.</td>
</tr>
<tr>
<td><strong>32. A pilot study to evaluate the role of brain integrity on post-hospital sarcopenia</strong> <em>(Woods, Manini)</em></td>
<td>The IRB for this study is under review. Upon approval, we will begin data collection. The past months have been spent negotiating the logistics of executing our ancillary study within the currently funded R01 held by Dr. Catherine Price. We have finalized data acquisition procedures with Dr. Price’s team and worked to maximize our ability to successfully collect data from participants’ pre and post-surgery. Neuroimaging procedure preparation and physical function assessment protocol preparations are complete.</td>
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<tr>
<td><strong>33. Effect of aging on chronic heart failure-induced dysfunction in skeletal muscle</strong> <em>(Adhihetty)</em></td>
<td>Data analyses of functional assays are currently being performed and biochemical analyses will commence</td>
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shortly. Animal mortality in the old animals was a limiting factor (too many old animals did NOT survive 4 months). An alternate approach to induce CHF will be used for greater survivability. Protocol amendment will be submitted within the next 2 weeks to allow for alternate procedure to be used to investigate CHF (monocrotaline injection) to reduce mortality and increase N.

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<tr>
<th>34. Age related post-transcriptional regulation of translation in skeletal muscle (Brocchieri)</th>
<th>We have obtained cDNA libraries for next generation sequencing of transcripts and, for the first time, of ribosome footprints from rat liver on our way to obtaining analogous libraries for muscle tissue. We have further developed computational software for the analysis of ribosome footprint. These methods will allow us to test the statistical significance of differences in gene expression and translation between young and old individuals. “A novel genome-wide approach to study translational regulation in muscle aging” NIH-NIA 1 R21 AG049317-01. $275,000 / 2yrs ($412,500 D+I). Not funded.</th>
</tr>
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<tr>
<td>35. Development of Clinical Methods to Evaluate Neural Function in Aging (Anton)</td>
<td>IRB approval obtained; equipment ordered; pilot testing ongoing and nearly complete. Enrollment planned for late spring early summer.</td>
</tr>
</tbody>
</table>
| 36. Gut-Microbiome Interactions, Aging and Intervention (Morgan) | 2 posters

Regulation of tryptophan metabolism and anxiety by gut microbiota
NIH R21MH106983-A1
Gary Wang, PI; Drake Morgan, Co-Investigator
Submitted 11/17/2014
Priority score 29 (12%): funding decision pending

The role of gut microbiota in regulating anxiety-like behavior
Department of Defense AR140050
Gary Wang, PI; Drake Morgan, Co-Investigator
Submitted 10/7/2014

Microbiome effects on serotonin functional imaging and anxiety
NIH R21/R33 MH 108157
Gary Wang, PI; Drake Morgan, Co-Investigator
Submitted 11/25/2014

Mechanism of microbial signaling to the brain: the role of serotonergic pathways
UF Opportunity Fund
Gary Wang, PI; Drake Morgan, Co-Investigator
Submitted 1/14/2015

Regulation of anxiety-like behavior by gut microbiota
VA Merit I01BX003820-A1
Gary Wang, PI; Drake Morgan, Co-Investigator
Submitted 3/15/2015 |
| 37. Inflammatory Mediators of Ethnic Differences in OA Pain and Functional Impairment (Fillingim) | Grant awarded (R01 AG033906-11 “Ethnic Differences in Responses to Painful Stimuli”). |

IV. PUBLICATIONS
<table>
<thead>
<tr>
<th>NIH Public Access Compliance</th>
<th>Citation</th>
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<tr>
<td>In process at NIHMS</td>
<td>Diving below the surface of progressive disability: considering compensatory strategies as evidence of sub-clinical disability. The journals of gerontology. Series B, Psychological sciences and social sciences. NIHMSID: NIHMS576638</td>
</tr>
<tr>
<td>In process at NIHMS</td>
<td>Geriatric Care Boot Camp: An Interprofessional Education Program for Health Care Professionals. Journal of the American Geriatrics Society. NIHMSID: NIHMS62461</td>
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<td>Status</td>
<td>Title</td>
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Recognition and Awards

Todd Manini, PhD, Mentor
- Duane Corbett, PhD—The Gerontological Society of America (GSA): Travel award
- Amal Wantinuga—The Leighton E. Cluff Aging Research Award

Christiaan Leeuwenburgh, PhD, Mentor
- Gauthami Balagopal—University Scholar Award
- Reema Patel—University Scholar Award

Thomas Foster, PhD
- Distinguished Professor

Michael Perri, PhD
- Skelton Distinguished Lecturer, Texas Tech University

Michael Marsiske, PhD
- University of Florida Research Foundation Professor

Christy Carter, PhD
- inducted as GSA Fellow

Natalie Ebner, PhD
- International Max Planck Research School on the Life Course (LIFE) Outstanding Alumni Award (sponsored by the APA Board of Educational Affairs Award to Advance Interdisciplinary Education and Training in Psychology)
- Conference Travel Award: Scientific Research Network on Decision Neuroscience and Aging Translational Workshop (sponsored by NIH/NIA)
- Conference Travel Award: Lifespan Approach to Affective Science Questions (Preconference of inaugural conference Society for Affective Science) (sponsored by NIH/NIA)

Natalie Ebner, PhD—Mentor
- Tian Lin—Jacquelin Goldman Single-Year Fellowship
- Tian Lin—Outstanding International Student Award
- Tian Lin—Decision Neuroscience of Aging Conference Travel Awards
- Anand Desai—Second Prize at the Undergraduate Research Forum
- Carla Strickland Hughes—Division 20 Graduate Student Research Travel Award
- Andrew Varan—Center for Undergraduate Research Travel Awards
- Katie Dillon—Oak Hammock ILR Aging Research Award
- Katie Dillon—Center for Undergraduate Research Travel Awards (received, $1,000)

Adam Woods, PhD
- Young Investigator Award in Neuromodulation from NYC Neuromodulation 2015

Shinichi Someya, PhD—Mentor
- Logan Walker - 2013 University of Florida-Howard Hughes Medical Institute Science for Life Spring Research Award

Shinichi Someya, PhD
- 2014 Certificate of Appreciation, University Minority Mentorship Program (University of Florida)
- 2014 University of Florida College of Medicine Exemplary Teacher
Roger Filingim, PhD
- R37AG033906: “Ethnic Differences in Responses to Painful Stimuli”.

Michael Marsiske, PhD, Mentor
- T32 AG020499: Minority Predoctoral Trainees—Paul Mangal and Amanda Garcia

Todd Manini, PhD, Mentor
- Amal Wantinuga—Pepper Minority Supplement “Physical, Cognitive and Mental Health in Social Context”
- David Gundermann, PhD—Minority Pepper Scholar

Constance Uphold, PhD, RN, Mentor
- Andrea Barnes, PhD, RN—VA Offices of Nursing Service Grant-Writing Program, postdoctoral nurse researcher
- Brittoria O’Neal, Intern—Intern, UF Health Education
- C. Granzer, Fellow—Stroke Literacy and Ethnically Diverse Veterans. Veterans Affairs Office of Academic Affiliations, Post-Doctoral Nurse Fellowship Program.

Christy Carter, PhD, Mentor
- Yu-Husan Tsai—The GSA Minority Travel Award

Shinichi Someya, PhD, Mentor
- Karessa White—The GSA Minority Travel Award

Natalie Ebner, PhD—Mentor
- Marilyn Horta—Jacquelin Goldman Research Award
- Marilyn Horta—Odum Institute for Research in Social Science at the University of North Carolina at Chapel Hill Summer Workshop
- Marilyn Horta—Departmental Travel Award
- Marilyn Horta—MNTP Summer Workshop in Neuroimaging travel stipend
- Marilyn Horta—Decision Neuroscience of Aging Conference Travel Awards

Yenisel Cruz-Almeida, PhD, Junior Scholar
University of Maryland
Claude D. Pepper Older Americans Independence Center
(UM-OAIC)

Jay Magaziner, Ph.D., M.S.Hyg.
Co-Principal Investigator
Professor and Chair, Department of Epidemiology and Public Health Department of Epidemiology
Phone: 410-706-3553
FAX: 410-706-4433
jmagazin@epi.umaryland.edu

Leslie Katz, M.D., Ph.D.
Co-Principal Investigator
Associate Professor, Division of Gerontology and Geriatric Medicine
Phone: 410-605-7248
FAX: 410-605-7913
lkatzel@grecc.umaryland.edu

Anne Sullens, M.A.
Program Director
Phone: 410-706-1695
FAX: 410-706-6053
asullens@epi.umaryland.edu

Address Correspondence:
University of Maryland Baltimore
660 West Redwood Street
Howard Hall, Room 217
Baltimore, MD 21201
I. CENTER DESCRIPTION

The mission of the UM-OAIC is to determine and evaluate the mechanisms and efficacy of motor learning based exercise rehabilitation that focuses on the restoration and maintenance of function, and the prevention of the functional decline that puts older adults with chronic diseases at risk for disability. This is accomplished by 1) conducting basic and clinical translational research that examines the mechanisms underlying the functional impairments associated with prevalent diseases in older people across the domains of neuromotor, muscular, metabolic and cardiovascular function; 2) translating these findings from the lab to the clinic to design novel efficacious motor learning based exercise interventions for community implementation; 3) supporting PES, DPs and externally funded grants examining the mechanisms underlying disability, the processes of recovery and the restoration and maintenance of function and 4) fostering the career development of junior faculty from multiple disciplines into independent geriatric academic scientists through mentor-based research training. Research Cores in Biostatistics, Informatics and Translational Research, Applied Physiology and Tissue Mechanisms, and Mobility Function and Neuromotor Plasticity collaborate in Research Working Groups (RWGs) which guide pilot and junior faculty studies from inception to publication. The RCDC provides mentor-based training with didactic courses to promote the career development of RCDC Scholars; a PESC supports novel interventions; and a novel RC3 DP examines mechanisms by which balance training reduces fall risk. The UM-OAIC multidisciplinary research team continues to demonstrate the skills and motivation to change clinical rehabilitation practice by developing innovative, motor learning based exercise rehabilitation programs that will improve the functional and clinical outcomes of older people with disabilities to promote independent living. The UM-OAIC’s translational approach to geriatrics and rehabilitation research is changing clinical practice by developing innovative, feasible rehabilitation interventions that will promote the functional independence and the health of older Americans.

The increased life expectancy of older Americans makes the maintenance of functional independence a major public health priority. The UM-OAIC’s outstanding environment for research and research training in geriatrics and rehabilitation sciences optimizes motor learning-based exercise rehabilitation treatments to reduce the morbidity and disability associated with chronic disease to prevent functional declines and to maintain functional independence.
II. RESEARCH, RESOURCES AND ACTIVITIES

A. CORES

1. Biostatistics, Informatics and Translational Research (RC1)
Core Leaders: John D. Sorkin, M.D., Ph.D., (Telephone: 410-605-7119, E-mail: jsorkin@grecc.umaryland.edu) and Jay Magaziner, Ph.D., M.S.Hyg., (Telephone: 410-706-2406, E-mail: jmagazin@epi.umaryland.edu)

RC1 provides biostatistical support to University of Maryland Older Americans Independence Center (UM-OAIC) investigators, fosters the design of motor learning-based exercise rehabilitation interventions that promote the restoration and maintenance of function, prevents the functional decline that puts older adults with chronic disease at risk for disability, and facilitates the translation of interventions from the laboratory to the clinic and the community. Research Working Groups (RWGs) provide a forum in which investigators from multiple disciplines collaborate on the design and conduct of research studies, and our informatics system provides an infrastructure that enhances our ability to manage studies, and facilitate the flow of information and data within the UM-OAIC. RC1 implements the following specific aims to achieve this goal:

1) Organizes multidisciplinary RWGs that will assist UM-OAIC investigators in the design and conduct studies, publish study results and promote translation of research;
2) Provides a centralized, user-friendly information management system that
   a) facilitates submission of requests for services, and tracks resource scheduling and utilization,
   b) facilitates recruiting of subjects,
   c) monitors study progress by tracking recruiting efforts and subject progress through studies,
   d) informs investigators and leadership of adverse events,
   e) facilitates data management,
   f) ensures confidentiality, physical security, and logical integrity of data, promotes data completeness, accuracy, and validity and improves laboratory quality control;
3) Provides biostatistical expertise to UM-OAIC investigators by performing sample size calculations, randomizing subjects, analyzing data and helping investigators with the interpretation and presentation of results; and
4) Provides training to UM-OAIC faculty, trainees, and staff in biostatistics and epidemiology.

2. Applied Physiology and Tissue Mechanisms (RC2)
Core Leaders: Alice Ryan, Ph.D., (Telephone: 410-605-7851, E-mail: aryan@grecc.umaryland.edu) and Leslie I. Katzel, M.D., Ph.D., (Telephone: 410-605-7248, E-mail: lkatzel@grecc.umaryland.edu)

Cardiovascular deconditioning, chronic inflammation, and endocrine-metabolic dysfunction are inherent to the pathophysiology of the physical impairments in older persons hindered by disabling chronic diseases of aging. Sarcopenia, poor fitness, inflammation, metabolic syndrome, and acute events related to disability such as stroke and hip fracture occur with advancing age which may worsen mobility and increase risk for cardiovascular disease (CVD) and metabolic abnormalities. The RC2 hypothesis is that exercise-focused rehabilitation, including aerobic and resistive training, can improve multiple physiological systems in older, mobility-limited individuals leading to improved functional performance, reduced cardiometabolic risk, and prevention of functional decline. By determining the structural, molecular, and metabolic abnormalities in skeletal muscle, adipose tissue, and vascular endothelium, and their response to exercise rehabilitation, we can optimize exercise and motor learning-based interventions with RC3 to improve muscle structure and functional outcomes, metabolic function, and CVD risk profiles in older adults with these chronic conditions. These interventions work to prevent subsequent morbidity and mortality. To achieve this goal, RC2 implements specific aims that:
1) Provides study support, mentors and trains UM-OAIC junior scholars, affiliated junior faculty, and OAIC researchers in the performance of applied exercise physiology and tissue mechanisms research relevant to exercise–based restoration of function and prevention of functional declines in older people with chronic disabling diseases through:
   a) participation in research working groups (RWGs) which provide educational and consultative resources to UM-OAIC junior and senior investigators in the design and implementation of their research,
   b) clinical applied training in translational research and the assessment of cardiovascular and physiological outcomes of exercise rehabilitation in aging, and
   c) laboratory training of standardized core methodologies in order to gain expertise in the performance of metabolic testing and cellular and molecular assays at the bench to facilitate their translational research;
2) Facilitates the conduct of musculoskeletal and tissue mechanistic exercise rehabilitation and preventive medical research in aging and disability across the UM-OAIC pilot projects, UM-OAIC junior scholars’ research and external NIH and VA funded research through:
   a) recruitment, the performance of medical assessments and cardiovascular screening of research volunteers to ensure patient safety and eligibility for research protocols,
   b) development and testing of novel exercise-based interventions (aerobic, resistance, multi-modal training) and
   c) phenotyping of older, disabled volunteers in UM-OAIC research at the whole body and tissue level.

The clinical and metabolic phenotype(s) of individuals with stroke, hip fracture and other functional limitations and disabilities are characterized in RC2 in order to develop successful disability specific rehabilitation strategies to improve their functional and clinical outcomes. Thus this core, in collaboration with the other cores, supports innovative studies that address critical areas of rehabilitation examining the effects of multisystem rehabilitation and preventive strategies on functional and physiological outcomes in older adults.

3. Mobility Function and Neuromotor Plasticity (RC3)
Core Leaders: Mark Rogers, Ph.D., P.T., (Telephone: 410-706-0841, E-mail: mrogers@som.umaryland.edu) and George Wittenberg, M.D., Ph.D., FASNR (Telephone: 410-706-4456, E-mail: gwittenb@grecc.umaryland.edu)

RC3 provides expertise and investigator resources to assess the multi-system neuromotor, biomechanical, motor learning and behavioral factors affecting mobility movement performance. RC3’s focus is on the joint design and conduct of novel motor learning based exercise interventions, determining and providing the quantitative measures of whole-body multi-segmental neuromotor control and understanding the mechanisms of exercise-mediated neuroplasticity of balance, locomotion, and upper limb activities in older people with chronic diseases. Deterioration in these fundamental motor functions is a primary cause of mobility disability and loss of functional independence in older Americans, which we believe can be prevented and restored with motor learning based exercise rehabilitation.

The consequences combination of physical impairments and a sedentary life in advancing age with such conditions as stroke, hip fracture, metabolic syndrome and Parkinson’s disease (PD) propagate result in multi-system physiological, neuromotor, behavioral, cognitive, and functional deficits that impact independence. In order to effectively develop disability and disease-specific motor-learning and exercise based therapies focused on activity dependent neuromotor plasticity, we must better understand the interaction of the multi-system deficits that impair control of whole-body movements for balance, locomotion, and upper limb activities to improve functional independence. RC3 applies this conceptual model to assist and train UM-OAIC investigators in the design of novel rehabilitation interventions, conduct and interpretation of quantitative movement performance outcomes that are coupled to methodologies delineating the mechanisms of brain plasticity to advance the neuroscientific basis of functional recovery in older people with functional limitations.
RC3 strives to define the mechanistic basis by which we build novel rehabilitation strategies to improve mobility function and independence in older people with chronic disease and disability. Robotic approaches are innovatively incorporated for assessing and training balance control during stance, locomotion, and upper limb activities. Advanced technologies of engineering-based computational modeling provide new analytic tools to understand distributed motor control of balance and arm use, and allow us to apply models of neuromotor control to everyday functional tasks and validate the clinical relevance of neuroplasticity across interventions.

RC3 collaborates across the UM-OAIC cores to advance the next generation of interventions to the community that will enhance mobility function in older adults with chronic disability with specific aims to:
1) Assist trainees, junior faculty, and UM-OAIC investigators in research working groups (RWGs) in the design and conduct of motor-learning and exercise based interventions that will be translated from the laboratory to the clinic and onto community practice to improve functional independence in older individuals with chronic disease associated disability;
2) Mentor junior faculty and train UM-OAIC investigators in the mechanistic study of neuromotor control, exercise-mediated neuroplasticity and processes of motor learning to advance the interdisciplinary inter-core development and conduct of new mechanistically driven motor learning based exercise interventions that will restore and maintain function, and prevent declines that lead to disability in older adults with chronic disease; and
3) Perform core testing, design and validation of new analytic tools, and training of UM-OAIC investigators in the RC3 Toolbox of methodologies needed to:
   a) quantify the neuromotor performance of gait, balance, postural control, upper limb activities, the disability phenotype, and more complex, multi-segmental tasks, and
   b) characterize the processes of neuromotor control and plasticity that underlie motor learning and exercise derived functional gains across UM-OAIC interventions.

4. Leadership and Administrative Core (LAC)
Core Leaders: Jay Magaziner, Ph.D., M.S.Hyg., (Telephone: 410-706-2406, E-mail: jmagazin@epi.umaryland.edu) and Leslie I. Katzel, M.D., Ph.D., (Telephone: 410-605-7248, E-mail: lkatzel@grecc.umaryland.edu)

The LAC fosters research interactions among the Center’s Cores Co-Leaders and the approximately 25 scientists from rehabilitation science, gerontology, neurology, psychology, exercise physiology, endocrinology, epidemiology, biostatistics and informatics. The LAC ensures the successful conduct of the University of Maryland Older Americans Independence Center’s (UM-OAIC) research aims, integration of research across the Cores to design and implement translational studies of rehabilitation, mentoring the career development of the UM-OAIC junior scholars, and effective allocation of resources to serve UM-OAIC projects. To meet the goals the LAC implements the following specific aims:
1) Oversee the coordination, integration, and administration of all aspects of the UM-OAIC with other research and training grants, and foster collaborations that will accomplish UM-OAIC goals, policies and regulatory responsibilities. This ensures the conduct of academically productive, innovative, high impact translational science within the UM-OAIC;
2) Expand resources for the conduct of translational basic, clinical, and population research in motor learning-based exercise rehabilitation in aging to restore and maintain function, and to prevent functional declines. A scientifically enriched environment for aging-related research has developed through collaborative interactions with other University of Maryland Baltimore Centers, schools, academic departments and programs. The availability of core resources and funding for Pilot and Exploratory Studies, Developmental Projects and junior scholars has enhanced investigators’ abilities to conduct translational clinical research in rehabilitation science and promote the careers of junior faculty;
3) Ensure independent review and oversight of UM-OAIC research progress, conduct of UM-OAIC projects, and training of junior scholars. The LAC has policies in place for the internal and external review of UM-OAIC programs, and receives guidance from internal and external advisors in the oversight of the research cores progress and review of internal UM-OAIC projects;

4) Foster the career development of junior scholars from multiple clinically relevant disciplines into independent investigators and academic leaders in aging-related research. Institutional support and fellowship grants are leveraged to ensure sufficient protected time for junior faculty and trainees;

5) Recruit outstanding junior and senior faculty and research staff to enrich the cadre of scientists conducting translational aging-related research at the basic and clinical levels in exercise science and motor learning-based exercise rehabilitation medicine, and at the population level to translate and evaluate interventions in the community. A critical mass of scientists will foster the translation between basic and clinical research to develop and test the best interventions to improve the functional and clinical outcomes of functionally impaired older people, and then implement and evaluate these interventions in the community; and

6) Evaluate the progress of UM-OAIC supported investigators, research cores, junior scholars, and projects. The LAC manages the utilization of UM-OAIC resources, and adherence to local and federal regulations to ensure compliance with the National Institute on Aging (NIA) and other federal policies. The LAC schedules meetings with the NIA program, UM-OAIC External Advisory Board and Data Safety Monitoring Board, and prepares progress reports and other administrative documents for the NIA.

5. Pilot and Exploratory Studies Core (PESC)
Core Leader: Mary Rodgers, P.T., Ph.D., F.A.P.T.A., F.A.S.B. (Telephone: 410-706-5658, E-mail: mrogers@som.umaryland.edu)

The PESC provides start-up support for high quality pilot and exploratory research to acquire information needed to select or design future crucial studies of the mechanisms underlying disability, recovery and prevention in older persons and the functional and clinical responses to rehabilitation. This goal is accomplished by the following specific aims:

1) Solicits and oversees the conduct of innovative pilot and exploratory research studies (PES) in the University of Maryland Older Americans Independence Center (UM-OAIC) foci from junior scholars receiving UM-OAIC support and other junior and senior investigators;

2) Ensures and monitors adherence to ethics, safety, privacy and protection of human subjects enrolled in PESC studies; and

3) Facilitates the development of PESC studies into independently funded grant applications.

The PESC works with the Leadership and Administrative Core (LAC), its Committees and Advisory Panels to provide leadership, advice and resources to ensure the coordination of innovative translational approaches to research in rehabilitation science and clinical investigation examining the mechanisms underlying the functional disabilities associated with stroke, hip fracture, and other chronic diseases prevalent in the elderly. The PESC Leaders, in conjunction with the research working groups (RWGs), stimulate and sustain aging research by assisting junior and senior UM-OAIC investigators in the development of novel pilot and exploratory research, providing resources for this research, monitoring progress and accomplishments, and cultivating interdisciplinary collaborations within the UM-OAIC, and other OAICs that advance rehabilitation.

6. Research Career Development Core
Core Leaders: Jay Magaziner, Ph.D., M.S.Hyg., (Telephone: 410-706-2406, E-mail: jmagazin@epi.umaryland.edu) and Leslie I. Katzel, M.D., Ph.D., (Telephone: 410-605-7248, E-mail: lkatzel@grecc.umaryland.edu)
The RCDC provides an enriched, mentor-based research training and educational environment to promote the career development of junior faculty toward independence as investigators in aging-related research and leaders in gerontology and geriatric medicine. The RCDC also supports the training of junior faculty and fellows pursuing research careers in aging emphasizing research training that crosses traditional disciplinary boundaries to adopt novel approaches to improving function and independence in older persons.

The specific aims of the RCDC are to:

1) Identify, select and support RCDC junior scholars;
   - Identify, select, and support promising junior faculty and prepare them as independent investigators in the design and implementation of exercise rehabilitation research to foster independence in older people with disabling chronic diseases.
2) Mentor RCDC junior scholars and affiliated junior faculty; and
3) Provide structured didactic training and opportunities for additional instruction and collaboration in areas relevant to aging-related research.
   - RCDC leaders promote the growth and success of the RCDC research-training program to meet the needs of the RCDC junior scholars, affiliated junior faculty, fellows, and graduate and professional school students pursuing academic careers in the field of aging-related research.

UM-OAIC Career Development Awardees

Currently Funded Awardees:

- **2012-2015: Michael Dimyan, M.D.** Assistant Professor, Department of Neurology School of Medicine, University of Maryland Baltimore (mentors Drs. George Wittenberg, Jill Whitall, Rao Gullapalli, Peter Gorman). Dr. Dimyan’s interests are in the dynamic modulation of interhemispheric inhibition and other measures of brain network activity as they relate to arm motor control, with a translational goal of understanding the loss of dexterity that occurs with aging and after hemiparetic stroke. His Pepper Center RCDC laid the foundation for a set of studies by providing pilot data demonstrating that paired pulse interhemispheric inhibition measures obtained via transcranial magnetic stimulation are a more reliable measure than ipsilateral silent period. In the 2014-2015 academic year, Dr. Dimyan was awarded an NINDS K23 award for “Modulation of interhemispheric inhibition and arm activity after stroke.” During this year, a participant user-interface and brain stimulation-triggering system has been coded from the ground up. This project has enrolled 4 participants in whom recruitment curves of corticospinal neurophysiologic efficacy and interhemispheric inhibition have been measured at different force-output levels during isometric contraction. The goal is to describe the dynamics of these brain network interactions and how they affect muscle control, and how those interactions are altered by aging and after stroke. Preliminary results will be presented at the 2015 American Society for Neurorehabilitation Conference. The goals for the upcoming year are to complete enrollment of healthy young and older participants and begin enrollment of patients with post-stroke hemiparesis.

- **2014-2017: Kelly Westlake, Ph.D., MSc, PT** Assistant Professor, Department of Physical Therapy and Rehabilitation Sciences, School of Medicine, University of Maryland Baltimore (mentor Drs. Mark Rogers, Andrew Goldberg and George Wittenberg) Dr. Westlake's research is focused on abnormal protective arm responses in older adults at risk of falling. She is investigating the integrative mechanisms of cognition and postural control to identify potential rehabilitation treatment targets. Preliminary results of this work indicate delays and errors in grasping responses, particularly in the group of older adults at high fall risk when forced to switch attentional focus. fMRI findings corroborate these results by demonstrating neural suppression within key cognitive brain regions in relation to the arm responses. Presently, one manuscript has been submitted and one is in preparation.
2014-2017: **Rishi Kundi, M.D.**, Assistant Professor, Department of Surgery, School of Medicine, University of Maryland Baltimore (mentors: Drs. Brajesh Lal and Steven Prior) Year 1. Dr. Kundi's 2014 Junior Scholar award is supporting investigations of both loss of functional mobility in older adults with peripheral arterial disease as well as the benefit to function effected by surgical and non-surgical treatment of PAD. The goal is to elucidate a PAD treatment strategy that addresses both clinical measures of perfusion as well as functional measures and deficits in quality of life. Enrollment is underway. Preliminary data has resulted in the award of a Clinical Seed Grant from the Society of Vascular Surgery as well as presentations at the recent annual meeting of the Society for Vascular Surgery and the upcoming meeting of the Eastern Vascular Surgical Society and will be used in the submission of a VA CDA application in the winter 2015 cycle.

**UM-OAIC Junior Scholars (Research supported by the UM-OAIC):**

**2001-2004**
- **Larry Forrester, Ph.D.**, Associate Professor, Department of Physical Therapy, School of Medicine, University of Maryland Baltimore
- **Marianne Shaughnessy, Ph.D., CRNP**, Program Analyst, Office of Geriatrics Programs, Veterans Health Administration
- **Denise Orwig, Ph.D.**, Associate Professor, Department of Epidemiology and Preventive Medicine, School of Medicine, University of Maryland Baltimore
- **Jacob Blumenthal, M.D.**, Assistant Professor, Department of Medicine, School of Medicine, University of Maryland Baltimore
- **Eun-Shim Nahm, Ph.D., RN**, Professor, Department of Organizational Systems and Adult Health, School of Nursing, University of Maryland Baltimore
- **Federico Villagra, Ph.D., PT**, Visiting Physiologist, Hospital Universitario Virgen del Rocio, Pamplona Spain

**2004-2007**
- **Kris Ann Oursler, M.D.**, Associate Professor, School of Medicine and Research Institute, Virginia Tech/Salem VA Medical Center
- **Ram Miller, M.D., CM, MSc, MBA, FRCPC**, Director of Clinical Development, Muscle Metabolism Discovery Performance Unit, GlaxoSmithKline
- **Sandy McCombe Waller, Ph.D.**, Associate Professor, Department of Physical Therapy and Rehabilitation Sciences, School of Medicine, University of Maryland Baltimore
- **Kathleen Michael, Ph.D., RN, CRRN**, Assistant Professor, Interim Chair- Department of Organizational Systems and Adult Health, School of Nursing, University of Maryland Baltimore

**2011-2014**
- **Douglas Savin, Ph.D.**, Assistant Professor, Department of Physical Therapy and Rehabilitation Sciences, School of Medicine, University of Maryland Baltimore
- **Avelino Verceles, M.D.**, Assistant Professor, Department of Medicine, School of Medicine, University of Maryland Baltimore
- **Michael Dimyan, M.D.**, Assistant Professor, Department of Neurology, School of Medicine, University of Maryland Baltimore
- **Kelly Westlake, Ph.D., MSc, PT**, Assistant Professor, Department of Physical Therapy and Rehabilitation Sciences, School of Medicine, University of Maryland Baltimore
- **Rishi Kundi, M.D.**, Assistant Professor, Department of Surgery, School of Medicine, University of Maryland Baltimore
B. RESEARCH

Below is a listing of the current Pepper Center supported studies followed by a listing and brief description of several independently funded supported studies.

### Major Grants Associated with the UM-OAIC

<table>
<thead>
<tr>
<th>Research Projects</th>
<th>PI</th>
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<tr>
<td><strong>UM-OAIC Scholar Projects</strong></td>
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<tr>
<td>Functional Benefit of Exercise Therapy after Endovascular Intervention in Older Patients with PAD</td>
<td>R. Kundi, MD; 2014-2017</td>
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<tr>
<td>Probing the Neural Basis and Influence of Cognitive Changes on Impaired Balance in Older Adults</td>
<td>K. Westlake, PhD, PT; 2014-2017</td>
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<tr>
<td><strong>Developmental Project</strong></td>
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<tr>
<td>Multi-system Exercise Intervention to Enhance Balance and Mobility in People with Type 2 Diabetic Nueropathy</td>
<td>M. Rogers, PT, PhD, FAPTA; 7/1/14-6/30/17</td>
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<tr>
<td>Task-Specific Effects of Two Different Balance Training Regimens</td>
<td>J. Barton, PhD; 10/01/11- 09/30/13</td>
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<td><strong>Year 1 UM-OAIC Pilot Projects</strong></td>
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<td>Improving walking symmetry and functional mobility in stroke survivors with split-belt treadmill training.</td>
<td>A. Bastian, PhD/D. Hanley, PhD</td>
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<tr>
<td>Aerobic exercise (AEX) to improve regulation of Endothelial Progenitor Cells (EPCs) and Vascular Function in T2DM.</td>
<td>S. Prior, PhD</td>
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<tr>
<td>Effects of Vitamin D repletion (D) with and without multi-component lifestyle exercise training (MLife) on muscle function, inflammation and glucose metabolism in D deficient older adults</td>
<td>E. Streeten, MD/H. Ortmeyer, PhD</td>
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<tr>
<td>Resistance training (RT) and protein (Pro) supplementation to improve muscle physiology and reduce fatigue in breast cancer survivors</td>
<td>M. Serra, PhD</td>
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<tr>
<td>A high-density Electroencephalography (EEG) neural Decoding study of Dynamical Cortical Mapping of Gait in Humans after Stroke.</td>
<td>J. Contreras-Vidal, PhD</td>
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<tr>
<td><strong>Year 2 UM-OAIC Pilot Projects</strong></td>
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<tr>
<td>Comparison of Reactive Step Training and Voluntary Task-Oriented Training to Induce Neuromotor Changes for Improving Balance and Preventing Falls</td>
<td>D. Savin, PhD, MPT</td>
</tr>
<tr>
<td>Development of a Rehabilitation Strengthening and Mobility Program for Ventilator Dependent Older Patients</td>
<td>A. Verceles, MD/C. Wells, PhD, PT, CCS, ATC</td>
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<tr>
<td>Probing the Neural Basis and Influence of Cognitive Changes on Impaired Balance in Older Adults</td>
<td>K. Westlake, PhD</td>
</tr>
<tr>
<td>Using Self-Triggered, Sensory-Enhanced Gaze Shift to Improve Axial Turning Deficits in Persons with</td>
<td>R. Creath, PhD</td>
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</table>
1. Early Exercise to Improve Muscle and Cardiometabolic Health after Stroke  
PI: R. Macko, M.D.  
R01 HD068712  
04/01/2011-03/31/2016

Stroke leads to profound physical deconditioning and abnormalities in paretic leg muscle including shift to fast twitch muscle phenotype, inflammation and gross atrophy that worsen cardiometabolic health by promoting insulin resistance. Yet, no prior studies have considered stroke as a catabolic syndrome in aging that can be modified by early exercise to improve muscle and cardiometabolic health. In chronic stroke, we have exercise models that improve mobility, restore fitness levels nearly 40%, and reverse impaired glucose tolerance (IGT) and T2DM status in 58% of cases, even years after stroke. Lab findings suggest our exercise programs increase total myofibrillar protein and proportion of slow twitch in paretic leg muscle, implicating both altered protein synthesis and regulation of muscle molecular phenotype as mechanisms underlying the benefits of exercise post-stroke. This study investigates the hypothesis that in African-Jamaican adults with recent stroke, structured exercise across the sub-acute recovery period and into the chronic phase of stroke care will improve P leg muscle and cardiometabolic health, compared to controls receiving best medical care.

Aims and associated hypotheses are to compare effects of 6 months structured and progressive exercise vs. best medical care implemented early after stroke in African-Jamaican adults on:

Aim #1. Paretic &non-paretic leg mixed muscle protein synthesis and breakdown in the fed and fasted state, TNF-1 expression, thigh muscle volume and strength. Hypothesis 1: Paretic leg muscle has reduced protein synthesis and increased breakdown compared to non- paretic leg. Exercise will increase mixed muscle protein synthesis and reduce breakdown to increase muscle volume and strength by mechanism(s) of reducing inflammation in paretic leg, compared to controls.

Aim #2. Glucose tolerance, fitness, and muscle phenotype. Hypothesis 2: Exercise will improve fitness levels, insulin and glucose response to oral glucose challenge, and increase paretic leg slow twitch muscle phenotype.

Supported by RC 3
2. Community Ambulation Following Hip Fracture  
PI: J. Magaziner, Ph.D., MSHyg  
R01AG035009-01A1  
09/01/2010-08/31/2017

Despite improvements in medical management, significant residual disability remains in older persons after a hip fracture. The goal of current clinical practice is independent, safe household ambulation two to three months after surgery. Hip fracture-acquired dependency in functional activities of daily living persists well beyond three months post-surgery. One year after hip fracture, 20% of patients need help putting on pants, 50% need assistance to walk, and 90% need assistance to climb stairs. This residual disability indicates that current standard Medicare-reimbursed post-hip fracture rehabilitation (i.e., usual care) fails to return many patients to pre-fracture levels of function. In contrast to stroke and heart disease, other commonly occurring acute conditions in the older population, there are few intervention trials focused on decreasing disability following hip fracture. None of the trials for hip fracture has examined the effect of early post-fracture intervention on the ability to ambulate at a level required for independent function in the community (i.e., community ambulation). Thus, there is a paucity of evidence to justify extending medical management beyond usual care in persons following hip fracture to achieve community, rather than merely household, ambulation.

The goal is to enable older adults who have experienced a hip fracture to recover sufficiently to become community ambulators. The primary outcome will be ability to walk 300 meters or more in six minutes at the end of the 16-week intervention period. In addition, the effect of the interventions on five precursors for community ambulation will be examined, as will the cost-effectiveness of the interventions, and the effect on a set of tertiary outcomes. Precursors to community ambulation include measures of endurance, dynamic balance, walking speed, quadriceps strength, and lower extremity function. Tertiary outcomes include activities of daily living (ADLs), quality of life, and physical activity, lower extremity physical performance, balance confidence, increase of 50 meters or more in distance walked in six minutes, nutritional status, cognitive status, and depressive symptoms.

Supported by RC 1, 2, 3

3. Epidemiology of Bone Strength and Muscle Composition after Hip Fracture in Men  
PI: J. Magaziner, Ph.D., MSHyg  
R01 AG029315  
03/01/2007-02/2/2016

Hip fracture, a disabling and costly condition to individuals and society, is typically thought of as a health problem of older women. Approximately 25 to 30% of the 350,000 hip fractures in the US occur in men, yet the number of men included in studies of hip fracture consequences has been small. It is estimated that by 2025, the incidence of hip fracture in men will be the same as that currently seen in women, making this an emerging public health concern for older men, their families, and the healthcare system.1, 3 Our working hypothesis is that men and women will have different trajectories of loss and recovery after hip fracture. Thus, men who fracture a hip will experience greater declines in bone mineral density and bone strength, muscle mass and strength, and will gain more fat than women who sustain a hip fracture, and men will experience less recovery and will recover more slowly than women in multiple functional domains. Men also will reduce their level of physical activity and be less active post-fracture than women and will be less motivated to engage in rehabilitative strategies to improve their chances of recovering. In addition, it is anticipated that bone turnover, hormone effects, and cytokine regulation following fracture will differ by sex. In evaluating these differences, we will test the hypothesis that at least moderately-sized sex difference in outcomes exists in many if not all areas of functional, physiological and metabolic change. Finally, it is hypothesized that men who fracture a hip will differ in functional, physiologic and metabolic outcomes from similar men who do not fracture, and that the amount of change will be greater among hip fracture patients.
The primary aims of the proposed study are to: 1) Describe the trajectories of components of bone strength, including bone mineral density, ultrasound properties, and bone geometry in men with hip fractures during the year after fracture and contrast this with these components in women with hip fractures; 2) Describe the trajectories of non-bone components of body composition, including muscle and fat mass, in men during the year after hip fracture and to contrast these with observations in women; 3) Describe the trajectories of physical activity, neuromuscular function (including strength), and physical functioning in men and to compare these to trajectories observed in women during the year after hip fracture; 4) Describe the trajectories of: a) psychosocial function (depression; social interaction; quality of life), b) cognition, and c) motivation (self-efficacy and outcome expectations) related to participation in rehabilitation/exercise and adherence to medication for the treatment of osteoporosis in men during the year after hip fracture, and to contrast these with women post hip fracture; 5) Describe metabolic factors, including biochemical markers of bone turnover (serum N-terminal cross-linking telopeptide of type I collagen and bone-specific alkaline phosphatase), hormones (testosterone, estrogen, sex hormone binding globulin, parathyroid hormone, insulin-like growth factor 1, and vitamin D) and the pro-inflammatory cytokine interleukin-6 during the year after hip fracture and to compare trajectories observed in men and women; 6) Determine the differences in selected aspects of bone, muscle, function, activity, and metabolism that are attributable to hip fracture vs. those that occur in similarly frail older men who do not sustain a hip fracture.

Supported by RC 1, 2

4. The Effects of Multi-Modal Exercise Intervention Post Hip Fracture
   PI: J. Magaziner, Ph.D., MSHyg
   R37 AG009901
   09/01/2011-08/31/2018

This proposed Merit Extension will continue a line of research initiated in 1983 that has evolved into an internationally recognized program, the Baltimore Hip Studies (BHS), dedicated to identifying, developing, and evaluating strategies to optimize recovery following hip fracture. This Merit Extension, which has two components, will extend findings from prior Merit Award studies and other BHS projects demonstrating that hip fracture results in dramatic changes in muscle, fat mass and muscle strength, bone density and strength, bone turnover markers, serum levels of hormones and inflammatory markers, as well as walking ability and other aspects of function. The goals are to: 1) study some of the key mechanisms on the pathway to changes in community ambulation in response to a Multi-modal Exercise Intervention (MMEI) delivered to this frail and disabled group of older persons (Component I);and 2) test, in a preliminary manner through a pilot/feasibility study of a different sample of patients, the additional benefit of adding a protein supplement following MMEI sessions to determine if there are important changes in bone, muscle, inflammation, and function (Component II). The MMEI, being tested in a recently funded Phase III randomized clinical trial (1R01AG035009) of 300 patients in three centers, is a home-based program that addresses deficits in endurance, strength, balance and function through 40 supervised sessions. The primary outcome of that RCT is the ability to ambulate independently in the community. Component I of this Merit Extension will be conducted as an ancillary study to the Phase III RCT by adding mechanistic measurements to the patients recruited in the Baltimore, Maryland clinical site (Minimum number enrolled = 60;30 per group). Component II will recruit 30 additional patients and provide a whey based protein and amino acid supplement immediately after completing each of the MMEI sessions to examine added mechanistic benefits and feasibility. Participants in both components will be assessed prior to randomization (within 2 months post hospitalization for hip fracture), and again 4 and 10 months later in order to examine the immediate effects (primary outcome) and the sustained benefits of interventions. We also will work with an international group of experts to identify strategies to accelerate development and testing of interventions for this group of older persons who experience this sudden disabling event.

Supported by RC 1
5. Effects of Aerobic Exercise on EPCs and Vascular Dysfunction in Aging and T2DM  
PI: S. Prior, Ph.D.  
K23 AG-040775  
08/01/2012-08/01/2015

Endothelial progenitor cells (EPCs) are bone marrow-derived circulating cells that differentiate into mature endothelium to participate in vascular growth and repair. EPC dysfunction may contribute to vascular dysfunction in type 2 diabetes (T2DM) and EPCs may be dysregulated in T2DM by reduced mobilization from bone marrow and impaired function once in the circulation. This study tests the hypothesis that reduced EPC mobilization and function adversely affect angiogenesis and endothelial function in T2DM, and improvements in EPC mobilization and function are mechanisms by which aerobic exercise training may increase angiogenesis and endothelial function in T2DM. The specific aims are to determine whether EPC mobilization and function are reduced due to impaired expression of EPC mobilization factors and regulatory factors in older adults with T2DM compared to normal controls, and 2) the mechanisms by which 6-month AEX training increase EPC mobilization and function in older adults with T2DM, and whether these are associated with improved vascular function.

Sedentary, overweight, older (50-75 years) adults with T2DM and sex-, age- and BMI-matched controls (age ± 3 yrs, BMI ± 2 kg/m^2) will be enrolled and studied at baseline; T2DM subjects will be studied before and after 6-months of aerobic exercise training. A single bout of exercise will be used to stimulate EPC mobilization to determine whether EPC mobilization is reduced in T2DM compared to normal controls and whether EPC mobilization improves with aerobic exercise training in T2DM. In the same subjects, *ex vivo* EPC tube formation and gene expression will be measured to determine whether specific markers of EPC function are reduced in T2DM and are improved with exercise training. Endothelial vasoreactivity and skeletal muscle capillarization will be measured to determine whether increases in EPC mobilization and function are associated with improved vascular function in older adults with T2DM.

This study will significantly advance our understanding of EPC and vascular dysfunction in T2DM and may lead to therapeutic and pharmacologic strategies to reduce vascular dysfunction in T2DM. This K23 award provides Dr. Prior with mentored training to perform the proposed studies and transition to an independent research career in clinical and translational research in vascular biology and diabetes research.

Supported by RC 1, 2 RCDC

6. Intervention to Enhance Lateral Balance Function and Prevent Falls in Aging  
PI: Mark Rogers, Ph.D., PT, FAPTA  
R01 AG033607-01A2  
09/01/2010-05/31/2016

Falls and their consequences are among the major problems in the medical care of older individuals. The long-term goal of this research is to establish the efficacy of a scientifically grounded and mechanism-based therapeutic intervention for improving balance function and preventing falls in older people. When human balance is challenged, protective stepping is a vital strategy for preventing a fall during activities of daily life. Many older people at risk for falls have particular difficulties with successfully stepping sideways as a protective response to loss of balance in the lateral direction. The hypothesis is that age-related declines in lateral balance function through impaired protective stepping that precipitates falls, result from neuromechanical (NM) limitations in hip abductor-adductor (AB-AD) muscle strength (torque and power). Moreover, these functional and NM impairments are reversible with combined high intensity induced step training and muscle strengthening. The specific aims are to conduct a double blind, randomized, and controlled trial with four training arms that will compare the effects of 12 weeks of training and assess its durability after 3
months of no training in community living older adults at risk for falls by determining: 1) the effect of (a) waist-pull induced step training, (b) hip AB-AD muscle strengthening, and (c) a combined step training and muscle strengthening program compared to (d) a standard flexibility and relaxation program involving minimal-intensity exercises (control) on the protective stepping response to an external balance perturbation, as measured by i) the number of multiple balance recovery steps, and ii) first step length; and 2) the effect of high intensity step training, with and without the strengthening intervention, compared to the control group on a) maximum hip AB-AD joint torque and power. A secondary aim will assess whether protective stepping performance and hip AB-AD muscle strength discriminate between a) fallers and non-fallers identified by retrospective fall history at the time of study enrollment, and b) the prospective fall frequency of the different intervention groups during 1-year follow-up post-training.

Supported by RC 1, 2, 3

7. **Aging, Inflammation and Exercise in Chronic Stroke**  
   **PI:** A. Ryan, Ph.D. / C. Hafer- Macko, M.D.  
   **R01 AG030075**  
   **05/15/2008-04/30/2016**  
   Inflammation is a risk factor for stroke and contributes to the progression of cardiovascular disease. Adipose tissue is a major source of cytokine production and contributes to an inflammatory state associated with insulin resistance. Moreover, inflammatory and anti-inflammatory skeletal muscle receptor activation affects intracellular signaling and muscle insulin sensitivity. Yet, there is a lack of understanding and exploration of the role of tissue inflammatory changes in stroke. We have definitive preliminary data that stroke patients are hyperinsulinemic and at increased risk for diabetes. Thus, our proposal seeks to study the mechanisms by which treadmill training reduces inflammation and improves insulin sensitivity in normal glucose tolerant and impaired glucose tolerant hemiparetic stroke patients.

Direct measurement of inflammatory modulators in adipose tissue and skeletal muscle would provide novel information as to whether selected cytokines adversely affect insulin signaling in the skeletal muscle and are associated with systemic insulin resistance in chronic stroke. Moreover, the studies proposed on the paretic leg will permit us to examine the specific abnormalities attributable to the upper motor neuron injury from stroke, while studies on the non-paretic leg will isolate the effects of disuse/deconditioning, and their respective response to exercise training. This proposal is the first to investigate the mechanisms by which post-stroke body composition abnormalities and physical inactivity interact to mediate inflammatory changes at the systemic and tissue level (both skeletal muscle and adipose tissue) and propagate insulin resistance, as well as the potential for exercise training to modify these abnormalities.

Supported by RC 1 and 2

8. **Randomized Trial of Exercise Training on Cognitive and Physical Function in CKD**  
   **PI:** S. Seliger, M.D., M.S.  
   **R01 DK090401**  
   **09/20/2011-08/31/2015**  
   Chronic kidney disease (CKD) is increasingly prevalent in the elderly and carries sequelae that extend beyond progression to kidney failure. These sequelae include neurocognitive and physical dysfunction, both of which occur at markedly higher rates in CKD patients, even after accounting for differences in common co-morbidities including underlying cardiovascular disease and diabetes. Factors that may explain these impairments include endothelial dysfunction and inflammation, both of which are more frequent in CKD and are associated with cognitive and physical dysfunction in the general population. To date, no medical interventions have been shown to prevent cognitive and physical dysfunction in this exceedingly high-risk population. However, several pilot studies in individuals with CKD have examined the effect of exercise on physical performance, aerobic
capacity, and health-related quality of life (HRQoL), suggesting that it may be possible to elicit functional improvements with supervised exercise training programs. Further, studies in healthy adults suggest aerobic exercise training may improve cognitive function, physical performance, vascular function, inflammation, and vascular risk factors.

This study examines the hypothesis that exercise training will improve neurocognitive function, physical function, and health-related quality of life in older non-dialysis CKD patients, and that these results are mediated in part by improvements in inflammation, vascular function, lipids, blood pressure and insulin resistance. This will be tested in a dual-center randomized parallel-group clinical trial to evaluate the effects of 12 months aerobic and resistance exercise training compared with directed health education control on neurocognitive function, physical performance, and HRQoL in 120 older community-dwelling adults with stage 3b–4 CKD. We will perform detailed measures at baseline and after 6 and 12 months of the following outcomes: 1) Neurocognitive tests of psychomotor speed, executive functions, and memory/learning; 2) Aerobic capacity (peak VO2); 3) Physical performance including submaximal walking speed, timed get up and go test, knee extensor strength, and short physical performance battery; 4) HRQoL (Short Form-36); 5) Microvascular function using laser doppler flowmetry; 6) Inflammation (hs-CRP and IL-6) and vascular risk factors (lipids, BP, insulin resistance). This cross-institutional collaboration of the NIA-funded Claude D. Pepper Older Americans Independence Centers affiliated with University of Maryland and Tufts University, provides the resources and experience necessary to conduct a long-term exercise clinical trial. The results of this trial will be essential in identifying methods to improve cognitive and ambulatory functional status and ultimately prevent disability in this high-risk CKD population.

Supported by RC 1, 2, 3

9. **Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial**
   
   PI: M. Terrin, Ph.D.
   
   R01 AG037120
   
   08/15/2011-07/31/2016

Abdominal aortic aneurysms (AAA) are a common (2-5% of the population e 65 years: 4-9% men; 0.5- 1.5% women) and lethal problem causing 15,000 deaths annually from rupture in the U.S. The only accepted treatment is repair of the AAA which is performed for 40,000 large AAA annually in the U.S. With recent, widespread screening, many more small (<5.0 cm in men, <4.5 cm in women) AAA will be detected. The natural history of AAA is expansion to a size at which the risk of rupture greatly increases. There is no proven medical intervention that will prevent or delay this progression, and surgical options are expensive and unnecessarily risky for small aneurysms. There is experimental and clinical evidence that a family of matrix degrading proteins called matrix metalloproteinase (MMPs) are involved in initiation and progression of AAA. Recent evidence from laboratory, animal models and observational studies demonstrate that doxycycline, working as an MMP inhibitor, can prevent progression of AAA. In recent studies, doxycycline has been shown to: (1) inhibit the growth of experimental abdominal aortic aneurysms;(2) inhibit MMP production in aortic smooth muscle cells and in explanted aneurysm tissue;(3) reduce MMP expression in aneurysm tissue when patients are treated prior to operation for aneurysm repair;(4) reduce circulating MMP levels in AAA patients;(5) decrease the growth rate of small AAA in a limited clinical trial. We have demonstrated that doxycycline is well-tolerated in patients with small AAA. We will bring together investigators with expertise in vascular surgery, clinical trial design, data analysis and management, image analysis of AAA and analysis of circulating biomarkers that reflect aneurysm growth. We will test primary and secondary hypotheses and mechanisms of action related to whether or not doxycycline will inhibit (>40%) the growth of small (3.5 - 5.0 cm in men, 3.5 - 4.5 cm in women) infrarenal AAA. We will determine the effects of doxycycline on the expansion rate of small AAA over a 24-month period for all patients with allowance made for outcomes missing for cause (death or aneurysm repair) or undetermined reasons. This will be done through a prospective,
double blind, placebo controlled clinical trial of 248 patients. Patients will be randomly assigned to receive placebo or doxycycline (100 mg bid). The primary end point will be aneurysm growth rate determined by semiannual CT scan. The public health impact of testing the safety and efficacy of doxycycline in the treatment of abdominal aortic aneurysms derives from the absence of any medical therapy to avoid open surgery or endograft repair. Without medical therapy, ultrasound screening is considered cost-effective in selected patients only. Effective medical therapy would make early detection even more acceptable by providing an alternative to invasive repair of AAA.

Supported by RC 1

10. Race, Socioeconomic Status and Brain: HANDLS Scan Substudy  
PI: S. Waldstein, Ph.D./site PI: L. Katzel, M.D., Ph.D.  
R01 AG034161  
09/01/2009-08/30/2015

Pronounced health disparities associated with race and socioeconomic status (SES) are noted for brain health endpoints including stroke (particularly at younger ages), dementia, brain structure on magnetic resonance imaging (MRI), cognitive decline, and functional disability. Efforts are needed to disentangle respective influences of race and SES on brain health, particularly early and subtle markers of pathology predictive of future stroke and dementia. MRI- assessed measures of gray matter (GM) and white matter (WM) volume and diffusion tensor imaging measures of WM microstructure offer such proven associations. Also critical is identification of multi-level mediators of the relations of race and SES to subtle brain pathology. Biomedical, behavioral, psychological, social and environmental factors have been implicated as potential mediators of the relations of race and SES to many physical health outcomes, but exceedingly little is known about these pathways with respect to brain health. MRI indices of subtle brain pathology may also mediate relations of race and SES to cognitive and physical function. Here we propose an interdisciplinary, ancillary study to the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS). HANDLS study is a new 20-year epidemiological investigation conducted by the National Institute on Aging's Intramural Research Program focused on understanding health disparities among 4,000 socioeconomically diverse African-Americans (AA) and Whites living in Baltimore, MD. HANDLS is uniquely designed to disentangle the respective relations of race and SES to health outcomes. In HANDLS SCAN we propose to obtain quantitative MRI data from 400 (200 AA, 200 White; ages 30-65+) stroke- and dementia-free HANDLS participants with a full range of SES to: (1) Examine race- and SES-related disparities in GM and WM volume, and WM microstructure (2) Examine multi-level mediators - biomedical, behavioral, psychological, social, and environmental - of the relations of race and SES to GM and WM; and (3) Examine whether GM and WM are proximal mediators of the relations of race and SES to cognitive and physical function. Structural equation modeling will be used to construct increasingly complex models to address these interrelated aims.

Supported by RC 1

11. Driving Cortical Plasticity for Rehabilitation of Reaching after Stroke  
PI: G. Wittenberg, M.D., Ph.D.  
R01 HD061462  
06/20/2011-04/20/2016

Stroke is one of the most common causes of disability and there is tremendous room for improvement in rehabilitation techniques. While neural plasticity likely supports much natural and practice-related recovery, such naturally occurring mechanisms for plasticity could be potentially enhanced to improved functional outcomes. We propose a hybrid approach to combining transcranial magnetic stimulation, long seen as an adjunctive method in neurorehabilitation, with upper extremity robotic therapy, another promising method. Our preliminary data shows the potential of brain stimulation to measure and induce plasticity in the motor cortex. We plan to: 1. Determine parameters of stimulation timing that enhance plasticity in normal volunteers; 2.
Determine parameters of stimulation location that enhance plasticity in normal volunteers; and 3. Determine feasibility and pilot data regarding effectiveness in chronic stroke patients. The resulting methods will be applicable to a wide range of motor disability found in stroke survivors and a wide range of methods that combine motor practice with other stimuli, whether natural (such as visual cuing) or artificial (such as magnetic stimulation.) When we have accomplished these aims, we will have established methods that can be used in a larger, multi-site clinical trial of combined stimulation and upper extremity robotic rehabilitation, and will also have uncovered valuable basic mechanisms regarding the induction of motor cortical plasticity through a precisely timed combination of stimulation and repetitive practice of movement in both normal and stroke affected populations. The data obtained by completing these aims will greatly impact future design of stroke rehabilitation paradigms.

Supported by RC 3

12. Reaching while Maintaining Balance in Three Dimensional Space
PI: J. Barton, Ph.D.
VA Career Development Award
10/01/2010-09/30/2015

The ability to maintain one’s balance while reaching in three dimensions (3D) is an essential prerequisite to mobility and independence. Advancing age and stroke (separately and together) can seriously impair balanced reaching performance, leaving affected individuals especially vulnerable to injurious and life-threatening falls. Despite its importance, little is known about the manner in which the central nervous system (CNS) controls and coordinates multi-“system” (gaze, reach, and posture), multi-“objective” (maintain gaze on target, reach to target, and maintain balance) tasks such as this; and less still about the ways in which it is affected by advancing age and/or stroke. An important aspect of this problem is that balance is perturbed not by some unanticipated external disturbance, but by volitional arm movements that healthy individuals are easily able to predict and compensate for. Extant research has largely focused on individual movement tasks (maintain gaze, reach to target, or maintain balance) carried out by healthy and impaired individuals subjected to unanticipated external disturbances. This precludes the opportunity to observe and study the manner in which the various movement systems interact with one another in the execution of multi-system tasks. Moreover, elements of the internal movement control system that compensate for predictable, volitional disturbances are never called into play so that their performance can be observed and analyzed. It is just these multi-system/objective self-perturbed tasks, however, that most commonly precipitate falls in the elderly and impaired. We believe that such falls are caused not only by degradations of individual movement systems (as would be identified by the single system/objective studies), but perhaps even more by impairments to these systems’ ability to interact with one another, as well as impairments to the neural mechanisms that coordinate and control them.

Movement scientists have long relied upon the engineering concepts and techniques of feedback control, systems engineering, and systems identification to investigate movement and its control. More recently it has been proposed that body and limb movement is controlled by Internal Models (IM’s)—neural structures that represent the kinematics and dynamics of the body and its parts, and the forces and constraints imposed upon them by the external environment—and whose function has been shown to be remarkably well predicted by stochastic optimal feedback control theory. Engineering methods in general and the IM paradigm in particular provide a powerful and versatile framework for a systematic, quantitative investigation of performance in multi-system/objective tasks such as balanced reach, but have heretofore only been utilized in single-system/objective studies. We therefore propose in this research to take the logical next step and employ the IM paradigm in an investigation of healthy and impaired performance in the multi system/objective balanced reach task; using the pertinent results of these prior studies as our point of departure. There is a growing need for more precise diagnostic instruments to assess fall risk and inform the design of more effective and efficient treatments. Diagnostic and therapeutic tools based on the IM paradigm have the potential to contribute to our understanding.
of the control systems involved in balance and reaching, and may help us to more precisely design new therapies that could translate into improvements in patient throughput, quality of care, and treatment costs.

The primary objective of this research is to develop, evaluate, and validate a quantitative diagnostic instrument based on the IM paradigm to assess the deficits associated with high fall risk (HFR), stroke and other neurological disorders in elderly individuals performing the balanced reach task in 3D space.

**Supported by RC 1, 2 and 3**

13. **Effects of Exercise and Cognitive Training on Executive Function in PD**  
   PI: F. Ivey, Ph.D.  
   VA RR&D Merit  
   0101/2010-09/30/2015

People with Parkinson's disease (PD) are often impaired in real life situations in which more than one activity needs to be performed at a time. These are called problems in "cognitive-executive function" memory. They are frequently seen early in PD. These memory problems get worse the longer someone has PD, resulting in disruption of daily activities like work, household chores, and managing affairs.

In the proposed project, we will compare the effectiveness of a treadmill aerobic exercise program (TAEX) versus a cognitive training program (TCOG) versus the combination of TAEX + TCOG to improve EF, DT performance and IADLs in our sample of veterans and others with PD. Our fundamental hypothesis is that 3 months of combined TAEX+TCOG will be most effective in improving EF, DT performance, and IADLs, compared to either regimen alone.

Each treatment intervention will last 3 months. The exercise only intervention will consist of progressive treadmill exercise with aerobic training 3 times/week. The memory intervention will consist of computerized memory training 3 times/week for 30 mins. The combined intervention will last 1 hour and 30 mins and will involve both exercise and memory training. Subjects in a control group (delayed entrance) will go through a period of no intervention for 3 months. During that time, they will not exercise or participate in any cognitive training activities. Following the 3 month delayed start period, they will be assigned to one of the intervention groups and will go through that intervention. Measures to test which treatment intervention worked best include: (1) memory testing with paper-and-pencil and computer-based tests of EF, (2) a “walking while talking” test of balance and memory (3) daily activity measures (4) Psychiatric Measures (5) Cardiorespiratory Function Measures.

Currently there is no effective treatment for the specific memory problems caused by PD. No studies have looked at the possible benefits of rehabilitation treatments to improve such problems. The study will help give us information about treatments for memory problems in patients with PD. They will pave the way for larger, future studies.

**Supported by RC 1, 2 and 3**

14. **Veterans with Stroke Translating Exercise Programs**  
   PI: F. Ivey, Ph.D.  
   VA RR&D Merit  
   10/01/2010-09/31/2015

This proposal directly compares the efficacy of two markedly different exercise models in veteran stroke survivors, within the context of an overall cardiovascular risk factor reduction program. We will gain insight into how these programs are translated into community settings, as well as the ideal order of initiation when participants are exposed to both interventions in a counterbalance manner over 12 months.
We hypothesize that initiating the proposed 12-month cross-over intervention with higher intensity treadmill training (HI-TM) (months 0-6) followed by a lower intensity group exercise program (LILI) (months 6-12) will result in the largest long-term impact on functional and behavioral outcomes.

The Specific Aims are: 1) Directly compare the effects of 6-months HI-TM, LILI and EC (education control) regimens on functional, cardiometabolic, behavioral, and quality-of-life outcomes in disabled veteran stroke survivors; 2) Assess whether order of implementation impacts gains in each outcome category during a cross-over period to 1 year; 3) Compare the durability and continuation of all outcome gains in cohorts performing ongoing formal center-based training versus cohorts undergoing only home-based exercise during months 12-18.

The work addresses a number of factors that will help define new evidence for rehabilitation models or current methods of stroke rehabilitation do not effectively prevent or reverse changes in metabolic fitness, function, and declining activity patterns, causing decrements to both physiological and psychological health. This will provide evidence for translating exercise models into the community where it has the greatest chance to benefit the largest number of disabled veterans who are most in need of help. This may ultimately change the current standard of care by providing evidenced-based reasons for dramatically altering the way disabled veteran stroke survivors are counseled and transitioned following completion of conventional therapy.

Supported by RC 1 and 2

15. Improving Balance and Function in Older Veterans

PI: L. Katzel, M.D., Ph.D.
VA SPIRE Pilot Study
04/01/2015-03/31/2017

Every 5 seconds an older American falls, yielding annual costs over $30 billion for fall-related injuries. Beyond financial concerns, for adults over the age of 65, falls are the leading cause of injurious death, non-fatal injuries, and hospital admissions for trauma. With more than 60% of current veterans over the age of 55, preventing falls and fall related injuries has become a major concern for the VA health system. Despite a wide variety of research into fall prevention, the state of the art fall prevention programs reduce falls by only 30%, suggesting more research is required. Falls are multifactorial in origin with a failure to negotiate environmental hazards, muscle weakness, impaired postural control, and gait and balance deficits being among the top contributors to falls in older adults. The multifactorial origins of falls require a multimodality approach to effectively reduce falls. Derivations of t’ai chi ch’uan (Tai Chi) have become popular in western society as low-impact balance and fitness programs suitable for older adults, and Tai Chi is the only modality specifically recommended by the CDC for fall prevention. However, while previous research has demonstrated that Tai Chi may be effective at improving balance and general lower body strength, there are questions concerning its actual effectiveness to prevent falls. The slow choreographic weight shifts central to Tai Chi may improve some aspects of balance and may provide a general lower body strengthening but do little to improve gait, negotiation of environmental hazards, nor dynamic balance recovery following perturbation. Targeted interventions focused on improving stepping and walking ability may be even more effective at improving balance and mobility.10 Preliminary studies demonstrate that our novel progressive group multimodality balance intervention (MMBI), focusing on lateral movements, lower extremity strengthening and dynamic obstacle negotiation, can improve balance, gait and strength in older adults at high risk for falls. It is our overall hypothesis that both MMBI and Tai Chi interventions will improve muscle strength and balance, but we hypothesize that MMBI will result in larger improvements in gait, balance and lower extremity strength in older veterans at high risk for falls and thereby result in fewer falls and lower fall rates in the MMBI group.

To test our hypotheses, we propose to conduct a pilot randomized clinical trial with the following specific aims:
Specific Aim 1: To compare the effectiveness of 6 months of a novel Multi-Modality Balance Intervention (MMBI) program versus Tai Chi exercise training to improving balance [Four-Square Step Test (FSST) and Functional Gait Assessment Tests (FGA)], gait (spatio-temporal gait parameters), lower extremity isometric strength (Biodex of Keyser) and mobility fitness (distance covered during a 6 minute walk) pre and post intervention in older veterans at increased risk for falling.

H1: MMBI will result in larger improvements than Tai Chi in balance, gait, lower extremity strength, and mobility fitness.

Specific Aim 2: To determine and compare the effectiveness of 6 months of MMBI versus Tai Chi exercise training to prevent falls and reduce the number of serious falls in older veterans at increased risk for falling.

H2: MMBI will result in greater decreases in serious falls than Tai Chi and this will be maintained for 6 months following the completion of the exercise program.

Supported by RC 1, 2 and 3

16. Center of Excellence
   PI: R. Macko, M.D.
   07/01/2011-03/30/2016

The focus of this center is to optimize functional recovery in individuals with mobility impairment due to stroke and other neurological conditions using a multi-systems approach investigating models of task-oriented exercise, robotics, and behavioral modification. Studies determine optimal exercise formulas to improve fitness and function, establish novel protocols integrating robotics with exercise to enhance motor learning, and establish strategies to translate these programs into VA care and the community.

Supported by RC 1, 2, 3

17. Resistive Training Combined with Nutritional Therapy after Stroke
   PI: A. Ryan, Ph.D./F. Ivey, Ph.D.
   VA Merit
   05/01/2015-04/30/2019

Stroke survivors experience severe muscle wasting during the chronic phase of recovery, with implications for strength, function and general health. Although resistive exercise training effectively combats this problem, it is unknown whether sub-optimal protein intake limits the observed gains in skeletal muscle growth. Healthy populations show better skeletal muscle adaptations when resistive training (RT) is combined with nutritional therapy in the form of post-exercise protein consumption. This study is the first to directly compare RT+protein supplementation to RT+placebo (same calories as protein supplement) in those with chronic hemiparesis caused by stroke, providing evidence-based rationale for combination therapy in the clinical care of this population. It assesses changes to the myostatin signaling network in both paretic and non-paretic leg skeletal muscle across a combined exercise and nutrition intervention.

Supported by RC1, 2

18. Neurocognition and Functional Performance in Older Veterans with CKD
   PI: S. Seliger, M.D. /L. Katzel, M.D., Ph.D.
   VA Merit
   12/09/2009-12/09/2015

Chronic Kidney Disease (CKD) affects 1 out of 5 older adults in the US including more than 400,000 older veterans yet is often unrecognized by affected individuals and even their healthcare providers. Older adults with CKD suffer from a markedly higher risk of cognitive and physical dysfunction, including a 40% greater risk of dementia and a 75% greater risk of physical frailty. The factors which account for this risk are unclear;
however, recent neuroimaging investigations suggest a greatly increased burden of covert brain pathology in
association with CKD and reduced kidney function.

We hypothesize that older veterans with CKD suffer from a greater burden of subclinical ischemic disease of
the brain, which results in impaired neurocognition and physical function. We will conduct an observational
cohort study of stroke-free community-dwelling older veterans (ages 60-85) with CKD not requiring dialysis
(N=150, evenly distributed among mild, moderate and severe CKD), and a control group without CKD but
frequency-matched on the common co-morbid conditions diabetes, hypertension and cardiac disease (N=50).
We will obtain quantitative measurements of 1) kidney disease and function (including albuminuria and the
renal biomarker cystatin C), 2) ischemic brain disease using MRI, 3) physical function and performance, and 4)
multiple domains of neurocognitive function. The overall aims are to estimate the association of CKD and renal
function measures with MRI-defined subclinical ischemic brain disease and cognitive and physical function.
The aims of this study are: 1) To examine the association of CKD and individual biomarkers of renal
dysfunction with subclinical ischemic brain disease, neurocognitive function, and physical function among
community-dwelling stroke- and dementia-free older veterans and 2) Using structural equations modeling
(SEM), examine whether a greater burden of subclinical ischemic brain disease mediates the relation of CKD
and its biomarkers to decreased cognitive and physical function among older veterans.

Supported by RC 1 and 2

19. Aerobic Training to Improve Energy Utilization and Antioxidant Capacity in Stroke
   PI: M. Serra, Ph.D.
   VA Career Development Award-2
   04/01/2015-03/31/2019

Fifteen to 30% of stroke survivors are permanently disabled, which usually leads to a sedentary lifestyle and
functional dependence following stroke. While it is known that hemiparetic gait elevates the energy cost of
ambulatory activity by 1.5- 2 fold, how chronic stroke affects total daily energy expenditure (TDEE) and dietary
intake is currently unknown. Altered energy balance ( expenditure ≠ intake) may result in impaired substrate
oxidation and skeletal muscle oxidative stress. Elevated oxidative stress in skeletal muscle is associated with
fatigue and decreased cardiovascular and muscular endurance. This randomized control study tests the
hypothesis that treadmill rehabilitation plus nutritional modification (“heart healthy” diet plus adequate protein)
(TM+N) versus stretching plus nutritional modification (ST+N) (nutrition control) will 1) improve energy
balance and substrate oxidation, 2) reduce systemic and tissue level oxidative stress, and 3) that the respective
comparison of these interventions (TM+N and ST+N) to treadmill (TM) and stretching (ST) controls from her
mentor’s current R01 will support the rehabilitative role of nutritional modification in stroke. Older (55-75
years), men and postmenopausal women (n=50) with chronic stroke (at least 6 months post stroke) with stable
neurological deficits will be recruited. Subjects will be randomized to participate in six months of dietary
modification (<30% of calories as fat, <10% as saturated fat, <2,400 mg sodium, 25 g/d of fiber, and 1.0-1.2
 g/kg/d of lean protein) plus aerobic exercise training or dietary modification plus whole body stretching.
Seven-day accelerometry and dietary records will be used to determine energy balance. Indirect calorimetry
will be used to determine substrate oxidation during fasting and a peak and submaximal exercise bout. Blood
draws and paretic and non-paretic vastus lateralis skeletal muscle biopsies will be performed to determine
changes in systemic and tissue level oxidative stress content (nitrate/nitrite and thiobarbituric acid reactive
substances) and antioxidant capacity (superoxide dismutase, glutathione peroxidase, and catalase) following
exercise rehabilitation or stretching with and without nutritional modification in chronic stroke survivors.

Supported by RC 1, 2 and 3

20. Brain Neurophysiological Biomarkers of Functional Recovery in Stroke
   PI: G. Wittenberg, M.D., Ph.D.
Background/Rationale: Stroke remains the leading cause of long-term disability in our veterans and the vast majority of stroke survivors experience significant motor impairments in the upper extremity. Survivors of stroke regain the most function during the early phases of recovery, a process that is likely mediated by changes in underlying neurophysiology. These changes, however, are not well understood in relation to voluntary reaching movements, but are nonetheless critical to successful rehabilitation.

Electroencephalography (EEG) is one of several methods to understand the mechanisms underlying recovery in stroke, but EEG-based investigations have mainly relied on global brain electrical activity (i.e. during resting state) to correlate with motor impairment and/or function. Our goal, therefore, is to better understand the neural mechanisms during planning and execution of volitional reach across critical periods of recovery. We intend to use EEG to identify changes in brain-derived biomarkers that reflect the timing and direction of the intent to reach, and determine how these change over the course of natural recovery, i.e., as stroke survivors progress from the subacute to chronic phases.

Objectives: Our preliminary data indicate that it is feasible to collect quality EEG in survivors of stroke as they volitionally perform motor tasks. Moreover, we detected brain-derived biomarkers that reliably encoded for aspects of reach, i.e., the intended direction to move and timing of movement onset. Specifically the first study demonstrated that when using the proposed task a brain-derived biomarker could be extracted which encoded for the intended direction of reach. The second study revealed that using this same task, a chronic stroke patient exhibited well-characterized cortical dynamics associated with volitional movement. Further, using these biomarkers as input to a Bayesian classifier robustly predicted the timing of the intent to move on a trial-by-trial basis. Thus, the classification will only improve when many more brain-derived biomarkers are available to this classification system with regard to timing and direction.

In line with these preliminary studies, our objective is to characterize the neurophysiological signals that best predict the onset and direction of volitional reaching movements in survivors of stroke, and determine how these identified signals change as stroke survivors recover from subacute to chronic stages.

Methods: A convenience sample of forty stroke patients will be studied in the subacute phase of recovery (2-6 weeks post-stroke) and followed to the chronic stage (> 6 months.) At each visit, participants will be asked to choose between, and reach to, one of two targets in an InMotion planar robot while EEG data are collected concurrently. The EEG time series corresponding to the period prior to movement onset will be extracted. These data will be processed in order to extract a multitude of functional EEG metrics (e.g., spectral power, coherence, and movement related cortical potentials.) These metrics will be used as inputs into a Bayesian classifier to determine which biomarkers reliably encode for volitional timing and direction of intended movement. Finally, the changes in these biomarkers as a function of recovery will be determined. Findings/Results: We predict that we will identify a subset of biomarkers from the multitude of EEG metrics that will consistently indicate the intended direction and timing of volitional movement. Further, we predict that these biomarkers will change as a function of recovery with regard to timing and location, and will therefore provide both mechanistic insights to recovery as well as data relevant to brain-computer interfaces.

Supported by RC 3

21. Neurophysiological and Kinematic Predictors of Response in Chronic Stroke
PI: G. Wittenberg, M.D., Ph.D.
VA Merit
07/01/2015-06/30/2019
Upper extremity hemiparesis has a profound and lasting negative impact on quality of life and independence in activities of daily living for stroke survivors, yet, despite many investigations, there are no gold standard treatments in current clinical practice. We have carried out a progressive research program that has demonstrated the effectiveness of robotic therapy in chronic stroke patients, and then optimizing the type of robotic therapy and associated therapy that these patients receive. But gains in the chronic group are modest on average, and despite an intuition that earlier intervention will be beneficial, there is little data to confirm that. Therefore, we propose to build upon our expertise with robot-assisted training for chronic stroke impairment in order to evaluate the potential of predictive models that would select patients with better chances of making functional gains. Our clinical hypothesis is that kinematic and physiological biomarkers of recovery potential exist, and include baseline motor ability in both functional tasks and in the robotic environment, and measures of corticospinal tract effectiveness determined by transcranial magnetic stimulation. Functional and anatomical measures of connectivity and plasticity relevant genotype are secondary biomarkers to test. Time after stroke is another promising marker to test, with strong implications for clinical practice. We also propose a secondary mechanistic hypothesis that maladaptive transhemispheric cortical inhibition will be altered by the intervention.

Specific Objectives: Create a predictive model of function and disability following the intervention. Measure the effects of 12 weeks of robot-assisted therapy and transition to task training at > 6 months after stroke. Create a model that predicts clinically meaningful change in Fugl-Meyer in response to the intervention and test the validity of the model. Determine the effect our hybrid method of training has on interhemispheric inhibition by using transcranial magnetic stimulation to study silent period and recruitment curve. Patients with moderate to severe arm dysfunction (based on Fugl-Meyer scores of 7 to 45) of >6 months duration who are medically stable and do not have contractures or other impairments that would interfere with training will be enrolled. 96 subjects will be assigned to a single study arm with a multiple baseline approach to ensure stability of measures. Evaluations will be conducted by an examiner who has no knowledge of the predictive model. The first four weeks of training will consist of wrist robot training sessions, the second four weeks will consist of planar robot training sessions and the third four weeks will consist of alternation wrist and planar training sessions. Robot training sessions will be 45 minutes in duration followed by 15 minutes of training on functionally relevant tasks (translation to task training (TTT)). Clinical evaluations will include Stroke Impact Scale (Primary Outcome), Fugl-Meyer Upper Extremity Motor Performance Section Test, Wolf Motor Function Test, Action Research Arm Test, and activity monitor of home arm use. Kinematic analysis will be conducted pre and post training. A majority of patients will be consented for TMS and MRI. In those subjects intrahemispheric inhibition will be determined at each outcomes measurement visit. MRI will be performed only at the baseline period, and will be used to define the lesion type, white matter integrity and functional connectivity of the corticospinal tract. At the conclusion of these aims we will have a method for clinical decision-making regarding intensive arm therapy late after stroke, and a better mechanistic understanding of how it works. The method will be disseminated throughout the VA medical system and beyond.

Supported by RC 3

C. PILOTS (Pilot Projects – Year 01 (1994) to Present)

Year 01 (1994-1995)

Effects of Exercise on Blood Pressure, Hyperinsulinemia and Renal Function in the Elderly
Donald R. Dengel, Ph.D., Research Associate (410) 605-7000 x5446 (Andrew Goldberg, M.D., Matthew Weir, M.D., Mentors)

Exercise Rehabilitation Programs for the Treatment of Claudication Pain
Andrew W. Gardner, Ph.D., Assistant Professor (410) 605-7000 x5426 (Eric Poehlman, Ph.D., Mentor)
Effect of Weight Loss and Exercise Training on Lipoprotein Lipid Metabolism in Elderly with Atherogenic LDL Phenotype
Leslie I. Katzel, M.D., Ph.D., Assistant Professor (410) 605-7000 x5422 (Andrew Goldberg, M.D., Mentor)

Costs of Congestive Heart Failure among the Elderly
Ernest Moy, M.D., MPH, Assistant Professor (410) 328-6598 (James Hudson, M.D., Mentor)

The Effects of Strength Training on Insulin Sensitivity and Glucose Tolerance in Post-Menopausal Women with Impaired Glucose Tolerance
Alice Smith Ryan, Ph.D., Research Fellow (410) 605-7000 x5449 (Dariush Elahi, Ph.D., Mentor)

Year 02 (1995-1996)

Cognitive Functioning of Hip Fracture Patients in the Hospital: Components, Predictors, Trajectories, Outcomes, and Implications for Intervention
Ann L. Gruber-Baldini, Ph.D., Research Associate (410) 706-2444 (Jay Magaziner, Ph.D., M.S. Hyg., Mentor)

Aerobic Exercise in the Elderly Stroke Population
Richard F. Macko, M.D., Assistant Professor (410) 605-7000 x0063 (Andrew Goldberg, M.D., Mentor)

Effects of Aerobic Exercise in Endogenous Fibrinolysis in Elderly Patients with Intermittent Claudication and Stroke
Lois Killewich, M.D., Ph.D., Assistant Professor (410) 605-7229 (William Flinn, M.D. and Andrew Goldberg, M.D., Mentors)

Assessment of Leg Perfusion in Intermittent Claudication
Andrew Gardner, Ph.D., Research Assistant Professor (410) 605-7000 x5426 (William Flinn, M.D., Mentor)

Year 03 (1996-1997)

The Effect of Risk Factor Modification (Diet, Weight Loss, Smoking Cessation, Exercise) on Endothelium-Dependent Brachial Artery Vasoactivity in Older Men and Women
Mary Corretti, M.D., Assistant Professor (410) 328-6190 (Stephen Gottlieb, M.D., Leslie Katzel, M.D., Ph.D., Mentors)

The Impact of Computer-Assisted Data Collection in a Geriatric Population
Roopak Manchanda, M.S. (410) 605-7000 x5430 and Mitchell Rosen, Ph.D. (410) 605-7119 (Douglas Bradham, Dr.P.H., Mentor)

Lower Extremity Strength in Vascularly Disabled Individuals: Peripheral Arterial Disease and Stroke
Kenneth Silver, M.D., Associate Professor (410) 328-6484 (Andrew Goldberg, M.D., James Hagberg, Ph.D., Mentors)

The Effect of Exercise on Recovery of Function Following Hip Fracture
Perry Colvin, M.D., Assistant Professor (410) 605-7217 (Jay Magaziner, Ph.D., Mentor)
Year 04 (1997-1998)

The Effect of Exercise on Recovery of Function Following Hip Fracture
Perry Colvin, M.D., Assistant Professor (410) 605-7217 (Jay Magaziner, Ph.D., Mentor)

The Effect of Risk Factor Modification (Diet, Weight Loss, Smoking Cessation, Exercise) on Endothelium-Dependent Brachial Artery Vasoactivity in Older Men and Women
Mary Corretti, M.D., Assistant Professor (410) 328-6190 (Stephen Gottlieb, M.D., Leslie Katzel, M.D., Ph.D., Mentors)

Electromagnetic Motor Evoked Potentials (MEPs) as a Prognostic Measure of Functional Outcomes in Stroke Patients
Gerald Smith, Ph.D., P.T., Assistant Professor (410) 706-7720 (Mary Rodgers, Ph.D., PT, Mentor)

Year 05 (1998-1999)

Muscle Fiber Plasticity in Hemiparetic Patients after an Aerobic Exercise Program
Patrick DeDeyne, Ph.D., MPT, Assistant Professor (410) 706-2703 (Andrew Coggan, Ph.D., Mentor)

Analysis of Cardiac Na/Ca Exchanger During Aging
Abdul Ruknudin, Ph.D., Research Assistant Professor (410) 706-6240 (John Lederer, M.D., Ph.D., Mentor)

Upper Extremity Training in Stroke Patients: A Feasibility Study
Sandra McCombe-Waller, M.S., Clinical Instructor (410) 706-7720 (Jill Whitall, Ph.D., Mentor)

Year 06 (1999-2000)

Neuroplasticity and Upper Extremity Training in Stroke Patients
Larry Forrester, Ph.D., PT, Associate Professor (410) 706-5212 (Jill Whitall, Ph.D., Daniel Hanley, M.D., Gerald Smith, Ph.D., PT, Mentors)

Year 07 (2001-2002)

The Construct of a Hip Fracture-Specific Functional Test and Feasibility of a New Training Program
Gad Alon, Ph.D., PT, Associate Professor (410) 706-7733 (Perry Colvin, M.D., Jay Magaziner, Ph.D., M.S. Hyg., Mentors)

Short-term Neural Adaptations with Treadmill Training in Chronic Hemiparetic Stroke Patients
Larry Forrester, Ph.D., Assistant Research Professor/Research Associate (410) 706-5212 (Daniel Hanley, M.D., Richard Macko, M.D. Mentors)

Development of a Rodent Model Using Aerobic Exercise as Rehabilitative Intervention after Focal Cerebral Ischemia
Daniel Hanley, M.D., Professor (Johns Hopkins University) (410) 614-5185
**Peripheral Arterial Occlusive Disease, Cognition, and Magnetic Resonance Abnormalities in Older Adults**
Shari Waldstein, Ph.D., Assistant Professor (410) 455-2567 (Leslie Katzel, M.D., Ph.D., Eliot Siegel, M.D., David Lefkowitz, M.D., Abraham Obuchowski, M.D., Mentors)

**Year 08 (2002-2003)**

**Muscle Protein Profile in Patients with Stroke**
Patrick G. DeDeyne, Ph.D., M.P.T., Associate Professor (410) 706-2703 (Richard Macko, M.D., Mentor)

**Progressive Rate Training (PRT) Post Stroke**
Carwile LeRoy, M.D., Associate Investigator/Fellow (410) 605-7000 ext 5452 (Richard Macko, M.D., Mentor)

**Assessing Treatment Fidelity in the Pepper Center: Enhancing Intervention Research**
Denise Orwig, Ph.D., Assistant Professor (410) 706-2406 (Jay Magaziner, Ph.D., M.S. Hyg., Mentor)

**Medical Cost Implications of Changes in Functional Status**
Bruce Stuart, Ph.D., Professor (410) 706-5389

**Central Motor Control Mechanisms Associated with Hand Dominance and Their Adaptability to Unilateral and Bilateral Training**
Sandra McComb Waller, MS, PT, Assistant Professor (410) 706-0787 (Jill Whitall, Ph.D., Mary Rodgers, Ph.D., Mentors)

**Year 09 (2003-2004)**

**Impedance-Controlled Ankle Robotics: A Novel Technology for Gait Rehabilitation after Stroke**
Larry Forrester, Ph.D., Assistant Professor (410) 706-5212 (Richard Macko, M.D., Igo Krebs Ph.D., Christopher Bever, M.D., Mentors)

**Age, Lifestyle, Muscle Mechanisms in Insulin Resistance (Training Only)**
Lyndon Joseph, Ph.D., Assistant Professor, (410) 605-7000 ext 5783 (Alice Ryan, Ph.D., Andrew Goldberg, M.D., Mentors)

**Morphometrical and Volumetrical Characteristics of the Lesioned Brain as Predictors of Therapeutic Benefits of BATRAC and AEX**
Andreas Luft, M.D., Assistant Professor, University of Tübingen, Germany +49 7071 967853 (Daniel Hanley, M.D., Mentor)

**Skeletal Muscle Size and Performance in HIV and Individuals of Differing Functional Status**
David Russ, P.T., Ph.D., Assistant Professor, (410) 706-7165 (Les Katzel, M.D., Ph.D., Andrew Goldberg, M.D.)

**Year 10 (2004-2005)**

**Adipose Tissue Production of Inflammatory Cytokines: Cellular Sources and Changes with Age**
Jacob Blumenthal, M.D., Assistant Professor, (410) 605-7000 ext 5426 (Susan K. Fried, Ph.D. Andrew P. Goldberg, M.D.)

The Effects of Exercise on Renal Function as Measured by Cystatin C Versus Creatinine-based Estimates of Glomerular Filtration Rate
Jeffrey Fink, M.D., Associate Professor of Medicine, (410) 605-7000 ext 5280 (Les Katz, M.D., Ph.D., mentor)

Does side of Stroke Affect Central Motor Control Mechanisms in Response to Short-term Unilateral Versus Bilateral Training?
Sandy McCombe Waller, Ph.D., PT, Assistant Professor, (410) 706-0787 (Jill Whitall, Ph.D., Daniel Hanley, M.D.)

The Effects of Resistive Training on Muscle Atrophy and Insulin Sensitivity in Hemiparetic Stroke Patients
Alice S. Ryan, Ph.D., Associate Professor, (410) 605-7851 and Fred Ivey, Ph.D., Assistant Professor, (410) 605-7297 (Richard Macko, M.D., Andrew P. Goldberg, M.D.)

Exercise Rehabilitation in Parkinson Disease
Frank Skidmore, M.D., Assistant Professor, (410) 299-1880 cell phone (Richard F. Macko, M.D., Lisa M. Shulman, M.D., William J. Weiner, M.D.)

Year 11 (2005-2006)

SAA Reduction as a Beneficial Mechanism of Weight Loss by Exercise
Da-Wei Gong, M.D., Ph.D., Assistant Professor (410) 706-1672 (Andrew P. Goldberg, M.D., Alice Ryan, Ph.D.)

Feasibility Study for the Measurement of Lower Extremity Muscle Strength, Muscle Composition and Cardiovascular Fitness Following Hip Fracture
Ram Miller, MDCM, MSc, Assistant Professor (410) 706-3907 (Jay Magaziner, Ph.D., Alice Ryan, Ph.D., Richard Macko, M.D., Charlene Hafer-Macko, M.D.)

Aging and HIV
Kris Ann Oursler, M.D., Associate Professor (410) 328-6056 (Les Katz, M.D., Charlene Hafer-Macko, M.D.)

Effects of Ambulatory Exercise Training on Risk Factors for Sudden Cardiac Death in Stroke Patients
Eric Rashba, M.D., Associate Professor (410) 328-6056 (Richard Macko, M.D., Frederick Ivey, Ph.D.)

Cerebral Hypoperfusion and Cognitive Dysfunction in Chronic Kidney Disease (CKD)
Stephen Seliger, M.D. MS, Assistant Professor (410) 605-5231 (Shari Waldstein, Ph.D., Les Katz, M.D., Ph.D., Jeffrey Fink, M.D., MS, Eliot Siegel, M.D.)

Year 12 (2006-2007)
The Effect of Treadmill Training on Recovery of Lower Extremity Function and Inflammatory Cytokines in Hip Fracture Patients
Ram Miller, MDCM, MSc, Assistant Professor (410) 706-3907 (Jay Magaziner, Ph.D., Alice Ryan, Ph.D., Richard Macko, M.D., Charlene Hafer-Macko, M.D.)

Mechanisms of Cellular Regeneration and Repair in the Functional Recovery of Skeletal Muscles from Older Animals Following Eccentric Injury
David Russ, P.T., Ph.D., Assistant Professor, (410) 706-7165 (Les Katzel, M.D., Ph.D., Andrew Goldberg, M.D.)

Larry Forrester, Ph.D., Assistant Professor (410) 706-5212 (Richard Macko, M.D., Igo Krebs Ph.D., Christopher Bever, M.D., Mentors)

Year 13 (2007-2008)
Adaptive Physical Activity in Hemiparetic Stroke
Kathleen Michael, Ph.D., Assistant Professor (410) 605-4844 (Richard Macko, M.D., Andrew Goldberg, M.D., Mentors)

Effects of Aerobic Exercise Training on VEGF, Angiogenesis and Glucose Metabolism in Older Adults
Steven Prior, Ph.D. Assistant Professor (410) 605-4129 (Alice Ryan, Ph.D., Andrew Goldberg, M.D., Heidi Ortmeyer, Ph.D., Mentors)

Immunologic Dysfunction in Elderly Subjects who undergo Aerobic Exercise Rehabilitation
Wilbur Chen, M.D., Assistant Professor (410) 706-5328 (Andrew Goldberg, M.D., Alice Ryan, Ph.D., Mentors)

The Effect of Home-Based Exercise Training on Recovery of Lower Extremity Function and Inflammatory Cytokines in Hip Fracture Patients
Ram Miller, M.D.C.M., Assistant Professor (410) 706-2406 (Jay Magaziner, Ph.D., Les Katzel, M.D., Ph.D., Mentors)

Resistive Training and Skeletal Muscle Insulin Action in Hemiparetic Stroke Patients
Alice S. Ryan, Ph.D., Professor, (410) 605-7851 and Fred Ivey, Ph.D., Assistant Professor, (410) 605-7297 (Richard Macko, M.D., Mentor)

Year 14 (2008-2009)
Endothelial Function and Cognitive Dysfunction in Chronic Kidney Disease
Afshin Parsa, M.D., Ph.D., Assistant Professor, (410) 706-6445 (Les Katzel, M.D., Ph.D., Mentor)

Hip Muscle Composition: Relationships with Neuromechanical Performance, Lateral Stability, and Risk of Falls in Older Adults
Mark Rogers, Ph.D., P.T. Professor, (410) 706-0841 (Andrew Goldberg, M.D. and Alice Ryan, Ph.D. Mentors)

UM-OAIC & MERCE Joint Pilot Collaboration
Assessment of Motor System Connectivity in Stroke Rehabilitation
Alan McMillan, Ph.D., Research Associate, (410) 328-6104 (Jill Whitall, Ph.D., Mentor)

Year 15 (2009-2010)
Impact of Inflammatory Bowel Disease and Aging on Body Composition and Functional Performance
Raymond Cross, M.D., MS, Associate Professor, (410) 706-3387 (Les Katzel, M.D., Ph.D., and Alice Ryan, Ph.D., Mentors)

The Effects of Aging on Airway Smooth Muscle Contraction and Relaxation
Deepak Deshpande DVM, Ph.D., Assistant Professor, (410) 706-1070 (Andrew Goldberg, M.D., Mentor)

Task-Oriented Exercise and Behavioral Intervention to Promote Activity in Stroke
Kathleen Michael Ph.D., RN, CRRN, Assistant Professor, (410) 706-0142 (Richard Macko, M.D. and Andrew Goldberg, M.D., Mentors)

UM-OAIC & MERCE Joint Pilot Collaboration

Cortical and Biomechanical Dynamics of Lower Extremity Robot Assisted Training at Different Levels of Motivational Incentive Implications for Stroke Survivors
Ronald Goodman, Ph.D., Research Fellow, (410) 605-7000 ext. 4349 (Richard Macko, M.D. and George Wittenberg, M.D., Ph.D., Mentors)

Myasthenia Gravis Exercise Program to Increase Physical Activity and Fitness and Reduce Cardiovascular Risk
Charlene Hafer-Macko, M.D., Associate Professor, (410) 328-3100 (John Sorkin, M.D., Ph.D. Mentor)

Plasticity, Kinetics and Kinematics of Bilateral Reaching Therapy in Chronic Stroke
Lauren Jones-Lush, Ph.D., Assistant Professor, (410) 706-5490 (George Wittenberg, M.D., Ph.D., Mentor)

Year 16 (2010-2011)
Role and Mechanism of Exercise Induced Facilitation of Recovery after Experimental Traumatic Brain Injury
Alan Faden M.D., Professor, (410) 706-4205 (Richard Macko, M.D., Mentor)

Pilot Study of Prehabilitation Prior to Elective Surgery in Older Adults
Ram Miller M.D., CM, Assistant Professor, (410) 706-2406 (Jay Magaziner, Ph.D., M.S.Hyg, Mentor)

Effect of a Progressive, Adaptive Physical Activity Regimen on Functional Outcomes and Musculoskeletal Composition in Elderly Survivors of Critical Illness
Giora Netzer, M.D., MSCE, Assistant Professor, (410) 706-3344 (Michael Terrin, M.D., CM, MPH, Mentor)

Functional and Metabolic Benefits of Rehabilitation in HIV
Does Strength Training Improve Balance Training in Older Adults?
Brock Beamer, M.D., Assistant Professor, (410) 605-7000 ext. 4870 (Andrew Goldberg, M.D., Mark Rogers Ph.D., PT, Mentors)

Year 17 (2011-2012)
Improving Walking Symmetry and Functional Mobility in Stroke Survivors with Split-Belt Treadmill Training
Amy Bastian, Ph.D., Assistant Professor, (443) 923-2718, Johns Hopkins University, Inter-Pepper collaboration (Daniel Hanley, M.D., Mentor)

Aerobic Exercise (AEX) to Improve Regulation of Endothelial Progenitor Cells (EPCs) and Vascular Function in T2DM
Steven Prior, Ph.D. Assistant Professor (410) 605-7000 ext. 4129 (Alice Ryan, Ph.D., Andrew Goldberg, M.D., Heidi Ortmeyer, Ph.D., Mentors)

Effects of Vitamin D Repletion (D) with and without Multi-Component Lifestyle Exercise Training (MLife) on Muscle Function, Inflammation and Glucose Metabolism in D Deficient Older Adults
Elizabeth Streeten, M.D., Associate Professor, (410) 328-6219 and Heidi Ortmeyer, Ph.D., Assistant Professor, (410) 605-7000 ext. 5419 (Andrew Goldberg, M.D., Mentor)

Resistance Training (RT) and Protein (Pro) Supplementation to Improve Muscle Physiology and Reduce Fatigue in Breast Cancer Survivors
Monica Serra, Ph.D., Research Fellow, (410) 605-7000 ext. 4199 (Andrew Goldberg, M.D., Alice Ryan, Ph.D., Mentors)

A High-Density Electroencephalography (EEG) Neural Decoding Study of Dynamical Cortical Mapping of Gait in Humans after Stroke
Jose Contreras-Vidal, Ph.D., Professor, (713) 743-4429, University of Houston (Richard Macko, M.D., Larry Forrester, Ph.D., Mentors)

Year 18 (2012-2013)
Comparison of Reactive Step Training and Voluntary Task-Oriented Training to Induce Neuromotor Changes for Improving Balance and Preventing Falls
Douglas Savin, Ph.D., P.T. Assistant Professor, (410) 706-5210 (Mark Rogers, Ph.D., P.T., Mentor)

Development of a Rehabilitation Strengthening and Mobility Program for Ventilator Dependent Older Patients
Avelino Verceles, MD, Assistant Professor, (410) 328-8141 (Andrew Goldberg, M.D. and Michael Terrin, M.D., C.M., M.P.H., Mentors)
Probing the Neural Basis and Influence of Cognitive Changes on Impaired Balance in Older Adults
Kelly Westlake, Ph.D., MSc., P.T., Assistant Professor, (410) 706-5919 (Mark Rogers, Ph.D., P.T., Shari Waldstein, Ph.D., Tula Adele, Ph.D., Rao Gullapalli, Ph.D., and George Wittenberg, M.D., Ph.D., Mentors)

Using Self-Triggered, Sensory-Enhanced Gaze Shift to Improve Axial Turning Deficits in Persons with Parkinson’s Disease
Robert Creath, Ph.D., Assistant Professor, (410) 706-5918 (Mark Rogers, Ph.D., P.T., Mentor)

Year 19 (2013-2014)
Early Mobilization of Older Adults after Emergency Surgery
Laura Buchanan, M.D., Assistant Professor, (410) 389-1559 (Jay Magaziner, Ph.D., M.S.Hyg, Mentor)

The Effect of Voluntary Exercise on Microglial Activation Phenotypes in the Aged Injured Brain
David Loane, Ph.D., Assistant Professor, (410) 706-5188 (Richard Macko, M.D. and Daniel Hanley, M.D., Mentors)

Pilot Trial of Aerobic and Resistance Exercise Training for Primary Prevention of Musculoskeletal Side Effects from Aromatase Inhibitors (AI) in Postmenopausal Breast Cancer Survivors
Susan Kesmodel, M.D., Assistant Professor, (410) 328-7820 and Monica Serra, Ph.D., Instructor, (410) 605-7000 ext. 4199 (Andrew Goldberg, M.D., Mentor)

Year 20 (2014-2015)
Ambulatory Activity in Elderly Patients in a Shock Trauma Center
Ivonne-Marie Berges, Ph.D., Assistant Professor, (410) 706-1379 (Jay Magaziner, Ph.D., M.S.Hyg, Mentor)
The purpose of our pilot study is to examine the ambulatory and mobility activity of persons following emergency abdominal surgery. Up to 60 subjects aged 60 and older randomized to intervention (including education, and targeted nursing and rehabilitation services) and control (education) will be tracked for up to one-month after discharge. Patterns of activity will be assessed for both groups and possible mediators including social support and depressive symptoms assessed. Our overarching hypothesis is that ambulatory and mobility activity (daily step count) will be greater in persons randomized to intervention. A secondary hypothesis is that social support and depressive symptoms will mediate this association. Greater social support will be associated with increased ambulatory and mobility activity within each group. Conversely, depressive symptoms will be associated with decreased ambulatory and mobility activity within each group.

Targeting Corticostriatal Plasticity for Parkinson’s Disease Treatment
Brian Mathur, Ph.D., Assistant Professor, (410) 706-8239 (Mark Rogers, Ph.D., P.T., George Wittenberg, M.D., Ph.D., Mentors)
Plastic changes at synapses in the brain allow for the acquisition of new information and the generation of diverse actions. However, very little is known about how dysplastic synaptic changes underlie neuropsychiatric disease states. In order to bridge this gap and to improve upon existing therapeutic approaches that activate neural circuits in patients suffering from Parkinson’s disease (PD), a mechanistic analysis of how noninvasive approaches such as transcranial pulsed current stimulation (tPCS) recruit plastic mechanisms at synapses is required. Here, we propose the novel hypothesis that tPCS confers therapeutic benefit for PD by inducing plastic changes at the corticostriatal synapse; the critical, first synapse in the processing of motor cortex input to the basal ganglia. This project intends to advance the work of noninvasive tPCS for the improvement of gait and balance in elderly PD patients. Three specific aims will be examined: 1) identify in a mouse model which neuromodulator mechanisms underlie the benefit afforded by tPCS alone, 2) examine whether tPCS induces synaptic plasticity on-line and how this correlates with behavioral improvement in mice and 3) assess
corticostriatal plasticity in PD patients treated with established and new tPCS protocols using functional imaging. The results of this research will help restore functional independence and ameliorate further functional decline in patients living with PD, a chronic and disabling neurodegenerative disease of aging.

**Circulating MicroRNAs in Older Adults**
Jeffrey Deiuliis, Ph.D., Assistant Professor, (410) 328-4096 (Alice Ryan, Ph.D., Mentor)
The overall objective of this proposal is to identify and study age-related microRNAs (miRs) unique to older adults in order to better understand the potential role of (miRs) in primary aging and in the age-related development of cardio-metabolic disease such as impaired glucose tolerance (IGT) and insulin resistance (IR). We believe this investigation has the potential to lead to the development of a clinical miR biomarker for age-related disease. In Aim 1, we will investigate levels of circulating miRs using global miR expression in the plasma of men over the age of 60 years. The older group will include individuals with normal or impaired glucose tolerance. We hypothesize that circulating levels of miRs will strongly correlate with patient age and multiple cardio-metabolic markers. In Aim 2, we will use bioinformatics approaches to predict miR gene targets. Pathway analysis will allow for selection of direct and indirect genes relevant to aging and age-related disease. To test these predictions, we will utilize in vitro methods to measure miR-specific repression of target gene expression. Collectively, the experimental findings have the potential to advance our limited understanding of the clinical and biological role of circulating miRs in older adults and age-related disease, as well as lead to extramural funding.

**Modulation of Interhemispheric Interactions and Arm Activity after Stroke**
Michael Dimyan, M.D., Assistant Professor, (410) 448-6345 (George Wittenberg, M.D., Ph.D., Mentor)
Even after comprehensive rehabilitation, 30% of stroke survivors are left with arm weakness. Chronic hemiparesis is significant because 50% of the reduction in quality of life for stroke survivors is due to arm weakness. Current treatments of hemiparesis are based on different models of how the two arms interact after stroke. However, these models are limited by an incomplete understanding of interhemispheric competition. In particular, we do not know how interactions between the two arms are dynamically modulated during arm activity. I will pursue this problem by 1) defining normal interhemispheric interactions between the two arms during unilateral arm activity and 2) discovering how aging and stroke impair those dynamics. This will be done by studying neurophysiological measures of corticospinal and interhemispheric interactions in hemiparetic patients and healthy controls performing an arm activity. The proposed research is innovative conceptually in its elaboration and addition to the model of interhemispheric interactions during movement and after stroke. The results of this research may significantly contribute to our understanding of the interaction between the two arms. The impact of this proposal is that it will allow us to design interventions that target specific neurophysiological impairments at specific time-points during movement to enhance rehabilitation after stroke. This research proposal addresses the NIH missions to reduce the burden of neurological disorders and enhance the quality of life of people with disabilities. This proposal also addresses the goals of the NIH BRAIN initiative to develop a dynamic picture of the human brain describing how neural circuits interact in time and space.

**Multimodal Rehabilitation and High Protein Supplementation to Minimize ICU-Associated Sarcopenia in the Elderly**
Avelino Verceles, MD, Assistant Professor, (410) 328-8141 (Andrew Goldberg, M.D. and Michael Terrin, M.D., Mentors)
Patients suffering from critical illness often require mechanical ventilation (MV), extended bed rest, medications and other therapies in the intensive care unit (ICU) that precipitate sarcopenia. Older patients admitted to ICUs are at greater risk for developing ICU related sarcopenia due to chronic preexisting comorbidities, lower premorbid skeletal muscle mass and baseline physical deconditioning. Our work with
older, ICU survivors suggested that addressing the physical rehabilitation needs after ICU discharge is too late to prevent sarcopenia, malnutrition, and associated functional disability. This study will test the hypothesis that a multimodal mobility-focused physical rehabilitation (MPR) program based on mobility and strength training, neuromuscular electrical stimulation (NMES), and high protein-calorie nutritional supplementation (PRO-NS) to promote protein synthesis will prevent sarcopenia, metabolic dysfunction, and mobility disability in older, ICU patients with ventilator dependent respiratory failure. This hypothesis will be tested in a randomized trial that assesses 1) the efficacy of a protocol that combines MPR, NMES, and PRO NS in preventing sarcopenia and mobility dysfunction in older ICU patients with ventilator dependent respiratory failure, and 2) determines the clinical impact of changes in muscle mass, strength and functionality on recovery, using weaning from MV and hospital discharge as the criteria of therapeutic success. Primary outcomes in aim #1 are SPPB, muscle strength and mass and, in aim #2, time to weaning and discharge disposition. We anticipate this rehabilitation intervention will prevent loss of muscle and function in older, ICU patients with ventilator dependent respiratory failure. This will speed patient recovery and improve clinical outcomes assessed as successful weaning from mechanical ventilation and time to hospital discharge. Physical functionality/disability will be assessed 4 weeks after discharge using the Pepper Assessment tool for Disability.
III. CAREER DEVELOPMENT

UM-OAIC Career Development Awardees and Subsequent Funding

Richard Macko, M.D., Professor, Neurology, Medicine/Gerontology, Physical Therapy and Rehabilitation Science University of Maryland School of Medicine & Baltimore VA Medical Center; Director, Academic Rehabilitation Program, UM-SOM, & the Maryland Exercise & Robotics Center of Excellence (MERCE)

- R29 AG014487: Effects of Exercise on Patients with Hemiparetic Stroke
- RCDA Award: Physiological and Functional Effects of Task-Oriented Aerobic Exercise in Older Patients with Hemiparetic Stroke
- VA Research Enhancement Award Program (REAP): Clinical and Translational Research in Stroke – Disability Reduction and Disease Prevention: Stroke Disability Reduction and Disease Prevention
- VA RR&D - VA Center of Excellence: Task-Oriented Exercise and Robotics in Neurological Disease
- Michael J. Fox DOPA 2006RFA: Treadmill Training and Gait Related Disability in Parkinson’s Disease
- VA RRDC- Cardiovascular Parameters for Loomed Training in Chronic Incomplete Spinal Cord Injury
- VA RR&D/ VA Center of Excellence: Community Infrastructure for Adaptive Physical Activity Research
- R01 HD068712: Early Exercise to Improve Muscle and Cardiometabolic Health after Stroke (Co-PI Forrester)
- VA Office of Rural Health: eMOVE: Exercise + MOVE for Chronic Disease Management of Rural Veterans
- VA Office of Rural Health: Interactive Video Exercise Tele-rehabilitation (IVET)

Larry Forrester, Ph.D., Associate Professor, Department of Physical Therapy and Rehabilitation Science, University of Maryland Baltimore

- VA RR&D Merit Pilot Project: Adaptive Ankle Robot Control System to Reduce Foot-Drop in Chronic Stroke (Co-PI Macko)
- VA RR&D Merit Pilot Project: Developing a Brain Machine Interface for Ankle Robot
- P60 AG12583: Short-Term Effects of Treadmill Exercise on Corticoid-Spinal Excitability of the Lower Extremity in Chronic Hemiparetic Stroke Patients (Pilot Study)
- VA Advanced Career Development Award: Development of Ankle Robot Module with Treadmill Training in Chronic Stroke
- P60 AG12583: Impedance-Controlled Ankle Robotics: A Novel Technology for Gait Rehabilitation after Stroke (Pilot Study)
- VA RR&D Plasticity Center of Excellence: Adaptations in Cortical Function Induced by Short-Term Robot-Assisted Training of Foot Movements in Chronic Stroke Survivors (Pilot Study)
- P30 AG028747: Robot-Assisted Training of Ankle Movements in Sub acute Stroke Survivors (Pilot Study)
- University of MD College Park Seed Grant: Non-Invasive Real-Time Neural Decoding of Walking From EEG Activity
- VA RR&D Center of Excellence: Task-Oriented Exercise and Robotics in Neurological Disease

Marianne Shaughnessy, Ph.D., CRNP, Program Analyst, Office of Geriatrics Programs, Veterans Health Administration

- Maryland Statewide Health Network Grant through the Maryland Cigarette Restitution Fund Program Exercise and Diet Programs to Improve Cardiovascular Health in a West Baltimore Faith Community
- VA RR&D: VA Center of Excellence Pilot: Task-Oriented and Robotics in Neurological Diseases (PI Macko)
- VA Merit: Strength Training for Skeletal Muscle Adaptation after Stroke (Co-PI Ivey)
- VHA: Delirium Toolbox Dissemination

Denise Orwig, Ph.D., Associate Professor, Department of Epidemiology and Preventive Medicine, University of Maryland Baltimore
- R01 AG028556: Biological Pathways of Acute and Chronic Stress in Aged Hip Fracture Caregivers (PI Fredman)
- R01 AG029315: Epidemiology of Bone Strength and Muscle Composition After Hip Fracture in Men (PI Magaziner)
- R37 AG009901: Effects of Multi-Modal Exercise Intervention Post Hip Fracture (PI Magaziner)
- U01 HL073958: Functional Outcomes in CV Patients Undergoing Surgical Hip Repair (FOCUS) (PI Carson)
- Multinational, multicenter, double-blind, randomized, placebo-controlled, parallel group study assessing the efficacy of intravenous zoledronic acid in preventing subsequent osteoporotic fractures after a hip fracture “HORIZON-RFT” (PI Lyles and Magaziner)
- R37 AG009901: Sequelae of Hip Fracture in Men: An Epidemiologic Study (PI Magaziner)

Frederick Ivey, Ph.D., Associate Professor, Department of Medicine, University of Maryland Baltimore
- K01 AG091242: Effects of Exercise on Endothelial Function in Chronic Hemiparetic Stroke Patients
- VA Career Development Award 2: Effects of Exercise on Endothelial Function in Stroke Patients
- VA Merit: Strength Training for Skeletal Muscle Adaptation after Stroke
- VA Merit: Veterans with Stroke Translating Exercise Programs (Co-PI Shaughnessy)

Jacob Blumenthal, M.D., Assistant Professor, Department of Medicine, University of Maryland Baltimore
- VA-Advanced Research Career Development Award: Cytokines, Central Obesity and Fat Metabolism in Aging
- VA Merit: Using MOVE! With Seriously Mentally Ill (PI Goldberg)
- VA Merit Review: Exercise, Inflammation and Prothrombotic Modulators in the Elderly (PI Ryan)
- VHA- Patient-Centric Alternatives to Institutional Extended Care Project: Decreasing Barriers to Care for Veterans with Dementia
- VHA: Preventing Institutionalization and Supporting Caregivers through Expanded Services (PISCES)

Eun-Shim Nahm, Ph.D., RN, FAAN, Professor, Department of Organizational Systems and Adult Health, Program Director Nursing Informatics, School of Nursing, University of Maryland Baltimore
- R01 NR011296: Dissemination of a Theory-Based Bone Health Program in Online Communities
- R21 AG026013: Effects of a Hip Fracture Prevention Website for Seniors
- R21 AG029578: Feasibility of a Theory-Based Online Hip Fracture Resource Center for Caregivers

Kris Ann Oursler, M.D., Associate Professor, School of Medicine and Research Institute, Virginia Tech/ Salem VA Medical Center
- K23 AG024896: Aging and Physical Functioning in HIV (PI Oursler)
- R01: Assessment of Cardiac Tests in Vacs Exercise Study (PI: Freidberg)
- VA Merit: Effect of Exercise Training on Inflammation and Function in HIV Infected Veterans

Sandra McCombe-Waller, PT, Ph.D., MS, NCS, Associate Professor, Department of Physical Therapy and Rehabilitation Sciences, University of Maryland Baltimore
• P60 AG12583: Does Side of Stroke Affect Central Motor Control Mechanisms in Response to Short-Term Unilateral Versus Bilateral Training? (Pilot Study)
• R21 HD052125: Combining Bilateral and Distal Arm Training to Promote Arm and Hand Recovery in Patients with Chronic Hemiparesis

Kathleen Michael, Ph.D., RN, CRRN, Associate Professor, Interim Department Chair, Department of Organizational Systems and Adult Health, School of Nursing, University of Maryland Baltimore
• P60 AG12583: Task Oriented Exercise and Behavioral Interventions to Promote Activity in Stroke (Pilot Study)

Afshin Parsa, M.D., M.P.H., Associate Professor, Department of Medicine, University of Maryland Baltimore
• P60 AG12583: Endothelial Function and Cognitive Dysfunction in Chronic Kidney Disease (Pilot Study)
• R01 DK090401: Exercise Training and Cognitive and Physical Function in CKD (PI Seliger)
• U01 DK060990: A Genome-Wide Association of Renal Progression in the CRIC Study (PI Feldman)

Stephen Seliger, M.D., M.S., Associate Professor, Department of Medicine, University of Maryland Baltimore
• R01 DK090401: Exercise Training and Cognitive and Physical Function in CKD
• R01 AG034161: Race, Socioeconomic Status and the Brain: HANDLS Scan Substudy (PI Waldstein)
• VA Cooperative Studies Program: NEPHRON-D study
• VA Merit: Neurocognition and Functional Performance in Older Veterans with CKD

Steven Prior, Ph.D., Assistant Professor, Department of Medicine, University of Maryland Baltimore
• K23 AG040775: Effects of aerobic exercise on EPCs and vasculature dysfunction in Aging and T2DM
• R21 HL098810: Translational Studies of a Novel Cardiovascular Disease Risk Factor: Endothelial Progenitor Cells (Co-Inv, PI Hagberg UMCP)
• P30 AG028747: Aerobic Exercise to Improve Regulation of EPCs and the Vasculature in T2DM (Pilot Study)
• VA Merit: Exercise Training, CACs and Vascular Function in Older Veterans with IGT
• VA Career Development Award 2: Aging, Angiogenesis and Metabolic Responses to Aerobic Exercise
• P60 AG12583: Effects of Aerobic Exercise Training on VEGF, Angiogenesis and Glucose Metabolism in Older Adults (Pilot Study)

Monica Serra, Ph.D., Assistant Professor, Department of Medicine, University of Maryland Baltimore
• P30 AG028747: Resistance Training and Protein Supplementation to Improve Muscle Physiology and Reduce Fatigue in Breast Cancer Survivors (Pilot Study)
• P30 AG028747: Pilot Trial of Aerobic and Resistance Exercise Training for the Primary Prevention of Musculoskeletal Side Effects from Aromatase Inhibitors in Postmenopausal Breast Cancer Survivors (Pilot Study)
• VA Career Development Award 2: Aerobic Training to Improve Energy Utilization and Antioxidant Capacity in Stroke

Avelino Verceles, M.D., Assistant Professor, Department of Medicine, University of Maryland Baltimore
• R03 GEMSSTAR: The Multimodal Rehabilitation of Older Ventilated Survivors of Critical Illness
- P30 AG028747: The Multimodal Rehabilitation of Older Ventilated Survivors of Critical Illness (Pilot Study)
- P30 AG028747: Development of a Rehabilitation Strengthening and Mobility Program for Ventilator Dependent Older Patients (Pilot Study)

**Douglas Savin, Ph.D., M.P.T., Assistant Professor, Department of Physical Therapy and Rehabilitation Science, University of Maryland Baltimore**
- P30 AG028747: Comparison of Reactive Step Training and Voluntary Task-Oriented Training to Induce Neuromotor Changes for Improving Balance and Preventing Falls (Pilot Study)

**Michael Dimyan, M.D., Assistant Professor, Department of Neurology, University of Maryland Baltimore**
- University of Maryland Baltimore County Seed Grant: Baseline Brain MR Imaging to Predict Response to Robotic Rehabilitation after Stroke (co-PI; co-PI M. Stuart)
- K23 NS088107: Modulation of Interhemispheric Interactions and Arm Activity after Stroke
- P30 AG028747: Modulation on Interhemispheric Interactions and Arm Activity after Stroke (Pilot Study)
IV. PUBLICATIONS

2014-2015


Hess AS, Kleinberg M, Sorkin JD, Netzer G, Johnson JK, Shardell M, Thom KA, Harris AD, Roghmann MC. Prior colonization is associated with increased risk of antibiotic-resistant Gram-negative bacteremia in cancer...


RC1


RC3


RC3


V. EXTERNAL ADVISORY BOARD MEMBERS

**Karen Bandeen-Roche, PhD**
Professor
Department of Biostatistics
Johns Hopkins Bloomberg School of Public Health
4 years of service

**Rebecca (Becky) Craik, PT, PhD, FAPTA**
Professor and Chair, Physical Therapy
Department of Physical Therapy
Arcadia University
13 years of service

**Thomas M. Gill, MD**
Professor of Medicine, Epidemiology & Public Health
Yale University School of Medicine
9 years of service

**Bret Goodpaster, PhD**
Senior Investigator
Translational Research Institute for Metabolism and Diabetes
Florida Hospital, Burnham Medical Research Institute
4 years of service

**Alan M. Jette, PT, PhD**
Director, Health & Disability Research Institute
School of Public Health
Boston University Medical Campus
9 years of service

**Stephen Kritchevsky, PhD**
R. Sean Morrison, MD
Director, National Palliative Care Research Center
Brookdale Department of Geriatrics & Adult Development
Mount Sinai School of Medicine
4 years of service

Mark Redfern, PhD
Co-Director, Medical Virtual Reality Center
Department of Otolaryngology
University of Pittsburgh
4 years of service
UM-OAIC Minority Research
2014-2015

Ongoing Initiatives
Minority Trainees:
Anindo Roy, Ph.D., Assistant Professor, School of Medicine, Department of Physical Therapy and Rehabilitation Sciences, University of Maryland Baltimore
Dr. Roy continues to conduct research in rehabilitation robotics, focusing on the development of novel applications for MIT’s newest Ankle Robot with Dr. Forrester in Pepper Center Core 3. He collaborates with Claude D. Pepper OAIC studies performing much of the on-site robot tests with Drs. Forrester, Macko and Wittenberg.

Derik Davis, M.D., Assistant Professor, School of Medicine, Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland Baltimore
Dr. Davis’ current research career is focused in musculoskeletal radiology examining the effects of increased visceral adipose tissue (VAT) and reduced skeletal muscle (SMM) on cardiovascular disease (CVD), diabetes and functional outcomes in older adults. He collaborates with Claude D. Pepper OAIC studies performing radiology imaging and reading with Dr. Alice Ryan.

Diversity/Minority Supplements:
P.I. Jay Magaziner, Ph.D., M.S.Hyg.
Project Title: Effects of Multi-Modal Exercise Intervention Post Hip Fracture- Grant # 3R01AG009901-17S1

• The primary objective of the diversity supplement is to provide Rasheeda Johnson with a series of learning experiences to enhance her capabilities to perform as an independent investigator. Ms. Johnson will contribute intellectually to research on ambulatory ability after hip fracture by identifying issues of biomedical and clinical significance to aging research and through her own mentored project where she will investigate an important and understudied aspect of functional performance and mobility in older adults. During this project period, Ms. Johnson will investigate whether leg length discrepancy (LLD), a common complication following hip fracture surgery, is a possible mechanism that negatively impacts various health outcomes such as functional performance, hip and/or back pain, gait parameters and quality of life. This has tremendous potential for identifying a modifiable mechanism to improve ambulation and functional recovery after hip fracture that has not been previously studied.

P.I. Mark W. Rogers, Ph.D., P.T.
Project Title: Intervention to Enhance Lateral Balance Function and Prevent Falls in Aging- R01AG033607-02

• The research training plan proposed as part of the diversity supplement will provide Ozell Sanders with structured activities aimed at acquiring new research skills, opportunities for interdisciplinary collaborations, and completion of relevant coursework. Thus the aims outlined for Ozell Sanders are:
  1) Join the parent grant project by participating as a member of the testing team of the ongoing randomized clinical trials
  2) Advance a new set of research questions that will be integrally linked with the ongoing research of the parent grant
  3) Build knowledge and skills in neurophysiological probes of aging changes in the central nervous system function in relation to balance and movement control
  4) Seek independent funding through submission of Kirschstein NRSA application by tear three of supplement.
Within the first year on the funding Mark Rogers, along with the Dr. Robert Creath and Dr. Douglas Savin have assisted Ozell Sanders in carrying the proposed diversity supplement research project “Characterizing postural response to sudden freefall in standing humans”. Data collected in young healthy participants were submitted for a poster presentation at the Society for Neuroscience 2013 Annual Meeting. Project participation is still ongoing and completion of the project will help foster a new set of questions that will comprise Ozell Sanders dissertation topic.
UM-OAIC Recognition and Awards
2014-2015

• Richard Macko, M.D. along with Anindo Roy, Ph.D. and Larry Forrester, Ph.D. received the 2015 Abell award at the Johns Hopkins University Technology Ventures and University of Maryland Annual Innovation Showcase in April 2015.

• Richard Macko, M.D. was named by the G.F. Strong Rehabilitation Center as the 2015 Visiting Professor of the Year and as an official judge for graduate and faculty research presentations.

• Barbara Resnick Ph.D., RN, CRNP, FAAN, FAANP will serve as president-elect in 2015-2016 of the Gerontological Society of America.

• Alice Ryan, Ph.D. received a VA Senior Research Career Scientist Award.

• George Wittenberg, M.D., Ph.D. became president of the American Society of Neurorehabilitation for a 2-year term.
University of Michigan
Claude D. Pepper Older Americans Independence Center

Jeffrey B. Halter, M.D.  734-764-3493  734-936-2116  jhalter@umich.edu
Director, UM Geriatrics Center
Program Director, OAIC

Raymond Yung, M.D.  734-647-9746  734-936-2116  ryung@umich.edu
Co-Director, UM Geriatrics Center
Co-Program Director, OAIC

Stephanie Gatica, B.A.  734-763-1118  734-936-2116  sgatica@umich.edu
Associate Director for Administration and Program Development, UM Geriatrics Center

Mailing address:
University of Michigan
Geriatrics Center
300 N. Ingalls St. 9th floor
Ann Arbor, Michigan 48109-2007

SECTION I. CENTER DESCRIPTION
Funded by the NIA as the nation's first Geriatric Research and Training Center in 1989, the University of Michigan (UM) Pepper Center has evolved to meet the objectives of the OAIC program with successful competing renewals as an OAIC in 1994, 1999, 2004, 2009 and 2015. Thus, our Center is completing its 26th consecutive year of operation in 2015. The overall goal of the UM Pepper Center is to enhance the ability of older people to live independently by maintaining activities of daily living (ADLs) and to function well by maintaining mobility and levels of physical activity. Impairments of these factors predict poor health outcomes, poor quality of life, and mortality. Drawing on the large base of research currently underway in the fields of geriatrics and gerontology at UM, the UM Pepper Center fosters collaborative multidisciplinary research to integrate basic science, clinical science, and health services research relevant to the health care problems of older adults. The UM Pepper Center grant supports important research activities of the UM Geriatrics Center. Founded in 1987, the Geriatrics Center is the umbrella organization for geriatrics research, education, and patient care at the University of Michigan.

The specific goals of the UM Pepper Center are:
1) To support research that will improve understanding of how metabolic factors and inflammation interact with age-related diseases and comorbidities to determine key health outcomes related to mobility and functional status.

2) To support translational research on the interaction of metabolic factors and inflammation with age-related diseases and comorbidities to improve health outcomes related to mobility and functional status. To achieve this aim, the UM Pepper Center will work closely with other UM
programs including the NIH funded Michigan Institute for Clinical and Health Research (MICHR), the home of the UM’s Clinical and Translational Science Award (CTSA).

3) To provide Resource Cores that support and assist investigator-initiated projects related to the UM Pepper Center’s research focus.

4) Through its Research Career Development Core (RCDC), to strengthen the UM environment for training of future academic leaders in geriatrics and aging who can conduct research related to the UM Pepper Center’s research focus.

5) Through its Pilot and Exploratory Studies Core (PESC), to attract UM junior faculty, as well as selected senior faculty not previously involved in aging research, to develop new research projects related to the UM Pepper Center’s research focus.

Faculty from the following UM Schools and Institutes are involved: the Institute of Gerontology, School of Public Health, Institute for Social Research, Medical School, College of Engineering, School of Nursing, School of Social Work, and College of Literature, Science, and the Arts. As of April 2014 there were 100 active NIA grants at the UM (29 of which are subawards for collaborative studies) with over $32 million/year of direct costs. The UM OAIC’s faculty participant data base includes a total of 239 current UM faculty who have 221 current external grants relevant to the UM Pepper Center’s focus totaling over $57 million/year direct costs.

SECTION II. RESEARCH, RESOURCES AND ACTIVITIES

A. CORES

1. BIOMECHANICS CORE

James Ashton-Miller, Ph.D., Core Leader 734-763-2320 jaam@umich.edu
Neil B. Alexander, M.D., Core Co-Leader 734-736-3172 nalexand@umich.edu

The Biomechanics Core, (BC) enables its personnel to devote time to assist and train investigators in the conduct of new and expanded research on how metabolic disease and inflammation interact with age-related disease to determine key health outcomes related to mobility and functional status, the biomechanics of aging, and to the training of geriatric physicians and other clinicians in the biomechanics relevant to impaired mobility, falls and fall-related injuries, urinary incontinence and prolapse in the elderly. They also enable substantial use by Core-supported investigators of the equipment and facilities that exist in the Biomechanics Research Laboratory of the Department of Mechanical Engineering, as well as facilities in the Mobility Research Laboratory at the Geriatrics Center.

2. METHODOLOGY, DATA MANAGEMENT AND ANALYSIS CORE

Andrzej T. Galecki, M.D., Ph.D., Core Leader 734-936-2138 agalecki@umich.edu

The primary goal of MDMAC is to provide methodological, data management, and analytical support to OAIC affiliated investigators, that address the focus of the OAIC - inflammation, metabolism, predictors and interventions for function of elderly people - as well as aging
research in general. In collaboration with other OAIC Cores MDMAC will improve the quality of OAIC research studies, help foster development of junior researchers, will nurture forming interdisciplinary research groups, and ultimately enhance quality of research on late-life processes. MDMAC faculty will address the following four aims: 1. Advise and assist OAIC investigators in methodological design, data management, and analytical tasks in conducting projects; 2. Training and mentoring for OAIC investigators; 3. Facilitate the access of OAIC investigators to (large) archived survey and administrative secondary data sets describing elderly persons; 4. Undertake a limited number of internal efforts/projects to identify in existing literature or develop novel methodological approaches, and implement and disseminate them as software tools.

3. CORE FACILITY FOR AGED RODENTS

Richard Miller, M.D., Ph.D., Core Leader 734-936-2122 millerr@umich.edu

CFAR, the Core Facility for Aged Rodents, has been a major feature of the University of Michigan Claude Pepper Center since its inception in 1989. CFAR will continue to serve the needs of Pepper Center investigators through four Specific Aims. Aim 1: We will continue work initiated in the previous five years on four varieties of mice: (a) Mice lacking PAPP-A, a protease that controls IGF-1 availability; (b) Mice overexpressing Syntaxin-4, a modulator of insulin sensitivity; (c) Mice in which p16-positive (senescent) cells can be pharmacologically deleted at adult ages; and (d) Mice treated by linagliptin, a modulator of post-prandial glucose spikes. Aim 2: We will develop new mouse models based on amino acid restriction, which follows our previous demonstration of slow aging and delayed disease in mice given limiting amounts of dietary methionine. Aim 3: We will explore the role of juvenile, adult, and liver-specific growth hormone responses to four drugs that extend mouse lifespan, specifically the TOR inhibitor rapamycin, the diabetic drug acarbose, the non-feminizing steroid 17--estradiol, and the anti-inflammatory agent NDGA. Aim 4: We will select one or two new mouse models per year, through collaboration with UM scientists, pilot project awardees, and colleagues at other research universities, for initial discovery research on questions related to the biology of aging, emphasizing interventions that alter metabolism and inflammation in ways that postpone late life illnesses and disabilities.

4. HUMAN SUBJECTS AND ASSESSMENT CORE

Raymond Yung, M.D., Core Leader 734-647-9746 ryung@umich.edu
Kenneth Langa, Ph.D., M.D., Core Co-Leader 734-615-8403 klanga@umich.edu
Linda Nyquist, Ph.D., Clinical Trials Coordin 734-936-6078 lnyquist@umich.edu

The University of Michigan Human Subjects and Assessment Core (HSAC) provides the infrastructure and resources critical to UM OAIC investigators performing clinical and translational research. The HSAC is closely aligned with the UM OAIC’s goal of integrating bench, clinical and outcome research with clinical practice. By working closely with the LAC, RCDC and the three other Resource Cores, the HSAC will assist OAIC-funded pilots and other externally funded projects (EPs) related the central research theme of the OAIC. Important priorities for the HSAC will be to support junior faculty new to aging research, the translation of basic research discoveries into human studies, and to support high impact clinical trials that have
the promise of reducing disability and improving physical/cognitive function in older adults. The specific aims of the HSAC are 1) to facilitate access to human subjects and related data sets by investigators implementing research related to the central OAIC theme, 2) to provide training and consultation to OAIC researchers on issues related to experimental design (pre- and post-award), recruitment/retention of human subjects, translation from animal into human studies, techniques to compare national databases, 3) to expand and promote research on racial, ethnic, and cultural influences affecting the predisposing factors, metabolic/inflammatory mediators, and functional and health outcomes in older adults. In the present cycle, the HSAC has leveraged substantial institutional resources to expand the HSAC Registry of human volunteer subjects, and to provide longitudinal physical and functional assessment in a cohort of subjects within the HSAC registry who are at heightened risk of developing physical and cognitive impairment.

5. RESEARCH CAREER DEVELOPMENT CORE (RCDC)

Neil B. Alexander, M.D., Core Leader 734-736-3172 nalexand@umich.edu

The overarching goal of the UM OAIC Research Career Development Core (RCDC/KL2) is to recruit, select, support, mentor, and train junior faculty to become independent investigators in aging-related research and academic leaders in geriatrics and gerontology within their respective disciplines. A key additional objective is to train the next generation of investigators about the UM OAIC focus of how metabolic factors and inflammation interact with age-related diseases and comorbidities to determine key health outcomes related to mobility and functional status. A substantial pool of UM junior faculty from a wide range of disciplines across the UM campus who are doing research relevant to the OAIC focus will be targeted to participate in the proposed RCDC training activities.

6. PILOT and EXPLORATORY STUDIES CORE (PESC)

Lona Mody, M.D., Core Leader 734-763-4002 lonamody@umich.edu

The goal of the Pilot and Exploratory Studies Core (PESC) is to provide support for studies that will develop and test new research ideas of high relevance to the Center’s overall theme: improve understanding of how metabolic factors and inflammation interact with age-related diseases and comorbidities to determine key health outcomes related to mobility and functional status. The PESC will thus fund pilot research studies over a wide range of disciplines, from basic, pre-clinical, clinical patient-oriented research through behavioral and health services research. Each submitted proposal will first receive an evaluation for scientific merit by at least three external reviewers and then be further evaluated by OAIC leaders for relevance to the Center objectives. The PESC has made 121 pilot grants since its inception in 1989, mostly to junior faculty, many of whom have now established themselves as productive independent researchers in geriatric medicine and cognate disciplines.

7. LEADERSHIP/ADMINISTRATIVE CORE

Jeffrey Halter, M.D., Program Director 734-764-3493 jhalter@umich.edu
Raymond Yung, M.D., Co-Program Director 734-647-9746 ryung@umich.edu

A well-defined and effective Leadership Administrative Core (LAC) that supports the activities of the OAIC is already in place at the UM Geriatrics Center. The faculty and staff in the LAC
have proven leadership and administrative skills. The LAC fosters interactions among the OAIC Program Director and Co-Program Director (who also serve as UM Geriatrics Center Director and Co-Director), the OAIC Core Directors and the leadership structure of the Institution as a whole. These interactions will be fostered by the administrative structure, which requires these interactions on a regular and ongoing basis, and by key advisory committees: the UM Geriatrics Center’s Research Operating Committee (ROC) and the OAIC External Advisory Board. The ROC provides coordination and oversight for all OAIC activities and an important advisory function for the OAIC Program Director and Co-Program Director. The membership of the ROC includes the Core Directors of the OAIC, four additional UM senior scientists, and Geriatrics Center administrative leaders.

The overall goal of the LAC reflects that of the OAIC as a whole: to create, enhance and maintain an intellectual, technological, and administrative environment to maximize geriatrics research that will improve understanding of how metabolic factors and inflammation interact with age-related diseases and comorbidities to determine key health outcomes related to mobility and functional status. The LAC has four Specific Aims: 1. To encourage, stimulate and guide the development and review of OAIC goals and policies by: integrating, monitoring and evaluating the activities of the OAIC’s components; and assisting them in achieving the OAIC’s goals and objectives. 2. To manage and to develop resources to effectively achieve the OAIC’s goals and objectives. 3: To ensure communication and interaction among members of the University community who are engaged in research and training in health care problems of the elderly. 4. To attract and develop outstanding faculty and staff to participate in the research and training missions of the OAIC; and to provide leadership training to junior faculty who may become future program directors in geriatrics and aging-related programs.

B. PILOT-PROJECTS - YEAR 01 TO PRESENT

5 Year Cycle 1989-1990

Year 01

Biomechanics of rising from a chair in the elderly
Neil Alexander, M.D., Assistant Professor of Internal Medicine (Geriatrics)

Gene expression in aging muscle
Kate Barald, Ph.D., Associate Professor of Anatomy

The role of Interleukin-6 in aging
Suzanne Bradley, M.D., Assistant Professor of Internal Medicine (Geriatrics)

Effect of aging on repair of the kidney following ischemic injury
David H. Humes, M.D., Professor of Internal Medicine (Nephrology)

Studies on receptor-mediated Polyphosphoinositide turnover and intracellular calcium metabolism in fibroblasts from Alzheimer’s patients and healthy controls
Alan Mellow, M.D., Ph.D., Assistant Professor of Psychiatry

Wisdom in later adulthood: Psychological correlates
Lucinda Orwoll, Ph.D., Research Fellow, Institute of Gerontology
Protease Nexin 1: A model for trophic factor production in normal and pathologic aging
Dorrie Rosenblatt, M.D., Ph.D., Assistant Professor of Internal Medicine (Geriatrics)

Sympathetic function in elderly human hypertensives
Mark Supiano, M.D., Assistant Professor of Internal Medicine (Geriatrics)

Pilot for a survey of Arthritis and disability in daily life
Lois Verbrugge, Ph.D., Research Scientist, Institute of Gerontology

Year 02 1990-1991
HSV-mediated gene transfer studies of Amyloid and NGF
David Fink, M.D., Associate Professor of Neurology

Effect of aging on acute phase response
Matthew Kluger, Ph.D., Professor of Physiology

Hospital admissions from VA nursing homes
David Mehr, M.D., Instructor of Family Practice

Gene regulation in senescent cells
Bruce Troen, M.D., Assistant Professor of Internal Medicine (Geriatrics)

Functional properties of nerve-repaired vascular intact grafts in young, adult, and old rats
Edwin Wilkins, M.D., Instructor of Surgery

Year 03 1991-1992
The cross-age effect in transplanted nerve segments
Bruce Carlson, M.D., Ph.D., Professor of Anatomy and Cell Biology

Genetic investigation of Alzheimer and Creutzfeldt-jakob diseases
John Fink, M.D., Assistant Professor of Neurology

The effects of aging on vascular gene expression
Rory Marks, M.D., Assistant Professor of Internal Medicine (Rheumatology)

Role of charge-transfer interactions in age-related protein modifications
Joseph Schauerte, Ph.D., Research Investigator, Biological Chemistry

Effect of aging on calcium channel function in gastrointestinal neuromuscular preparations
John Wiley, M.D., Assistant Professor of Internal Medicine (Gastroenterology)

Year 04 1992-1993
Gene expression in the aging hepatocyte
Bahri M. Bilir, M.D., Lecturer, Internal Medicine (Gastroenterology)
Characterization of protein Tyrosine phosphates in yeast activation of the kinase cascade in mitogenic growth factor signal transduction
Kunliang Guan, Ph.D., Assistant Professor and Assistant Research Scientist, Biological Chemistry and Assistant Research Scientist, Institute of Gerontology

Aging and immunologic homeostasis: Regulation of Osteopontin production in T-lymphocytes
Laurie K. McCauley DDS, Assistant Professor of Periodontics/Prevention/Geriatrics, School of Dentistry

Myosin phenotype and altered contractile function in heart during aging
Joseph M. Metzger, Ph.D., Assistant Professor of Physiology

Trends in self-reported health and the prevalence of chronic conditions
Timothy A. Waidmann, Assistant Professor of Public Health Policy and Administration, School of Public Health

Assessing the quality of medical care in nursing homes using routinely collected information
Brent C. Williams, M.D., Instructor of Internal Medicine (Geriatrics)

Year 05 1993-1994
The impact of chronic diseases on health outcomes
Caroline Blaum, M.D., Lecturer, Internal Medicine (Geriatrics)

Stability of gene repression during mammalian aging
David Burke, M.D., Assistant Professor of Human Genetics

Characterization of protein Tyrosine phosphates in yeast activation of the kinase cascade in mytogen mitogenic growth factor signal
Kunliang Guan, Ph.D., Assistant Professor and Assistant Research Scientist, Biological Chemistry and Assistant Research Scientist, Institute of Gerontology

Transcriptional regulation in T cells from mice of different ages
David Markovitz, M.D., Assistant Professor of Internal Medicine (Infectious Diseases)

Expression of the extracellular matrix protein Thrombospondin in the aging
Sue K. O'Shea, Ph.D., Assistant Professor, Anatomy and Cell Biology

Age-dependent changes in adhesion molecule expression and function on T lymphocytes
Yoji Shimizu, Ph.D., Assistant Professor, Microbiology and Immunology

5 year Cycle 1994-1995
Year 06
Effects of nerve growth factor on age-associated changes of neuronal calcium signaling
Karen Hall, M.D., Ph.D., Research Investigator, Internal Medicine (Gastroenterology)

T cell mediated host defenses in the lungs of aged mice
Gary B. Huffnagle, Ph.D., Research Investigator, Internal Medicine (Pulmonary)

Telomere sequence variations as a possible mechanism of programmed cellular senescence
Vladimir L. Makarov, Ph.D., Assistant Research Scientist, Biophysics Research Division

Breathlessness during maximal exercise in elderly humans
Fernando Martinez, M.D., Assistant Professor of Internal Medicine (Pulmonary)

Neurobehavioral studies of age-related changes in working memory
Patricia A. Reuter-Lorenz, Assistant Professor of Psychology

Year 07 1995-1996
The use of Mupirocin as a model for the prevention of Staphylococcal infection and emergence of antibiotic resistance in elderly patients
Suzanne F. Bradley, M.D., Assistant Professor of Internal Medicine (Geriatrics)

New diagnostic measures of balance performance in elderly
Arthur D. Kuo, Ph.D., Assistant Professor of Mechanical Engineering and Applied Mechanics, Assistant Professor of Biomechanical Engineering, College of Engineering, Institute of Gerontology

Regulation of IL-4 production and its role in aging
Cheong-Hee Chang, Ph.D., Assistant Professor of Microbiology and Immunology

Year 08 1996-1997
The contribution of antagonistic interactions among T cell subsets
Igor Dozmorov, Ph.D., Assistant Research Scientist (Pathology)

Nursing home to nursing home transfers: The neglected transition
Richard A. Hirth, Ph.D., Assistant Professor of Health Management (SPH)

Vasomotor insulin resistance in NIDDM: Endothelial mechanisms
Robert Hogikyan, M.D., Assistant Professor of Internal Medicine (Geriatrics)

The effect of aging on cell mediated immunity in the lungs
Gary B. Huffnagle, Ph.D., Assistant Research Scientist of Internal Medicine (Pulmonary)

Relationship of age to the osteogenic potential of marrow stroma
Paul H. Krebsbach, Ph.D., Assistant Professor of Dentistry
NOS MRNA expression of the gastric myenteric plexus
Toku Takahashi. M.D., Ph.D., Assistant Research Scientist of Internal Medicine (Gastroenterology)

**Year 09 1997-1998**

Health care outcomes and utilization in older patients with coexisting dementia and depression
Helen Kales, M.D., Lecturer in Psychiatry

The effect of Acetyl-L-Carnitine on the quality and function of senescent skeletal muscle
Lisa Larkin Ph.D., Assistant Research Scientist, Internal Medicine (Geriatrics)

Corticosteroid receptors and the aging hippocampus
Maria Morano, Ph.D., Research Investigator, Mental Health Research Institute

Lymphocyte homing in age
Raymond Yung, M.D., Assistant Professor of Internal Medicine (Geriatrics)

**Year 10 1998-1999**

Genetic mapping of qualitative trait loci using four-way crosses
Andrzej Galecki, Assistant Research Scientist, Institute of Gerontology

Recipient age as a determinant of GVHD
James Ferrara, M.D., Director, Combined BMT Program

**5 Year Cycle**

**Year 11 1999-2000**

Effects of age and exercise training on skeletal muscle protein turnover
Donald Dengel, Ph.D., Assistant Research Scientist of Internal Medicine (Geriatrics)

Prospective evaluation of losartan in preventing age-dependent endothelial dysfunction (PREVAILED)
Sanjay Rajagopalan, M.D., Assistant Professor of Internal Medicine (Cardiology)

Leukotriene overproduction and aging
Thomas Brock, Ph.D., Assistant Research Scientist of Internal Medicine (Pulmonary)

**Year 12 2000-2001**

Age associated alterations in T cell activation revealed by gene expression analysis
Igor Dozmorov, Ph.D., Assistant Research Scientist (Pathology)

Effect of aldosterone receptor blockade on cardiovascular aging
Marvin Boluyt, Ph.D., Assistant Professor (Kinesiology)

Inter-relationships between diabetes and periodontal disease in aging veterans
George W. Taylor, DM.D., DrPh, Associate Professor, School of Dentistry

Year 13 2001-2002
Hospice utilization and end-of-life costs among end-stage renal disease patients
Richard Hirth, Ph.D., Associate Professor, Health Management & Policy, School of Public Health

Skeletal muscle gene expression profile in aging and exercise
Lisa Larkin, Ph.D., Assistant Research Scientist (Geriatrics)

Home training of elderly CHF patients
Peter Vaitkevicius, M.D., Assistant Professor (Geriatrics)

Relationship of stem cell numbers to aging of the immune system in UM HET-3 mice
Michael Clarke, M.D., Professor of Internal Medicine (Hematology/Oncology)

Year 14 2002-2003
Functional stratification of older adults with diabetes
Caroline Blaum, M.D., Assistant Professor, Internal Medicine (Geriatrics)

Cognitive demands while walking in older individuals with and without cognitive impairment
Carol Persad, Ph.D., Clinical Assistant Professor, Division of Neuropsychology

Year 15 2003-2004
Age-related declines in bimanual coordination: neural mechanisms and potential for compensation
Rachael Seidler, Ph.D., Assistant Professor, Division of Kinesiology and Department of Psychology

Oxidative stress in age-related hearing loss
Suhua Sha, M.D., Research Investigator, Kresge Hearing Research Center

Alcohol trajectories of older persons in Japan
Gilbert Gee, Ph.D., Assistant Professor, Department of Health Behavior and Health Education, School of Public Health

A tailored physical activity program for patients with congestive heart failure
Kimberler Gretebeck, Ph.D., Assistant Professor, School of Nursing

New 5 yr Cycle
Year 16-2004-2005
Insulin responses of muscle cells in vitro
Gregory D. Cartee, Ph.D., Professor of Kinesiology
Patterns and predictors of alcohol use trajectories among aging Americans
Gilbert C. Gee, Ph.D., Assistant Professor of Health Behavior and Health Education, School of Public Health

Mechanical consequences of genetically-influenced bone composition
McCreadie, Barbara, Ph.D., Research Investigator, Orthopaedic Research Labs

Factors moderating falls risk while turning among frail and healthy old adults
Carol Persad, Ph.D., Clinical Assistant Professor, Division of Neuropsychology

Year 17-2005-2006
Anal sphincter structure-function relationships in aging and fecal incontinence
Dee Fenner, Associate Professor of Obstetrics and Gynecology

Role of mineralocorticoid receptor in age-related deficits in hippocampal function
Audrey Seasholtz, Research Professor of Biological Chemistry

Influence of PKC isoform expression on myocyte contractile function during aging
Margaret Westfall, Assistant Professor of Surgery

Using electronic pharmacy fill and refill data to understand and promote appropriate medications use among elderly patients with hypertension
Michele Heisler, Assistant Professor of Internal Medicine

Perceptions of oral health adequacy and access in long-term care
Barbara Smith, Assistant Professor of Periodontics

Year 18-2006-2007
Age-dependent dendritic cell function: implication for cancer vaccine therapy
Annabelle Grolleau, Ph.D., Research Investigator, Division of Geriatric Medicine

Modulation of stress resistance and aging in mice
James Harper, Ph.D., Research Investigator, Pathology

Non-fatal suicidal behavior in home care elderly: The role of physical symptoms, functional disability, and cognitive impairment
Lydia Li, Ph.D., Associate Professor of Social Work, School of Social Work

Enhancing caregiver support for chronically ill older adults
John Piette, M.D., Associate Professor of Internal Medicine

Role of fatty acid transport in aging Drosophila heart
R.J. Wessells, Ph.D., Clinical Lecturer, Division of Geriatric Medicine

Lymphocyte apoptosis in elderly emergency patients
John Younger, M.D., Associate Professor of Emergency Medicine
Year 19-2007-2008
A tailored clinical intervention for older adults with leg OA
Susan Murphy, M.D., Assistant Professor, Physical Medicine and Rehabilitation

Use of a single underfoot perturbation to assess how age, peripheral neuropathy, and divided attention affect gait stability
Joseph Nnodim, M.D., Assistant Professor, Division of Geriatric Medicine

Molecular mechanisms of oxidative stress in frailty and diabetes
Subramaniam Pennathur, M.D., Assistant Professor of Nephrology

REM sleep modulation as a target for age-related learning and memory deficits
Gina Poe, M.D., Associate Professor of Anesthesiology

Year 20-2008-2009
Do depressive symptoms lead to disability and vice versa?
Xiao Xu, Ph.D., Research Investigator, Department of Obstetrics and Gynecology, Medical School

Utility of aerobic rat models for the study of frailty
Lauren Koch, Ph.D., Assistant Professor, Department of Physical Medicine and Rehabilitation, Medical School.

The relationships between brain white matter abnormalities, cognition and the biomechanics of (dual task) balance and gain in older adults
Martijn Mueller, Ph.D., Research Investigator, Department of Radiology Medical School

Molecular epidemiology of methicillin-resistant Saphylococci in nursing homes
Lona Mody, M.B.B.S., Assistant Professor, Department of Internal Medicine, Medical School.

Falls and urinary incontinence in the older adult population
Christine Cigolle, M.D. Clinical Lecturer, Department of Family Medicine, Medical School

The prevalence of cognitive decline in older adults with chronic heart failure
Tanya Gure, M.D., Clinical Lecturer, Department of Internal Medicine, Medical School

The effect of dietary fatty acids on the sarcopenia of aging
Angela Subauste, M.D., Lecturer, Department of Internal Medicine /MEND

The role of cognitive and affective variables in explaining increased risk of falls
Sara Wright, Ph.D. Clinical Lecturer, U-M Department of Psychiatry, Medical School

Randomized, placebo controlled study to evaluate the safety and efficacy of efalizumab
Bruce Richardson, M.D., Ph.D., Professor, Rheumatology, Department of Internal Medicine, Medical School

**Functioning after severe sepsis**
Theodore Iwashyna, M.D., Ph.D., Assistant Professor of Internal Medicine, Pulmonary & Critical Care, Medical School

**Year 21-2009-2010**
**Elucidation of the role of mitochondrial protein acetylation in calorie restriction in mammals**
David B. Lombard, M.D., Ph.D., Assistant Professor of Pathology, Medical School

A **theory-informed intervention to reduce hip fracture**
Lustig, Cindy A., Ph.D., Assistant Professor, Psychology

**The effect of COMT genotype on age-related declines in motor function**
Rachael Seidler, Ph.D., Associate Professor, Psychology and School of Kinesiology.

**Estimating health trajectories in old age: How much does selection bias matter?**
Wen Ye, Ph.D., Assistant Professor in the Department of Biostatistics, School of Public Health

**Year 22- 2010-2011**
**Protection of auditory function in late life by heat shock factor 1**
David Kohrman, Ph.D., Associate Professor Department of Human Genetics, Department of Otolaryngology/Head and Neck Surgery

**Racial differences in cognitive decline: The influence of stroke**
Deb Levine, M.D., M.P.H., Assistant Professor of Internal Medicine and Neurology

**Nitric oxide in aging and longevity**
Nancy Linford, Ph.D., Research Investigator of Molecular and Integrative Physiology

**Improvement of immune function in CD4 cell from old mice.**
Gonzalo Garcia, Ph.D., Research Investigator of Pathology

**P2X7 Receptors in the retinal pigment epithelium: Effect of aging.**
Dongli Yang, M.D., Ph.D., Research Investigator of Ophthalmology and Visual Sciences

**Hospitalists and the care of older adults**
Lena Chen, M.D., M.S., Clinical Lecturer of Internal Medicine

**Diabetes management in the oldest old adults**
Pearl Lee, M.D., Assistant Professor, Geriatrics

**Year 23- 2011-2012**
**MicroRNA-21 modulates fatty acid metabolism in renal aging**
Markus Bitzer, M.D., Assistant Professor, Internal Medicine - Nephrology

**Improving the repair and rehabilitation of rotator cuff tears in old rats by autologous satellite cell transplantation**
Christopher Mendias, Ph.D., Assistant Professor, Kinesiology

**Hippocampal response to oxidative stress in long-lived mutant mice**
Liou Sun, Ph.D., Research Investigator, Pathology

**Does age-related visual decline index GABA depletion?**
Daniel Weissman, Ph.D., Assistant Professor, Psychology

**C. difficile isolates, biomarkers, and gut microbiota in younger vs. older patients**
Seth Walk, Ph.D., Research Investigator, Internal Medicine – Infectious Diseases

**Year 24- 2012-2013**
**Do available measures of hospital quality predict long-term outcomes among older patients?**
Lauren Hersch Nicholas, Ph.D., Research Investigator, Survey Research Center, Institute for Social Research

**The role of myeloid-derived suppressor cells in immunosenescence**
Ryan Wilcox, M.D., Ph.D., Assistant Professor, Internal Medicine – Hematology/Oncology

**The role of Sestrin 2 and 3 against age and obesity associated metabolic derangements**
Jun Hee Lee, Ph.D., Assistant Professor, Molecular and Integrative Physiology and Institute of Gerontology

**Predictors of mortality among older patients with cirrhosis: Is MELD sufficient?**
Mina Rakoski, M.D., Clinical Lecturer, Internal Medicine - Gastroenterology

**Improving diabetes management among older adults by enhancing informal caregiver effectiveness**
Ann-Marie Rosland, M.D., M.S., Assistant Professor, Internal Medicine – General Medicine

**Influence of age on rectal mechanics in men with dysynergic defecation**
Richard J. Saad, M.D., M.S., Assistant Professor, Internal Medicine - Gastroenterology

**Vulnerable elderly surgical patient assessment (VESPA)**
Kathleen M. Diehl, M.D., Associate Professor, General Surgery

**Year 25- 2013-2014**
**Molecular markers for early detection of renal function decline in older adults**
Wenjun Ju, Ph.D., M.S., Research Assistant Professor, Internal Medicine – Nephrology
Clinical, microbiological, and biochemical predictors of severe Clostridium difficile infection in older adults
Krishna Rao, M.D., Clinical Lecturer, Internal Medicine – Infectious Diseases

Prevalence, patterns and problems associated with long-term venous access in skilled nursing facilities: A mixed-methods study
Vineet Chopra, M.D., M.Sc., Assistant Professor, Internal Medicine – General Medicine

Mechanisms of functional disability among older patients with Cirrhosis
Michael Volk, M.D., M.Sc., Assistant Professor, Internal Medicine – Gastroenterology and Hepatology

Aging is associated with an impaired regulatory T cell function
Sanjay Garg, Ph.D., Assistant Research Scientist, Internal Medicine – Geriatrics and Palliative Medicine

Hypothalamic regulation in crowded litter mice: Early life control of aging and longevity
Marianna Sadagurski, Ph.D., Assistant Research Scientist, Internal Medicine – Geriatrics and Palliative Medicine

Development of an injurious fall outcome measure in older individuals
Lillian Min, M.D., Assistant Professor, Internal Medicine – Geriatrics and Palliative Medicine

Year 26-2014-2015
Body-composition Phenotypes, Inflammation, and Functional Status in Older Adults
Anda Botoseneanu, Ph.D., M.D., Assistant Professor, Health Policy Studies

Assay of archived specimens from participants in the Michigan Study of Women’s Health Across the Nation (SWAN) for the anti-inflammatory biomarker interleukin-10 (IL-10)
Carrie Karvonen-Gutierrez, M.P.H., Ph.D., Assistant Research Scientist, Epidemiology

Microbial Concordance Between Urinary and Wound Cultures in Institutionalized Adults
Jennifer A. Meddings, M.D., M.Sc., Assistant Professor, Internal Medicine – General Medicine

Hypothalamic regulation in crowded litter mice: early life control of aging and longevity
Marianna Sadagurski, B.Sc., Ph.D., Assistant Research Scientist, Internal Medicine – Geriatrics and Palliative Medicine

The feasibility of a lifestyle intervention for older adults with diabetes
Pearl Lee, M.D., M.S., Assistant Professor, Internal Medicine – Geriatrics and Palliative Medicine

SECTION III. Career Development (Listing from 2004-2015). Current academic titles are provided. All at University of Michigan, unless noted otherwise.

Carol Persad, Ph.D., Associate Professor, Division of Neuropsychology (2003-2005)
Grants Awarded
NIH “Neurobiology of the Menopausal Transition” Persad, CC-Co Investigator. Period of Award 06/01/2006 to 03/31/2010

Rachael Seidler, Ph.D., Associate Professor, Division of Kinesiology and Department of Psychology (2003-2005)
Grants Awarded
NASA NBEI Award, UM Biomedical Engineering Department, 2003. Seidler, Co-Investigator Project 1 leader, “Neural and Neurovascular Changes in Simulated Microgravity”
NIH RO1 “Skill Acquisition in Older Adults” Seidler-PI, Period of Award 09/01/2005 to 07/31/2009
Gustavus and Louise Pfeiffer Foundation “Parkinson's Disease: Interactions Between Stage of Disease, Treatment, and Motor and Cognitive Performance” Seidler-PI. Period of Award 01/01/2008 to 12/31/2008
NIH “Cortex Changes in Real / Imagined Movement in ALS (Amyotrophic Lateral Sclerosis)” Welsh-PI. Period of Award 09/30/2007 to 05/31/2011. Role-Co-PI
Honors, awards, promotions:
Promoted to Associate Professor, 2009

Su-Hua Sha, M.D., Research Investigator, Kresge Hearing Research Center (2003)

Gilbert Gee, Ph.D., Associate Professor, Department of Health Behavior and Health Education, School of Public Health, University of California, Los Angeles (2003-2004)
Grants Awarded
Peter F. McManus Charitable Trust “Drinking Trajectories of Aging Women” Gee-PI, Period of Award 01/01/2003 to 12/31/2003

Gregory D. Cartee, Ph.D., Professor of Kinesiology (2004)
Grants Awarded
NIH “Aging, Calorie Restriction and Insulin Signaling” Cartee-PI, Period of Award 01/01/2004 to 04/30/2006.
NIH “Aging, Calorie Restriction and Insulin Signaling” Cartee-PI. Period of Award 07/01/2007 to 05/30/2012.
Honors, awards, promotions:
2005  Fellow, American Academy for Kinesiology and Physical Education (AAKPE)

Barbara McCreadie, Ph.D., Assistant Professor, Orthopedic Surgery (2004)
Grants Awarded
AFAR “Age-Related Response to Trabecular Bone Microdamage” McCreadie-PI, Period of Award 07/01/2004 to 06/30/2005.

Kimberlee Gretebeck, Ph.D., Assistant Professor, School of Nursing (2003-2005)
Grants Awarded
American Diabetes Association “A Tailored Behavioral Intervention to Promote Physical Activity Adoption and Maintenance for Older Adults with Type 2 Diabetes” Gretebeck-PI, Period of Award 01/01/2006 to 12/31/2006.
Michigan Center for Health Intervention (MICHIN) pilot grant (P30 NR009000), Gretebeck, K.A., PI. A Tailored Physical Activity Intervention to Improve Neuropathy and Mobility in Older Adults with Early Diabetes. 2006-2007.
John A. Hartford Foundation “The Influence of Environmental and Behavioral Determinants on Walking in Older Adults” Gretebeck-PI, Period of Award 07/01/2007 to 8/31/2009.

James Harper, Ph.D., Research Investigator, Pathology (2006-2008)
Grants Awarded

Allison Aiello, Ph.D., Associate Professor, Epidemiology, School of Public Health (2006-2008)
Grants Awarded
NIH “Reducing Transmission of Influenza by Face Masks” Monto-PI, Period of Award 09/30/2006 to 9/29/2008, Aiello, Co-PI.
5R01DA022720 “Ecologic Stressors, PTSD, and Drug Use in Detroit” Galea-PI, Period of Award 09/01/2007 to 8/31/2012, Aiello, Co-PI.
NIH “Neighborhood cultural isolation and biomarkers of cardiovascular disease among Latinos” A. Aiello-PI, Part of larger consortium grant P60 (PI: A. Diez-roux), Period of Award 09/01/07-08/31/12.
1R56DK087864“Life Course Socioeconomics, Acculturation, & Type-2 Diabetes Risk Among Latinos” A. Aiello-PI, 5/1/2010-4/30/2011
Annabelle Groleau-Julius, Ph.D., Research Investigator, Internal Medicine (Geriatrics), left University 2010 (2006)

Cindy Lustig, Ph.D., Associate Professor of Psychology, College of Literature, Science and the Arts (2006)

Grants Awarded
NSF “Acetylcholine, Cortex and Control” Lustig-PI, Period of Award 08/01/2007 to 02/28/2010

Honors, awards, promotions:
2009-10 Henry Russel Award

Allison Rosen, M.D., Ph.D., Associate Professor, University of Massachusetts Medical School, Department of Quantitative Health Sciences (2006)

Grants Awarded
Harvard University “Development of National Health Accounts” Rosen-PI, Period of Award 07/01/2006 to 06/30/2007
HHS-NBER “NBER Center for Aging and Health Research” Rosen-PI, Period of Award 09/01/2007 to 06/30/2008
John A. Hartford Foundation, Center of Excellence in Geriatrics.

Gonzalo Garcia Ph.D., Research Investigator, Department of Pathology

Grants Awarded

Pearl Lee M.D., Assistant Professor, Division of Geriatric Medicine, Department of Internal Medicine (2008-2010)

Grants Awarded
John A. Hartford Foundation, Center of Excellence in Geriatrics. 7/1/2010-6/30/2011.
NIA: AG024824, University of Michigan Older Americans Independence Center; Pilot/Exploratory Studies Core Diabetes Management and Physical Function of Older Adults Role: Pilot project PI 07/01/2009- 06/30/2010.

Angela Subauste M.D., Assistant Professor, Division of Endocrinology, Department of Internal Medicine (2008-2010)

Grants Awarded
John A. Hartford Foundation, Center of Excellence in Geriatrics, Pilot Grant. 7/1/2010-6/30/2011.
The University of Michigan OAIC, Pilot Grant “Modulation of Age Related Sarcopenia by Fatty Acids” Subauste, PI, Period of Award 9/1/2008-8/31/2009.
University of Michigan Metabolomics and Obesity Center, Pilot Grant, “Role of AGPAT in obesity induced insulin resistance” Subauste, PI, Period of Award 7/1/2007-6/30/2008.

Lan Yao Ph.D., RN, Assistant Professor, College of Nursing, Michigan State University (2008-2009)
Grants Awarded
Michigan Center for Health Intervention, Pilot Study Grant, “Effects of a positive emotion-charged Tai Chi home program on mobility, balance, and fall risks in elders with Alzheimer’s disease: a pilot controlled trial” Yao (Pilot PI), Period of Award 05/01/2007-04/30/2009.
American Academy of Nursing/John A. Hartford Foundation, Claire M. Fagin Postdoctoral Fellowship “Effects of a positive emotion-charged Tai Chi home training program on elders with Alzheimer’s Disease and their caregivers” Yao (Awardee), Period of Award 07/01/2006-12/31/2008.
University of Michigan Integrative Health Care Pilot Research Grant, “Feasibility of a positive emotion-charged Tai Chi home training program and its effects on patients with dementia and caregivers,” Yao (Pilot PI), Period of Award 12/01/2006-11/30/2008.

Sara Wright Ph.D., Assistant Professor, Department of Psychiatry (2008)
VA Career Development Award, Level One, “The Role of Psychological Factors in Predicting Fall Risk in Elders,” (Wright), 9/2008-9/2010, Principal Investigator
Jack L. Berman, M.D. and Barbara A. Berman, Ph.D. Depression Research Fund Award (Geriatric Depression), University of Michigan Department of Psychiatry Depression Center, “The Role of Cognitive and Affective Variables in Explaining Increased Risk of Falls among Patients with Geriatric Depression,” (Wright), 5/2008- 9/2010, Principal Investigator
Meader Research Fund for Depression/Genetics/Pain, University of Michigan Department of Psychiatry Depression Center, “Neurobiological Measures of Lifetime Depression Burden: Stability and Relationship with Treatment Status,” (Langenecker/Wright), 01/2008- 01/2011, Co-Principal Investigator
Michigan Alzheimer’s Disease Research Center Pilot Grant Fund, “Investigation of Neuroanatomical Networks to Understand Late Onset Depression,” (Langenecker/Wright), 6/2009-06/2011, Co-Principal Investigator
VA Career Development Award, Level Two, “Cognitive, Clinical, and Neural Markers of Late Life Depression,” (Wright), Principal Investigator, Intent to Award Letter Received.

Kara Zivin Ph.D., Assistant Professor, Department of Psychiatry, (2008)
Grants Awarded
VA CDA-1 examining the relationship between depression and older adult workforce participation

**Anjali Desai Ph.D., Project Manager, Trialynx Inc. (2008-2010)**

Grants Awarded
American Heart Association Scientist Development Grant, “Role of erythropoietin and iron therapy in the development of atherosclerosis in chronic renal disease,” Desai (PI), 1/1/03-12/31/05.
Renal Research Institute Grant “Role of Alpha-Tocopherol (Vitamin E) in reducing oxidative Stress, Endothelial Dysfunction and Advanced Glycosylation End Products in Chronic Renal Insufficiency: a Pilot Study” Saran, PI; Desai Co-Investigator, 9/1/01-3/30/06.

**Amir Sadghi-Akha M.D., Ph.D., Research Investigator, Department of Pathology** (2009)

**Tanya Gure M.D., Assistant Professor, Department of Internal Medicine (2009-2010)**

Grants Awarded
John A. Hartford Foundation, Center of Excellence in Geriatrics, Pilot Grant. 7/1/2010-6/30/2011.
MICHR KL2, “The prevalence of cognitive impairment among older adults with heart failure” 7/1/10-8/31/11

**Christine Cigolle M.D., Assistant Professor, Department of Family Medicine (2011)**

Grants Awarded
National Institute on Aging, K08 AG031837 Mentored Clinical Scientist Research Career Development Award (Cigolle PI) Geriatric Conditions and Disablement in the Older Adult Population 9/30/2010-9/29/2015
Hartford/AFAR National Centers of Excellence Career Development Award 7/1/2010-6/30/2012
Michigan Center on the Demography of Aging (MiCDA) 2010 Pilot Grant (Cigolle PI), Cognitive Impairment and Frailty in the Older Adult Population: Do the Outcomes Differ? 7/1/2010-6/30/2011
Department of Veteran Affairs Innovative Patient Alternatives to Institutional Extended Care Bridging the Gap: Care Management Targeting Veterans with Cognitive Impairment at Times of Transition (Cigolle PI) 10/1/2009-9/30/2011

**Daniel Leventhal, M.D./Ph.D., Clinical Lecturer, Neurology (2011-2012)**

Grants Awarded
Dystonia Medical Research Foundation (Leventhal PI), Optogenetic manipulation of striatal fast spiking interneurons in vivo, 4/15/2010-4/14/2012
Tourette Syndrome Association (Leventhal PI) In vivo striatal fast spiking interneuron suppression using optogenetic techniques 7/01/2010-6/30/2011

**Lillian Min, M.D., M.S.H.S, Assistant Professor, Department of Internal Medicine/Geriatrics (2011-2012)**

Grants Awarded
Hartford/AFAR National Centers of Excellence Career Development Award 7/1/2011-6/30/2013
Older American Independence Center (Halter PI) Research Career and Development Core (RCDC) Career Development Award (50% salary support x 1 year, renewable to 2 years), 9/1/2010-8/30/2012
R21 HS017621-01 (Min PI) $250,000/3 years, DHHS/Agency for Health Care Research and Quality Prioritizing care of complex elders using survival and functional status outcome, 9/1/2008-8/30/2012

Mark Palmer, M.D., Ph.D., Assistant Professor, Department of Movement Science, School of Kinesiology, Department of Biomedical Engineering, College of Engineering (2011-2012)

Seth Walk, Ph.D., Research Investigator, Internal Medicine (2012-2013)

Kathleen H. Sienko, Ph.D., Associate Professor, Department of Mechanical Engineering (2013)
Grants Awarded (relevant only)

Jun Hee Lee, Ph.D., Assistant Professor, Department of Molecular and Integrative Physiology (2013-2014)
Grants Awarded
American Liver Foundation/American Association for the Study of Liver Diseases, “Protective role of Sestrin2 against obesity-associated pathologies in liver” Liver Scholar Award (PI: Lee, Jun Hee) 07/01/2012-06/30/2015
Ellison Medical Foundation (AG-NS-0932-12), “Sestrins at the crossroads between nutrition, aging and metabolism” New Scholar Award in Aging (PI: Lee, Jun Hee) 08/01/2012-07/31/2016
ADA Basic Science Award (PI: Lee, Jun Hee) 01/01/2013-12/31/2015
American Diabetes Association (1-13-BS-106), “Maintenance of insulin signaling sensitivity by sestrin2-mediated feedback loop” ADA Basic Science Award (PI: Lee, Jun Hee) 01/01/2013-12/31/2015

Emily Joy Nicklett, Ph.D., M.S.W., Assistant Professor, School of Social Work (2013-2014)
Grants Awarded

Krishna Rao, M.D., Clinical Lecturer, Internal Medicine – Infectious Diseases (2014-2015)


SECTION IV. PUBLICATIONS: Provide only those that are a direct result of Pepper Center resources and list publications published in the 2014 funding year only (9/1/14 – 8/31/15).


improvement. *Infection Control and Hospital Epidemiology*, 2015;36(4):470-473. PMCID Pending.


Sadagurski M*, Landeryou T, Cady G, Bartke A, Bernal-Mizrachi E and Miller RA. Transient early food restriction leads to hypothalamic changes in the long-lived crowded litter (CL) mice. (Corresponding author) *Physiological Reports* 2015. Accepted


Skupien, J., Warram, J.H., Niewczas, M.A., Gohda, T., Malecki, M., Mychaleckyj, J.C., Galecki, A.T., Krolewski, A.S. (2014) Synergism between circulating tumor necrosis factor receptor 2 and HbA1c in determining renal decline during 5-18 years of follow-up in patients with type 1 diabetes and proteinuria Accepted for publication in *Diabetes Care, April 22, 2014*


Tallaksen-Greene SJ, Sadagurski M, Zeng L, Mauch R, Perkins M, Banduseela VC, Lieberman AP, Miller RA, Paulson HL, Albin RL. Differential effects of delayed aging on phenotype and


**SECTION V. EXTERNAL ADVISORY BOARD:** Members names, institutions and years of service.

We do not have a standing EAB. We invite different external reviewers each year, depending on the focus. External reviewers during the past year included James L. Kirkland, M.D., Ph.D., Professor and Consultant, Departments of Medicine and Physiology, and Director, Robert and Arlene Kogod Center on Aging, Mayo Clinic; Andrzej Bartke, Ph.D., Professor and Director of Geriatric Medicine, Departments of Internal Medicine and Physiology, and Distinguished Scholar, Southern Illinois University School of Medicine; Adam Antebi, Ph.D., Director, Max Planck Institute for Biology of Ageing, Cologne, Germany, and Associate Professor, Huffington Center on Aging and Dept. of Molecular and Cellular Biology, Baylor College of Medicine; Randal Kaufman, Ph.D., Director, Degenerative Disease Research, Center for Neuroscience, Aging, and Stem Cell Research, Sanford|Burnham Medical Research Institute; Dongsheng Cai, M.D., Ph.D., Professor, Department of Molecular Pharmacology, Albert Einstein College of Medicine.
Recognition and Awards: Prize or honors, NOT grant awards, should be a listing of all major scientific awards received by your center’s personnel in 2015.

Andrzej Galecki, director of the OAIC Methodology, Data Management and Analysis Core was made a Fellow of the American Statistical Association.

James Ashton-Miller, director of the OAIC Biomechanics Core received three honors: H.R. Lissner Medal, American Society of Mechanical Engineers “for outstanding research contributions in the biomechanics of injuries, particularly neuromuscular mechanisms of fall-related injuries in the elderly, and strain-induced birth-related injuries and their sequelae in women”; Chair-Elect, Health Science section, Gerontological Society of America; and the 2014 Cabaud Memorial Award, American Orthopedic Society for Sports Medicine.

A scientist mentored by the OAIC Pilot and Exploratory Studies Core, Carrie Karvonen-Guiterez was invited to be a presenter at the Arthritis Foundation Great Lakes Region Emerging Investigator Conference. She was also invited to be a Junior Faculty Participant at the OAIC National Meeting.

Ken Langa, a member of the OAIC Leadership and Administration Core, received three honors: 2014 Plenary Lecture, Alzheimer’s Association International Conference; 2014 Elected Member, American Society for Clinical Investigation (ASCI); 2015 Plenary Lecture, NIH Alzheimer’s Disease Research Summit.
Minority Research: List activities with minority trainees and research focusing on hypotheses dealing with minority health. Clinical research that has an expected number of minority subjects (a NIH requirement) is NOT what is desired for this section. Only work that has a comparison of minority members to majority members such as work on health disparities should be included.

The Human Subjects and Assessment Core has been instrumental in the success of the University of Michigan recruitment of minority participants for the NIA-sponsored ASPREE (Aspirin in Reducing Events in the Elderly) Study. This multicenter clinical trial of low-dose aspirin has a targeted enrollment of 70% minorities across the U.S. sites. The University of Michigan enrolled only non-Caucasians until March 2014 and has exceeded site-specific enrollment goals since joining the study in 2012. Currently 85% of enrollees at the UM site are non-Caucasian.

The Human Subjects and Assessment Core is supporting the doctoral research of Annie Harman, School of Public Health, through our linkages with Wayne State University Institute of Gerontology Research Participant Program. Based on this linkage, Ms. Harmon will oversample older African Americans in her study entitled “Expectations and Planning for Future Transportation-Related Mobility in Adults 55-84.”

Minority Trainee(s):

Joseph Nnodim MBBS, PhD, Assistant Professor, Department of Internal Medicine, is mentored by James Ashton-Miller (Core Leader, Biomechanics Core). Dr. Nnodim has been funded with a PESC pilot award.

The RCDC Retreat, 2015, included underrepresented junior faculty from Wayne State University School of Social Work, Tam E. Perry, who has received pilot funding from the Michigan Center for Urban African American Aging Research, Heidi Zapata, from Yale University Internal Medicine, and Ishtar Govia from the University of West Indies.

Trainees Focusing on Minority Health Issues.

Deborah Levine, M.D., Assistant Professor, Departments of Internal Medicine and Neurology, was funded with a PESC award and is mentored by Ken Langa (Co-Leader, Human Subjects and Assessment Core): Dr. Levine’s research interests are the epidemiology, prevention and care of stroke and cardiovascular disease with a focus on vascular risk factors, medication adherence, and health disparities.

Dr. Emily Nicklet, Assistant Professor, School of Social Work, was an RCDC awardee. Dr. Nicklett’s current research focuses on contextual predictors of diabetes management among native elders and is funded through the NIA’s Resource Center for Minority Aging Research Health and Aging Policy (RCMAR) Native Elder Research Center (NERC).

Research Articles:
Levine DA, Langa KM, Rogers MA. Acute infection contributes to racial disparities in stroke mortality. *Neurology* 2014;82(11):914-921. PMCID: PMC3963005


Section I. Description of Center

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

Our specific aims for the current cycle are to:

1. Promote multidisciplinary research into the causes, consequences and treatment of age-related changes in mobility and balance.

2. Building on the exceptional expertise of our research team, extend our successful work into two new high potential areas: a) the biologic and physiologic causes and clinical consequences of interactions between multiple body tissues (nerve, muscle, bone and fat) as they impact on aging, mobility and balance; and b)
community and health system uptake of interventions to enhance mobility and balance.

3. Train young investigators from multiple disciplines in an intellectually vibrant, collaborative environment.

4. Serve as a resource and partner to investigators, research programs, institutions, OAICs and the public.

The Program has 6 Cores:
- Leadership/Administration Core
- Pilot Exploratory Studies Core
- Research Career Development Core
- Clinical Populations Outcomes Core
- Integrative Systems Core
- Data Management, Analysis and Informatics Core

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

**Research strategies to achieve OAIC goals.** Our strategies to achieve these goals are:
1. Use Resource Cores to share expertise among projects and investigators.
2. Use pilot and developmental funds to extend existing studies and develop new studies.
3. Promote and reward collaborative multidisciplinary teams of investigators with complementary expertise by prioritizing them for funds and support
4. Encourage new partnerships with highly productive investigators and programs by offering to partner with our expertise and resources.
5. Reward development of new methods and techniques.
6. Facilitate the use of a common set of core measures of mobility, balance and falls in human studies so results can be merged or compared.
7. Leverage resources by collaborating with other Centers at Pitt, other OAICs, and Centers around the US.
8. Sponsor seminar series to promote general awareness of expertise and resources, review progress in ongoing projects and facilitate new collaborations.
9. Support the new OAIC KL2 career development program with salary funded Pepper Scholars in addition to resource support for Novice, Transition to Independence, and Visiting Scholars, with a focus on multidisciplinary teamwork, thematic knowledge, and specific skills.
10. Promote national discussion through programs at national meetings and other dissemination methods.
11. Provide administrative infrastructure, intellectual leadership, and oversight.
Section II. Research, Resources and Activities

A. Primary Cores

Leadership/Administration Core (LAC)
Core Leader: Susan L. Greenspan, MD, Professor of Medicine, 3471 Fifth Avenue, Suite 1110 Kaufman Bldg, Pittsburgh PA 15213, PH: 412-692-2477, Fax: 412-692-2486

Core Co-Leader: Anne Newman, MD, MPH, Professor and Chair, Department of Epidemiology, 130 DeSoto Street, Room A529 Crabtree Hall, Pittsburgh, PA 15261, PH: 412-383-1302, Fax: 412-624-3737

Administrator: Megan Miller, BS, CBDT, 3471 Fifth Avenue, Suite 1110 Kaufman Bldg, Pittsburgh PA 15213, PH: 412-692-2477, Fax: 412-692-2486

The Leadership Administration Core is responsible for the overall coordination, monitoring, compliance and reporting functions of the OAIC. It promotes internal coordination, institutional interactions and external relationships. It supports the External Advisory Committee and sponsors a seminar series, annual retreat, website, publications committee, visiting professor series, topical workgroups, grant planning retreats and national and local conferences.

Our specific aims are to:
1. Foster communication and multidisciplinary collaboration among OAIC investigators, cores and projects.
2. Promote increased attention and involvement in our work with relevant investigators and research programs in and outside the University of Pittsburgh.
3. Represent the OAIC to the University through an Institutional and Community Advisory Boards.
4. Represent the OAIC to other OAICs, the larger academic, NIH, clinical and lay communities.
5. Through the External Advisory Committee, maintain independent oversight of OAIC processes, resources and progress toward goals.
6. Through the External Advisory Committee and ad hoc reviewers, provide independent oversight to the pilot, developmental projects and Pepper Scholar programs.
7. Through the RCDC Advisory Committee provide oversight for the RCDC Scholars program.
8. Establish and operate a Safety Monitoring Board for all OAIC human studies.
9. Sponsor a Research Seminar series, an Annual Retreat, a Visiting Professor Series, Workgroups, publication/communication committee, formal grant reviews, and new partnership initiatives.
10. Increase basic and translational research partnerships.
11. Maintain meticulous financial records.
12. Provide administrative support and oversight for the RCDC, PESC and three research cores.
13. Promote quality and timeliness in all OAIC activities.
14. Collaborate outside the Institution for OAIC related themes.

**Pilot Exploratory Studies Core (PESC)**
Core Leader: Joseph Hanlon, PharmD, 3471 Fifth Avenue, Suite 500 Kaufman Bldg, Pittsburgh PA 15213, PH: 412-692-2364

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

The Specific Aims of the PESC are to:
1. Promote innovative multidisciplinary research on mobility, balance and aging
2. Encourage supplements to ongoing studies
3. Promote innovative techniques and methods for research on mobility, balance and aging
4. Partner with other UPITT groups [i.e., Clinical and Translational Science Institute (CTSI) and Aging Institute] that also offer pilot study awards to increase overall funding for individual pilot projects
5. Promote, evaluate, and select for funding Standard pilot projects, Small pilots, and Developmental projects
6. Conduct post-award processes (e.g., monitor adherence to ethics, safety, privacy, tracking of subsequent productivity and other related matters) for Standard, Small RCDC pilot projects, and Developmental projects

See section II. C. Description of Current Pilots

**Research Career Development Component (RCDC)**
Core Leader: Susan L. Greenspan, MD, Professor of Medicine, 3471 Fifth Avenue, Suite 1110 Kaufman Bldg, Pittsburgh PA 15213, PH: 412-692-2477, Fax: 412-692-2486

Core Co-Leader: Doris Rubio, PhD, Professor of Medicine, Biostatistics, Nursing and Clinical and Translational Science, 200 Meyran Avenue, Suite 200, Pittsburgh, PA 15213, PH: 412692-2023, Fax: 412-246-6954

The goal of the Research Career Development Component (RCDC) of the Pittsburgh Older Americans Independence Center (OAIC) is to create a new generation of investigators with expertise in age-related mobility and balance research. These investigators will have expertise in basic, translational, and clinical approaches and will lead and participate in collaborative multidisciplinary projects. To accomplish this goal, the RCDC uses a range of learning strategies for trainees. The program integrates training
in basic and clinical research, creates a structured but flexible rich learning environment and provides core competencies, self-assessment tools, availability of research project support and access to a talented and established source of funded senior investigators from multiple disciplines dedicated to mobility and balance research and mentoring.

Our specific aims are to:
1. Promote careers in mobility, balance, and aging research for Pepper Scholars (junior faculty who have achieved an initial level of expertise and productivity and have salary support from OAIC funds for 2-3 years).
2. Promote careers of Novice (mentees in the initial levels of training) and Transition to Independence investigators (those who have received independent career awards) whose salary sources are from outside the OAIC.
3. Provide structured career development through mentored multidisciplinary research experiences, research and career development seminars, retreats, and formal didactic programs for basic and clinical research skills through the Clinical and Translational Science Institute education programs.
4. Promote translational and cross-training between clinical and basic science.
5. Coordinate access to experienced mentors.
6. Provide feedback, career guidance, and support to trainees and mentors and advise trainees on their training and career development.
7. Oversee the promotion, recruitment, selection, monitoring, and evaluation of trainees and the program.
8. Provide financial support for trainees through stipends, pilot funds, and additional resources.
9. Manage RCDC resources.
10. Collaborate with other cores and units within and outside the institution for OAIC related themes.

B. Research Support Cores

**Clinical Populations Outcomes Core (CPOC)**
Core Leader: Steven Albert, PhD, Professor and Chair, Department of Behavioral and Community Health Sciences, 208 Parran Hall, 130 DeSoto St, Pittsburgh, PA 15261, PH: 412-624-3102

Core Co-Leader: Jennifer Brach, PhD, Associate Professor, Department of Physical Therapy, 222 Bridgeside Point 1, Pittsburgh PA, 15213, PH: 412-383-6533

The Clinical and Population Outcomes Core (CPOC) provides recruitment, cohort study resources, and clinical research expertise to promote a multidisciplinary approach to the assessment of mobility and balance in OAIC clinical research studies.

Our specific aims are to:
1. Engage older adults from the community and long-term care settings in research.
2. Provide access to ongoing cohort studies, specimens, clinical trials and existing databases.
3. Provide expertise in clinical assessment methodology by providing a standardized set of forms to promote a common data set of core measures for mobility, balance, and falls.
4. Utilize noninvasive, portable technology to examine mobility, balance, and physical activity in clinics and in the field through our novel mobile laboratory.
5. Provide access to space and equipment for OAIC related studies with our SMART Center.
6. Support the research training mission of the Pepper Center.
7. Evaluate the functions and productivity of the Core and manage its productivity.
8. Collaborate with all the other cores and units within and outside the institution for OAIC related themes.

**CPOC Developmental Project 1: Refinement of an Interactive Voice Response (IVR) Phone System for Fall and Physical Activity Assessment during a Randomized Clinical Trial of Group-Based Exercise**

PI’s: Jennifer S. Brach, PhD, PT; Steven Albert, PhD; Bethany Barone Gibbs, PhD.

Significance: Fall reduction is a focus of the OAIC and PCORI. An efficient and valid tool for fall assessment is needed. A challenge for public health is to reduce falls without reducing physical activity; therefore any fall assessment should also consider physical activity. We developed an Interactive Voice Response (IVR) phone system to assess falls and physical activity and have implemented this system within a statewide fall prevention program. Hypothesis: Reported physical activity and falls, as measured by the IVR system, will be positively correlated with an objective measure of physical activity (i.e., Actigraph accelerometer recording). Approach: The IVR system is an automated monthly calling system which generates two calls each day for up to 8 days until the phone is answered and the interview completed. Currently the automated call elicits whether a person has fallen, weekly physical activity, hospitalization, and emergency department use in the prior 3 days. We will add the IVR system to our currently funded PCORI trial (Brach PI), which will examine the effectiveness of the “On the Move” exercise program. To validate the IVR system measurement we will compare the weekly physical activity data obtained from the IVR to an objective measure of physical activity (Actigraph accelerometer – worn for 7 days) and established measures of mobility and physical function.

**Integrative Systems Core (ISC)**

Core Leader: Caterina Rosano, MD, MPH, Associate Professor of Epidemiology, 130 N. Bellefield Street, Room 507, Pittsburgh, PA 15213, PH: 412-383-1294, FAX: 412-383-1308

Core Co-Leader: J. Timothy Greenamyre, MD, PhD, Professor of Neurology, Chief, Movement Disorders Division, 3471 Fifth Ave, Suite 810 Kaufmann Medical Bldg, Pittsburgh, PA 15213, PH: 412-692-4920
Problems of mobility and balance in the aged require multidisciplinary study because they are complex and multifactorial. Advances require integrating expertise and technical resources from biomechanics, physiology, neural control of movement and biology. Thus, the goal of the Integrative Systems Core (ISC), previously referred to as the “Technology” Core, is to provide integrative, multidisciplinary knowledge, skills and techniques that foster an understanding of the biomechanical, structural, functional, physiological and biological influences on age-related mobility and balance.

The Specific Aims of the Integrative Systems Core are to:
1. Provide expertise through use of an integrative systems approach spanning neuroimaging, biomechanics, physiology and biology.
2. Provide consultation to investigators about existing infrastructure and facilitate the use of laboratories.
3. Coordinate and prioritize the utilization of resources within the Core.
4. Develop new technologies and integrative, complimentary approaches for investigators.
5. Support the research training mission of the Pepper Center.
6. Collaborate with other cores and units within and outside the institution on OAIC theme-related activities.

ISC Developmental Project 2: The Aging Brain and Environmental Negotiation in Older Adults
PI: Andrea Rosso, PhD (Epidemiology); Co-I’s: Caterina Rosano, MD (Epidemiology); Howard Aizenstein, MD, PhD (Psychiatry); Jennifer Brach, PhD, PT (Physical Therapy); Ted Huppert, PhD (Bioengineering)

Significance: Community mobility, the ability to maintain independence outside the home, is determined by many factors beyond functional and cognitive status and includes environmental factors. While mobility research has focused on individual gait and CNS contributions by using dual-tasking paradigms, few have included real world challenges that reflect environmental limitations of mobility in the elderly. This DP applies a translational approach to bring real world challenges into the laboratory setting in order to further our understanding of mobility control while being exposed to stimuli and challenges that are similar to those experienced in the community. We anticipate that the neural mechanisms involved in negotiating environmental conditions are different than those involved with steady-state gait in environmentally sterile conditions. This experimental paradigm may also be used in the future to test the ability of interventions to improve community mobility. Hypothesis: Exposure to real world challenges will negatively affect gait characteristics (e.g. speed, variability) of older adults compared to unchallenged walking. Older adults with the least amount of difficulty with these tasks will be those who have the greatest prefrontal activation as measured by near-infrared spectroscopy (NIRS). Approach: The goal is to recreate in the lab characteristics of the community environment that are typically experienced as challenges or obstacles to mobility (for example: uneven surfaces, obstacles, noise). A second goal is to study changes in mobility characteristics and brain function in participants negotiating
community challenges while wearing a wireless NIRS system and walking on a gait mat. We will test 20 elderly adults recruited from the Pepper registry and compare gait performance, executive function, structural MRI, and NIRS activation during unchallenged and challenged conditions.

**Data Management, Analysis and Informatics Core (DMAIC)**
Core Leader: Subashan Perera, PhD, Associate Professor of Medicine, 3471 Fifth Ave, Suite 500 Kaufmann Medical Bldg, Pittsburgh, PA 15213, PH: 412-692-2365

Core Co-Leader: Doris Rubio, PhD, Professor of Medicine, Biostatistics, Nursing and Clinical and Translational Science, 200 Meyran Avenue, Suite 200, Pittsburgh, PA 15213, PH: 412-692-2023, Fax: 412-246-6954

The overarching goal of the Data Management, Analysis and Informatics Core (DMAIC) is to continue to provide a central source of expertise and services by a team of faculty and staff familiar with the theme and methods used in the Pittsburgh OAIC. Services are most effective when they are provided by personnel intimately familiar with the unique issues of the theme, its special research questions, methods, populations and measures. We will continue to achieve increased efficiencies due to standardized data entry and management and quality control processes across studies. In addition, we provide special expertise required to address the unique issues involved in studying balance and mobility in older adults, such as methods for falls surveillance, informative censoring and management of related missing data, and novel application of complex techniques for quantifying subtle features of gait.

Our specific aims are to:
1. Meet data management requirements of Pittsburgh OAIC PESC, RCDC, DPs and EPs
2. Support quantitative analysis needs of Pittsburgh OAIC PESC, RCDC, DPs and EPs.
3. Provide informatics expertise to Pittsburgh OAIC projects.
4. Support the training mission of the Pittsburgh OAIC with Pepper Scholars and Pepper trainees.
5. Develop new techniques and novel application of existing methods to address OAIC theme-related methodological challenges.
6. Collaborate with other cores and units within and outside the institution on OAIC theme-related activities.

**DMAIC Developmental Project 3: Scaling Exponent Estimation from Stride Interval Time Series and Steps-ahead Prediction**
PI: Ervin Sejdic, PhD; Co-I’s: Jennifer Brach, PhD; Subashan Perera, PhD

Significance: With increasing use of technologies such as accelerometers, we are able to obtain stride interval time series that are sufficiently long to apply sophisticated time series analytic methods to identify the structure of longitudinal dependence among strides, and use the said structure to potentially predict the next stride with a certain degree of accuracy. The dominant approach for uncovering complex inter-dependencies among stride intervals is long-range (fractal) modeling and scaling exponent $\alpha$. 
estimation, where $\alpha$ describes the structure of dependence. But controversies remain about the method of estimation of $\alpha$. Commonly used de-trended fluctuation analysis estimation method depends on the choice of initiation parameters, has many other drawbacks such as irrelevance, false positives, equivalent results from short-range models, nonlinear trend artifacts, estimator bias, lack of robustness, and difficulties with short walks. In contrast, we have previously shown wavelet-based estimation methods are more accurate for scaling exponent analysis. Aims-(1) Systematically evaluate, via simulation, several methods for predicting the next stride; (2) understand how many strides ahead we can accurately predict; and (3) apply the methods to subpopulations with gait abnormalities.

Approach: First, we will simulate 1,000 series of 10,000 stride intervals each from walks with a known $\alpha=0.5$-$1.5$ associated with gait. Second, we will use wavelet methods for prediction of several future strides.

Third, predictive accuracy will be quantified using mean square error (MSE) of predicted stride intervals against the “observed truth” in simulated data. Fourth, we will repeat simulations with shorter series of length=150-200 strides to mimic a typical 6-minute walk. Fifth, the method with the smallest MSE is clearly preferable, and we will provide a computational evidence-based recommendation of a prediction method either uniformly better in all situations, better in certain situations involving short/long series and/or for specific subpopulations with gait abnormalities such as Parkinson’s disease (PD) based on their $\alpha$. Finally, using the recommended methods from simulation above, we will predict last few stride intervals from our previous OAIC pilot study and Physionet (de-identified data) including PD (N=118), peripheral neuropathy (N=10), Huntington’s disease (N=20), amyotrophic lateral sclerosis (N=13) and healthy controls (N=99); and compare to observed values. We will use MATLAB® software (The MathWorks, Inc., Natlick, Massachusetts) for simulation and $\alpha$ estimation, and SAS® (SAS Institute, Inc., Cary, North Carolina) for summarization of results. Upon completion, we will provide evidence-based recommendations of prediction methods to be used with stride interval time series to predict future strides.

C. Current Year Pilots

PES 1: Physical activity effects on blood biomarkers of neurogenesis, angiogenesis, and inflammation and its impact on mobility

Project Leaders: Caterina Rosano, MD, MPH (Assoc Prof Epi); Abbe N. de Vallejo, PhD (Assoc Prof Ped and Immunology)

Co-Investigators: C. Elizabeth Sarles, MPH; Andrea Rosso, PhD; Nancy W. Glynn, PhD

Significance: Cerebral small vessel disease (SVD) is common with aging even among adults without overt neurological disorders. SVD imparts a significant population-level of disease burden as it increases risk for poor health outcomes including mobility disability, dementia, and mortality. Cardiometabolic and inflammatory disorders are strongly related to pathogenesis of SVD and they have also been related to mobility disability. However, these associations have not been tested among very old and frail adults. Importantly, cardiometabolic and inflammatory measures can be modified by physical activity (PA). However, the pathways linking PA with cardiometabolic/ inflammatory measures, SVD,
and mobility have not been examined in older and frail adults. Specific Aims: We aim to: 1) Characterize the determinants of venular density, a novel measure of brain small vessel disease (SVD); 2) Characterize the relationship of physical activity (PA) with subclinical vascular risk factors and blood biomarkers; and 3) Explore the pathways linking PA, SVD, and mobility.

Approach: As part of this pilot study, we propose to complete additional assays on existing banked blood within the Lifestyle Interventions and Independence For Elders study, a randomized controlled trial of PA to reduce the risk of major mobility disability. The assays are for biomarkers of neurogenesis (brain-derived neurotrophic factor), angiogenesis (vascular endothelial growth factor), metabolism /aging (Klotho), inflammation (interleukin 6), and oxidative stress (oxidized low-density lipoprotein) in LIFE participants for whom MRIs have already been acquired at baseline and at follow-up (n=91). In addition, up to 60 participants matched for age, race, and gender who did not complete MRIs at baseline will be assessed, allowing us to quantify selection bias via propensity scores. The study uses venular density, a measure obtained by 7 Tesla MRI as a novel measure of SVD. These biomarkers along with subclinical vascular risk factors and SVD will be examined as potential pathways through which PA has an effect on brain health and mobility.

PES 2: Impact of ergonomic and individual factors on tripping risk of multifocal lens wearers
Project Leaders: Kurt Beschorner, PhD (Asst Prof Bioengineering); Joseph Furman, MD (Prof Otolaryngology)

Significance: Multifocal lens glasses (progressive, trifocal and bifocal lens glasses) are known to increase fall risk in older adults, negatively influence functional vision and impact gait dynamics. Specifically, MfLs lead to increased falls because MfLs cause wearers to improperly locate their foot, which increases the number of trips and stumbles during stepping or obstacle negotiation. Balance and fall risk, however, are also dependent on a number of other personal factors (sensory acuity, ability to compensate for incomplete/inaccurate sensory information) and environmental factors (lighting, contrast of steps). Deficiencies in sensory systems caused by aging or sub-optimal environmental conditions may limit the ability of older adults to maintain balance while wearing MfLs. Thus, a critical need exists to understand the individual and environmental factors that contribute to MfL-induced changes in foot dynamics so that high-risk individuals can be targeted and so that effective countermeasures can be executed. The proposed research will examine the impacts of individual sensorimotor functioning and environmental conditions on MfL-induced gait changes. Specific Aims: Aim 1: Quantify the interaction between the environmental conditions (lighting and step edge contrast) and the use of multifocal lens glasses (MfLs) on foot placement during stair ascent, stair descent and obstacle crossing. Aim 2: Quantify the interaction between individual sensorimotor functioning (contrast sensitivity, depth perception, visual dependence of balance and balance under challenging sensory circumstances) and MfLs on foot placement during stair ascent, stair descent and obstacle crossing.
Approach: Twenty mobile and older adults between the age of 65 and 80 years, who are free of visual (other than presbyopia) and other significant sensorimotor disorders will be recruited. Subjects will complete testing to characterize their vision, balance and functional gait. Vision testing will utilize standard approaches to quantify contrast sensitivity and depth perception at a distance. Four balance conditions will be considered including two vision conditions (eyes open and eyes closed) combined with two support surface conditions (fixed and compliant surface). The functional balance task will include walking up and down stairs and stepping over an obstacle. During the functional balance task, environmental conditions will be altered including the contrast of the step and obstacle edges and lighting. The outcome measures during the functional balance task will be step placement since these measures have previously been associated with tripping risk.

PES 3: Peripheral nerve function changes with exercise intervention after total knee replacement
Project Leaders: Elsa S. Strotmeyer, PhD, MPH (Asst Prof Epi); Sara R. Piva, PhD, PT, OCS, FAAOMPT (Assoc Prof PT)

Significance: Sensory nerve deficits in knee OA have been cross-sectionally and prospectively associated with poor physical performance. Animal studies and small trials in diabetic adults indicate that exercise improves peripheral nerve function. The role of exercise in modifying the sensory nerve deficits or the related poor physical function in knee OA has not been previously evaluated. The specific aims are 1) to relate neuropathic symptoms and impaired monofilament detection to total knee replacement (TKR) and physical function after TKR and 2) to evaluate the effect of a 3-month exercise intervention in participants with total knee replacement (TKR) on improvement in neuropathic symptoms and monofilament detection and related physical function.

Approach: Participants will be >60 years of age with a unilateral total knee replacement (TKR) and enrolled in a post-TKR exercise intervention trial funded by PCORI (N=100 pre-intervention: 80 exercise intervention, 20 control; and N=60 at 3-month follow-up after the intervention: 48 exercise intervention, 12 control) to improve physical function. Sensory nerve function will be measured with neuropathic symptoms and 1.4-g light and 10-g standard monofilament tests. WOMAC-PF will measure self-reported function and performance measures will include usual gait speed, time for 5 chair rises, single leg stance test, stair ascent/descent, six minute walk test, and sitting-rising test.

PES 4: Assessing muscle energetics non-invasively in the oldest old
Project Leader: Hoby Hetherington, PhD (Prof Radiology); Co-Is: Anne Newman, MD, MPH (Prof Med and Epi, co-leader LAC core); Adam Santanasto, PhD (Epi of Aging Fellow and proposed RCDC novice).

Significance: Loss of ability to regenerate adenosine triphosphate (ATP) in skeletal muscle mitochondria may be of major importance in explaining the loss of muscle performance and mobility with age. In well-functioning older adults, ATP regeneration
(ATPmax), measured with 31P magnetic resonance spectroscopy (MRS), was strongly associated with in vitro measures of mitochondrial function, citrate synthase activity, maximal mitochondrial (state 3) respiration and maximal whole-body aerobic capacity (VO2 peak). Further validation of our 31P MRS protocol, during which participants perform repeated leg contractions, as an integrated measure of in vivo mitochondrial function could circumvent the need for muscle biopsy. This noninvasive measure would allow us to examine the importance of mitochondrial function in larger populations. Finally, if valid and related to 400 meter walk performance, it would support the hypothesis that mitochondrial function is an important predictor of mobility and a potential target for intervention in larger studies. Hypothesis: Mitochondrial ATP regeneration (ATPmax) will 1) be strongly associated with oxidative capacity of muscle assessed in biopsy specimens using high resolution respirometry 2) as well as with 400 meter walk performance.

Approach: Muscle biopsy was recently collected for in vitro assessment of mitochondrial function in the Health ABC study (n=40 aged 88.4 ± 2.3 years, 62.5% women and 35% black). We will add 31P MRS to assess maximal recovery of ATP (ATP Max) and a 400 meter walk to measure walking performance. We will also measure oxygen consumption during the walk and calculate the energy cost of walking. We will repeat the 31P MRS protocol in 8 participants to determine reproducibility. Analysis of the spectral waveforms will be conducted by Dr. Santanasto with support from the MR Research Center.

PES 5: CNS dosage measures with falls/fractures in older high risk nursing home residents
Project Leader: Carolyn Thorpe, PhD (Asst Prof, Pharm, RCDC novice); Co-Is Joseph T. Hanlon, PharmD, MS (Prof, Med, Pharm, and Epi, PESC leader); Subashan Perera, PhD (Assoc Prof, Med, DMAIC co-leader; David Nace MD, MPH (Asst Prof, Med, CPOC LTC director; Susan Greenspan, MD (Prof Med, OAIC PI)

Significance: Both falls and use of CNS medications are common in older nursing home patients. There is no consensus on how best to measure aggregate CNS medication dosage burden as it relates to fall/fracture risk. This is a clinically relevant gap because providers need to reduce overall CNS medication dosage to reduce injurious falls/fractures, yet there is little guidance on how best to measure such exposure. Hypothesis: CNS summated standardized dosage measure (SDD) has greater predictive validity than sedative drug burden index (DBI).

Approach: This national longitudinal study will use Medicare Parts A, B, and D data merged with Minimum Data Set (Mor et al, 2004) for nearly 200,000 older (65+) beneficiaries admitted to nursing homes (NH) in 2009/10. We will include long-stay residents with a history of injurious falls/non-vertebral fractures excluding non-ambulatory, bedridden, comatose or those with fractures due to cancer/trauma. The main outcome measure will be incident injurious falls/fractures as documented by emergency room/hospitalization ICD-9 codes. Using Medicare Part D data, we will create a time-varying CNS SDD measure for antidepressants, antipsychotics, benzodiazepine receptor
agonists, anticonvulsants, opioids and skeletal muscle relaxants by dividing total daily dose by the minimum effective geriatric daily dose aggregating across medications.\(5\) Sedative DBI measure will be created similarly but will differ by the drugs included and the logarithmic daily dosage calculation. We will control for important demographic and health status factors (including common indications) that could potentially confound an association between CNS medication use and injurious falls/fractures. We will use multivariable logistic regression modeling, odds ratios and area under ROC curve (c-statistic) to quantify predictive validity.

**PES 6: An Exercise Intervention on cognition, functional status, mobility in Parkinson’s Disease**

Project Leader: Kirk Erickson, PhD (Assoc Prof Psychology, former Scholar); Co-Is: Howard Aizenstein, MD, PhD (Assoc Prof Psychiatry); Tim Greenamyre, MD, PhD (Prof Neurology and ISC co-leader); David Wert, PT, PhD (Assist Prof PT, RCDC trainee).

Significance: Parkinson’s Disease (PD) is an age-related neurodegenerative disease that is characterized by the loss of dopaminergic neurons in the substantia nigra that leads to significant motor dysfunction and falls and impacts half a million Americans. However, individuals with PD also exhibit cognitive symptoms. Current medications target the motor symptoms of PD, thus underscoring the need to attenuate the cognitive symptoms reported by PD patients. Aerobic exercise is a potent method to treat cognition in neurologically healthy older adults, with the strongest effects seen in the same cognitive symptoms that PD patients exhibit. Hypothesis: Our hypotheses include 1) Exercise is a feasible treatment option for both mobility and cognitive dysfunction in PD, 2) an exercise intervention will show improvements in cognitive function, mood, and mobility and 3) exercise will result in improvements in measures of brain connectivity, especially in basal ganglia and prefrontal networks affected by Parkinson’s disease.

Approach: We will enroll 30 participants with mild to moderate PD and randomly assign them to either an aerobic (treadmill walking or cycling) or nonaerobic stretching exercise group for 12 weeks. Assessments of cognitive ability, physical function, brain morphology, and neural functional connectivity will be collected prior to and after the exercise intervention as well as standard tests of gait speed, walking, and balance.
Section III. Career Development

**Novice Program:** The novice program is for investigators who have an interest in balance, mobility and aging research. Candidates must have a sponsoring mentor involved in the OAIC. These trainees have been funded through T32s, predoctoral awards, and other early career development awards.

**Transition to Independence:** The purpose of this program is to promote development into an independent investigator by fostering experiences in leadership and collaboration with investigators and supplementing skills as desired. These young investigators already have independent career awards in areas relevant to age-related balance and mobility.

**RCDC Scholars 2014-2015:**

**Bethany Barone Gibbs, PhD** (2014-2015) is an Assistant Professor, Department of Health and Physical Activity. She obtained her PhD in Epidemiology from Johns Hopkins. She has published over 28 manuscripts and 3 since joining the RCDC. Dr. Barone Gibbs is the PI on a Pitt Research Development Award to examine varying physical activity on arterial stiffness. She became a scholar in late spring 2014. She plans to examine mechanisms and the impact of reducing sedentary behavior in the elderly. She has recently received a Pepper pilot. Her goal is to increase activity in older adults who have sedentary behavior to improve functional outcomes. Her mentoring team includes Drs. John Jakicic, Jen Brach, and Ervin Sejdic. Her competencies and long term goals include: 1) gaining expertise in aging outcome measures for function, gait, mobility; 2) obtaining R01 funding; and 3) multidisciplinary collaborations.

**Shachi Tyagi, MD,** became a novice RCDC member in 2013-14. In this capacity she was able to utilize OAIC resources to initiate a secondary analysis of a study that had assessed adherence to physical activity in sedentary post-menopausal females. Her findings were surprising: even in this cohort of healthy, younger women (aged 50-65 years), sleep correlated significantly not only with objective balance measures but also with subjective balance and confidence. Further pursuit of this relationship between sleep and balance provides the rationale for her project as a Pepper Scholar in our current Pepper grant (2014-15). She became a Pepper Scholar in Aug 2014 to look at the association between insomnia, falls and mobility with Dr. Buysse as her primary mentor. In this way, Dr. Tyagi will continue as a scholar for an additional year (2015-2016) to further develop a career in translational research.

**Laurie H. Sanders, PhD,** has been a novice member of the RCDC (2013-2014) and was involved in a Pepper pilot project to examine mtDNA damage in muscle cells in older patients following exercise (PI Greenamyre, Goodpaster). She is beginning as a RCDC scholar (in summer 2014) and is determining whether brain regions associated with mobility and balance selectively accumulate mtDNA damage (as a surrogate – and possible cause of – mitochondrial dysfunction) in a progeria mouse model. In an effort to become more involved in translational research, her recent work involves investigating the utility of mtDNA damage as a biomarker of PD using human blood samples. Her
preliminary findings were unanticipated; increased mtDNA damage was found in blood from sporadic PD patients. This relationship between mtDNA damage (and mitochondrial dysfunction) and PD status has now become the basis of her KL2 proposal. Specifically, with Dr. Kirk Erickson, she will examine whether exercise, which has been shown to improve mitochondrial mass and function in elderly subjects as well as to improve PD motor function, has measurable beneficial effects on the mtDNA damage found in PD patients. In this way, Dr. Sanders will continue as a scholar for an additional year (2015-2016) to further develop a career in translational research.

RCDC Scholars at University of Pittsburgh OAIC 2004-present

<table>
<thead>
<tr>
<th>Name</th>
<th>Dates</th>
<th>Dept</th>
<th>Grants</th>
<th>Current Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jennifer Brach, PT, PhD</td>
<td>2004-05</td>
<td>PT</td>
<td>Beeson K23, Co-I R01, NSF, PCORI, R01</td>
<td>Assoc Prof PT, Pepper Core Director</td>
</tr>
<tr>
<td>Caterina Rosano, MD, MPH</td>
<td>2004-05</td>
<td>Epi</td>
<td>Beeson K23, R03, 3 R01’s, Co-I 2 R01’s, U13</td>
<td>Assoc Prof Epi, Pepper Core Director</td>
</tr>
<tr>
<td>Susan Hardy, MD, PhD</td>
<td>2005-06</td>
<td>Geri</td>
<td>Beeson K23, R03, U01, AGS Aging Foundation</td>
<td>Assoc Med Dir PACE, Mass.</td>
</tr>
<tr>
<td>Rollin Wright, MD, MS</td>
<td>2005-06</td>
<td>Geri</td>
<td>Hartford Scholar, GACA, Co-I GWFEP HRSA</td>
<td>Asst Prof Med</td>
</tr>
<tr>
<td>Laurie Lavery, MD</td>
<td>2006</td>
<td>Geri</td>
<td>K23 unfunded</td>
<td>Hospitalist Pvt Pctc</td>
</tr>
<tr>
<td>Stasa Tadic, MD</td>
<td>2007</td>
<td>Geri</td>
<td>Hartford Scholar, K23</td>
<td>Asst Prof Med</td>
</tr>
<tr>
<td>Kimberly Faulkner, PhD</td>
<td>2007-08</td>
<td>Epi</td>
<td>NIOSH grants</td>
<td>NIOSH Proj Officer</td>
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<td>Theodore Huppert, PhD</td>
<td>2007-09</td>
<td>Rad Bioeng</td>
<td>R01, R21, DARPA Co-I, SBIR Co-I</td>
<td>Asst Prof</td>
</tr>
<tr>
<td>Kirk Erickson, PhD</td>
<td>2009-10</td>
<td>Psych</td>
<td>R01, Co-I R01, Co-I DOD, UPMC Res Foundation</td>
<td>Assoc Prof</td>
</tr>
<tr>
<td>Elizabeth Hile, PT, PhD</td>
<td>2010-11</td>
<td>PT</td>
<td>Komen Foundation, PCORI Co-PI</td>
<td>Asst Prof, OUHSC</td>
</tr>
<tr>
<td>Neelsh Nadkarni, MD, PhD</td>
<td>2010-12</td>
<td>Geri</td>
<td>Hartford Scholar, K23</td>
<td>Asst Prof</td>
</tr>
<tr>
<td>Ervin Sejdic, PhD</td>
<td>2011</td>
<td>Bioeng Elec Eng</td>
<td>R01</td>
<td>Asst Prof</td>
</tr>
<tr>
<td>Zachary Marcum, PharmD</td>
<td>2011-14</td>
<td>Geri Pharm</td>
<td>Co-I R01, Magee Foundation, Beckwith Foundation</td>
<td>Asst Prof, Univ of WA</td>
</tr>
<tr>
<td>Gelsy Torres-Ovieda, PhD</td>
<td>2013</td>
<td>Bioeng</td>
<td>U of Pgh Career Dev, NSF BRIDGE, American Heart Assoc SDG, NSF Grant</td>
<td>Asst Prof</td>
</tr>
<tr>
<td>Linwah Yip, MD</td>
<td>2013-14</td>
<td>Surgery</td>
<td>Hartford Scholar, R03</td>
<td>Asst Prof</td>
</tr>
<tr>
<td>Name</td>
<td>Year</td>
<td>Field</td>
<td>Institution</td>
<td>Title</td>
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<tr>
<td>Bethany Barone-Gibbs, PhD</td>
<td>2014</td>
<td>Health</td>
<td>American Heart Association</td>
<td>Asst Prof</td>
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<tr>
<td>Shachi Tyagi, MD</td>
<td>2014-15</td>
<td>Geriatrics</td>
<td>Hartford Scholar</td>
<td>Asst Prof</td>
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<tr>
<td>Laurie Sanders, PhD</td>
<td>2014-15</td>
<td>Neurology</td>
<td>CTSI Grant</td>
<td>Asst Prof</td>
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</tbody>
</table>
Section IV. Publications

2014


Nikiforov YE, Carty SE, Chiosea SI, Coyne C, Duvvuri U, Ferris RL, Gooding WE, Hodak SP, LeBeau SO, Ohori NP, Seethala RR, Tublin ME, Yip L, Nikiforova MN. Highly accurate diagnosis of cancer in thyroid nodules with follicular neoplasm/suspicious for a follicular neoplasm cytology by ThyroSeq v2 next-generation sequencing assay. Cancer. 2014 Dec 1;120(23):3627-34. doi:


Gujral S, Manuck SB, Ferrell RE, Flory JD, Erickson KI. The BDNF Val66Met


Alley DE, Shardell MD, Peters KW, McLean RR, Dam TT, Kenny AM, Fragala MS, Harris TB, Kiel DP, Guralnik JM, Ferrucci L, Kritchevsky SB, **Studenski SA**,


2015


Gates E, Dolansky MA, Zullo M, **Forman DE**. Octogenarians Receiving Cardiac Valve Surgery and Post-Acute Care: Clinical Implications to Improve Recovery. Healthcare. In press


Kalra A, **Forman DE**, Goodlin SJ. Medical Decision Making for Older Adults: An international perspective comparing the United States and India. J Geriatr Cardiol. 2015;12:329-34


Bender CM, Merriman JD, Gentry AL, Ahrends GM, Berga SL, Bruksy AM, Casillo FE, Dailey MM, **Erickson KI**, Kratofil FM, McAuliffe PF, Rosenzweig MQ, Ryan CM, Sereika SM. Patterns of change in cognitive function with anastrozole therapy.


Nace DA, Lin CJ, Ross TM, Saracco S, Churilla RM, Zimmerman RK. Randomized,


Tian Q, Glynn NW, Erickson KI, Aizenstein HJ, Simonsick EM, Yaffe K, Harris TB, Kritchevsky SB, Bouzreau RM, Newman AB, Lopez OL, Saxton J, Rosano C; Health ABC Study. Objective measures of physical activity, white matter integrity and


Section V. External Advisory Board Members 2014-2015

Nicolaas Bohnen, MD, PhD, Professor Radiology, Professor Neurology, University of Michigan – 5 Years

Pamela Duncan, PT, PHD, Professor Neurology, Wake Forest University – 10 Years

Luigi Ferrucci, MD, PhD, Scientific Director, NIA/NIH – 10 Years

Joe Verghese, MD, Professor of Medicine, Division of Geriatrics, Albert Einstein College of Medicine – 9 Years
Section I. Description of Center
The UTMB Claude D. Pepper Older Americans Independence Center (OAIC) has been continuously funded since 2000. From the very beginning, we have nurtured a multidisciplinary translational research culture to fulfill our mission, which is to improve physical function and independence in older adults. Central to this mission has been the career development and training of the next generation of leaders in geriatric research. Our scientific focus has evolved over the years from a narrow interest in the mechanisms of sarcopenia to the translation of our findings in much needed patient-centered interventions to improve physical function and independence. This evolution derives not only from the natural progression of our research from basic discoveries to healthy humans and from healthy humans to patients, but also from a deliberate effort of the OAIC leadership to promote and support collaborations between scientists in muscle aging and investigators in population health and outcomes research on aging and rehabilitation. This second line of research has always been present from the beginning of our OAIC, but was conducted in parallel with muscle research. The intersection of these two lines has accelerated the development of new research foci. An example is the rapid development of patient-centered outcomes research in the elderly, which culminated with the funding of a large infrastructure grant and, more recently, with our participation in the trans-Pepper patient-centered multicenter pragmatic clinical trial STRIDE Study.

The theme for the current cycle of our OAIC is to “Identify pathways of physical function loss and gain and develop targeted interventions to improve functional recovery from illness in older adults”.

We will develop patient centered interventions to promote functional recovery from illness and prevent disability and dependence in older adults by translating our discoveries in the basic biology of aging muscle and our understanding of the trajectories of care and recovery from hospitalization.

Our general hypothesis is that aging induces mild but significant biological and metabolic changes that — in combination with patient factors (e.g., ethnicity, physical activity, nutrition, living setting, chronic diseases) — progressively lead to functional loss and predispose to potentially catastrophic declines in physical function during bouts of acute illness and hospitalization. Once hospitalized, variations in hospital and post-hospital care will significantly determine whether geriatric patients will recover physical function after their illnesses. Thus, we hypothesize that interventions involving rehabilitation, nutritional supplementation, pharmacologic anabolic treatments, as well as changes in decision making and healthcare delivery can prevent the age- and disease-induced functional loss and improve functional recovery from illness in older adults.

The specific aims of the UTMB OAIC are as follows:
1. Stimulate the growth of additional multidisciplinary translational research to improve physical function and functional recovery from illness in older adults by:
   a. Funding pilot project research to generate preliminary data in promising new areas of investigation
   b. Funding developmental projects to develop innovative technologies
2. Train future leaders in geriatric research on the mechanisms, prevention and treatment of functional loss and recovery in older adults
3. Recruit established investigators with expertise relevant to muscle function and functional
recovery in older adults into interdisciplinary translational research related to the OAIC focus.

4. Provide core support and add value to funded translational research on functional loss and recovery in older adults.

5. Foster collaborations between UTMB investigators and investigators at other OAICs and other institutions on studies of physical function and functional recovery in older adults.

These specific aims will be accomplished by supporting Multidisciplinary Translational Teams (MTT) via coordination and integration through the Leadership/Administrative Core (LAC) of the activities of our Research Career Development Core/KL2 program (RCDC/KL2), the Pilot/Exploratory Studies Core (PESC) and the three highly productive Resource Cores (RC) that encompass the major areas of our multidisciplinary translational research model: Clinical Research RC1, Metabolism and Biology RC2, and Biostatistics and Data Management RC3.

For more information on the current UTMB OAIC, please visit the Pepper website at: http://www.utmb.edu/scoa/pepper/index.asp

Administration and Leadership        Phone        Fax        Electronic Mail
Elena Volpi, MD, PhD        (409) 772-1977      (409) 772-8931    evolpi@utmb.edu
OAIC Principal Investigator Leader, Administrative Core Director, Sealy Center on Aging

James S. Goodwin, MD        (409) 772-1988      (409) 772-8931    jsgoodwi@utmb.edu
OAIC Co-Leader, Administrative Core Professor, Division of Geriatrics

Section II. Research, Resources and Activities

A. Cores

1. Leadership/Administrative Core (LAC)
Core Leader: Elena Volpi, MD, PhD
Co-Leader: James S. Goodwin, MD
OAIC Tracking and Evaluation Leader: Jean Freeman, PhD
OAIC Administrator: Stephanie Burt, MS

The overall goal of the Leadership/Administrative Core (LAC) is to provide the administrative infrastructure and leadership to support the activities and growth of the entire UTMB OAIC, and fulfill our mission, which is to stimulate translation of the research findings to improve physical function and independence in older adults.

The LAC specific aims are:

1. Provide overall leadership and direction for all activities of the UTMB OAIC. We will:
   a. Evaluate new opportunities for research and collaborations at the local, national and international level with support from our Internal Advisory Committee (IAC) and External Advisory Committee (EAC);
b. Attract new investigators by providing training opportunities, as well as pilot and developmental projects;
c. Coordinate and integrate Core functions, promoting scientific coherence, access to Core resources and expertise, and new utilization of Core resources;
d. Coordinate and leverage OAIC Cores with other institutional resources;
e. Foster collaborations between UTMB OAIC investigators and Cores with other OAICs and institutions.

2. Administer the UTMB OAIC program. This includes:
   a. Monitor all fiscal matters;
   b. Track and evaluate Core utilization, productivity, quality and efficiency (timeliness), with reallocation of resources among cores as appropriate;
   c. Assure compliance with university and governmental policies regarding human subjects, animal care, and the responsible conduct of research;
   d. Organize research and administrative meetings, including the Scientific Review Panel (SRP) meetings for selection of pilot/developmental projects and scholars;
   e. Organize participation of UTMB investigators at the annual OAIC national scientific meeting.

3. Communicate with the NIA and the community. We will:
   a. Prepare all administrative documents;
   b. Maintain open communication with the scientific community, and healthcare professionals, older adults and caregivers to translate our research findings to the geriatric population;
   c. Maintain and expand the UTMB OAIC website.

The Leadership/Administrative Core is closely tied administratively to the Sealy Center on Aging, the Institute for Translational Sciences Clinical Research Center, the newly refunded UTMB CTSA, the Office of Biostatistics, and other UTMB administrative entities. The Sealy Center on Aging provides administrative and secretarial resources as well as office supplies, telephone, etc. OAIC governance and administrative issues are brought before the Executive Committee, which meets monthly and is comprised of Dr. Volpi as Chairperson, plus the Core Leaders and Co-Leaders, and other senior investigators. An Internal Advisory Panel, comprised of chairpersons of relevant clinical and basic science departments and the deans of the Schools of Nursing, Allied Health Sciences, and Graduate Biomedical Sciences, meets twice yearly to review progress of the Center, particularly in faculty development.

2. Research Career Development Core (RCDC)
Core Leader: Kenneth Ottenbacher, PhD, OTR
Co-Leader: James S. Goodwin, MD
Co-Leader: Rebeca Wong, PhD

The UTMB RCDC has been recruiting scholars and providing them with the skills and research experience necessary to become independent investigators and future leaders and mentors in aging research for the past fifteen years. The RCDC career development program is based on a model of mentor-driven research training that occurs in the context of a multidisciplinary team.

Since 2000 we have supported twenty-two RCDC scholars with OAIC funds. They have become directors of geriatrics divisions at academic health science centers (M. Raji), received NIH (S. Ajala-Torred, S. Al Snih, E. Børsheim, M. Drummond, H. Dryer, W. Durham, L. Killewich, M.
Moore, G. Ostir, D. Paddon-Jones, K. Peek, G. Sharma, and E. Volpi) and DOD (M. Kinsky) funding, have been promoted to full professor (L. Killewich, M. Moore, G. Ostir, D. Paddon-Jones, K. Peek, M. Raji, G. Sharma, and E. Volpi), and are making important research contributions at other universities across the nation (E. Ajala-Torres, E. Børseth, H. Dryer, J. Dickinson, M. Drummond, K. Timmerman).

An important new component of the RCDC is the introduction of the KL2. The KL2 represents a substantial expansion of the career development component of the OAIC. The requirements associated with the KL2 allow us to operationalize our team-based mentor-driven training in more detail. One change associated with the KL2 is the requirement that each RCDC scholar devote 75% effort to research during the period of OAIC support. The scholars may be supported for a period of up to three years on OAIC/RCDC funds at this level of effort. To address the requirements of the KL2 program we have made modifications in the recruitment and selection process for scholars.

The goal of the RCDC Program is to increase the number of rigorously trained, extramurally competitive, and scientifically competent scholars who will conduct translational investigations in aging, lead multidisciplinary research teams, and eventually mentor the next generation of investigators in aging research. To achieve this goal, the RCDC Program will address the following objectives.

**Objective 1:** Identify, recruit and select qualified scholars who are beginning their academic/scientific careers in aging and demonstrate the potential for multidisciplinary translational research.

**Objective 2:** Create Individualized Career Development Plans for each scholar that identify a lead mentor and mentoring team with defined roles, and document expected milestones of research progress including publications, presentations, and submission of grant proposals, and training in the scientific integrity and the responsible conduct of aging related research.

**Objective 3:** Develop and implement a high quality program of education and training activities integrated with mentoring experiences that provide RCDC scholars with the skills necessary to establish productive scientific careers.

**Figure 1.** Components of RCDC (KL2) Faculty Development Program:
3. Clinical Research Resource Core (CR-RC1)

Core Leader: Elena Volpi, MD, PhD
Co-Leader: Douglas Paddon-Jones, PhD
Co-Leader: Gulshan Sharma, MD

The Clinical Research Resource Core (CR–RC1) continues to function as the primary UTMB-OAIC resource for subject recruitment, tracking and retention activities, and for training of our Scholars in clinical research. The core supports research studies on: 1) the biological mechanisms underlying functional loss and recovery; 2) physical function and disability in healthy and frail community-dwelling older adults, and in patients admitted to the hospital; and 3) studies in patient-centered outcomes research (PCOR) on recovery from illness.

The Specific Aims of the CR-RC1 are:

1. Recruit, track and retain older adults for scholar projects, external projects, developmental and pilot studies
2. Provide standardized health screenings, physical exams, functional status and disability assessments for OAIC investigators
3. Maintain a health outcomes database on patients admitted to the UTMB Acute Care for Elders (ACE) Unit and the Intensive Care Unit (ICU)
4. Coordinate training in recruitment and retention, and functional assessments.
5. Ensure compliance with regulations governing clinical investigations involving human subjects
6. Develop novel methodologies to improve research subject recruitment, retention and satisfaction.

Anchored by our expertise in muscle biology, nutrition, and metabolism in aging, the UTMB-OAIC is a leader in translational research in healthy and clinical older populations. Our evolving, translational focus on interventions to prevent functional loss and improve recovery in older adults, demands a coordinated and efficient recruitment, tracking and retention strategy to ensure continued productivity and faculty development.

The core supports three streams of investigator-initiated activities. First, it provides expertise and resources for translational and mechanistic investigations on the pathophysiology of muscle aging and sarcopenia. Second, the core provides expertise and resources for the assessment of functional status and disability using a standardized battery of subjective and objective measures. Third, we also provide support for innovative qualitative studies and pragmatic clinical trials in patient centered outcomes research (PCOR) in recovery from illness and fall prevention, a new area of research in which several of our investigators are funded and have initiated studies.

Recruitment efforts target older adults from the community, patients seeking healthcare in our clinics, and patients admitted in the ACE unit. We have also initiated the development of a research unit in the ICU. Many MICU patients are older adults subsequently transferred to the ACE Unit after critical care. By expanding our hospital research lab to the ICU we will be able to capture these patients earlier and follow their recovery. The CR–RC1 will also continue to prioritize the recruitment and retention of a diverse subject population including women and older adults of racial/ethnic minority origin.

4. Metabolism & Biology Resource Core 2 (MB-RC2)

Core Leader: Blake Rasmussen, PhD
Co-Leader: Labros Sidossis, PhD
The Metabolism and Biology Resource Core (MB-RC2) of the UTMB OAIC supports and promotes integrative and translational research on the metabolic and biological mechanisms underlying functional loss and recovery in older adults. The MB-RC2 also supports biological sample storage, tracking and handling for larger clinical trials. The specific aims are:

1. Provide analytical support and add value to funded translational research on sarcopenia, physical dysfunction and recovery requiring cell culture, molecular, morphological, or stable isotope tracer methodologies
2. Leverage other institutional analytical core resources and simplify access for OAIC investigators
3. Develop new translational methods to study the biological and metabolic mechanisms of sarcopenia, physical function and recovery in older adults
4. Train young investigators on the analytical and methodological aspects of translational research on physical function in older adults.

The MB-RC2 is the engine of analytical innovation of our OAIC. We strive to develop new methodologies and modify existing methods to meet our investigators’ analytical needs to discover the pathways of functional loss and recovery in older adults. Translational research requires integration of expertise and methodologies to understand the complexity of the biological and metabolic processes that lead to muscle dysfunction and functional loss, and identify specific targets for innovative interventions.

5. Biostatistics & Data Management Resource Core (BDM-RC3)
Core Leader: Kristofer Jennings, PhD
Co-Leader: Yong-Fang Kuo, PhD

The OAIC Biostatistics and Data Management Resource Core 3 (BDM-RC3) is new. Previous training and services in biostatistics were embedded in the RCDC. The growing interest of our scholars and investigators in clinical trials, biomarker discovery, and research with large datasets has increased our need for biostatistical and data management support. The goal of the BDM-RC3 is to develop an infrastructure that leverages institutional biostatistical and bioinformatics resources to provide a broad set of advanced and innovative tools for OAIC research. Core personnel are highly qualified researchers who provide support with expertise in study design, data management, and statistical analysis of data from a wide range of research applications. Core faculty also have a strong record of developing statistical methods to address questions resulting from studies of observational and clinical interventions. The specific aims of the BDM-RC3 are:

1. Train OAIC faculty and RCDC scholars in biostatistics and data management to help them plan, conduct, and draw conclusions from their investigations in aging.
2. Support and add value to funded projects related to the theme of the OAIC by actively participating in the design, monitoring, data management, and statistical analysis of studies on pathways of and interventions to improve physical function and recovery in older adults.
3. Develop novel methods and tools for aging research. We will build on our expertise in machine learning, nonparametric and resampling methods, and survival analysis as approaches to addressing issues of pragmatic trials, clinical interventions, and comparative effectiveness research in aging.
4. Enhance the OAIC current information systems infrastructure to assist in procurement, management, and processing of data collected from extant databases as well as new clinical study outcomes.
From its inception, the UTMB OAIC has had strong involvement from biostatisticians, epidemiologists, and other data scientists from the Office of Biostatistics (OBIOS), the UTMB Sealy Center on Aging (SCOA), and the Institute for Translational Sciences (ITS). The relationship between members of the new BDM Core and the RCDC will formalize the involvement of individual biostatistical investigators in OAIC research, ensuring access to all researchers of the biostatistical and data management resources they need to effectively conduct their investigations.

6. Pilot/Exploratory Studies Core (PESC)
Core Leader: Melinda Sheffield-Moore, PhD
Co-Leader: Kyriakos Markides, PhD

The goal of the Pilot/Exploratory Studies Core is to stimulate new research addressing the issues of functional loss and gain and promoting functional recovery from serious illness in the elderly. We target early stage investigators, and we also investigators well established in other areas who can turn their expertise to studies consistent with the OAIC theme. The PESC funds one or two-year pilot grants with budgets of up to $30,000 per year, and also small exploratory projects with seed money budgets of up to $10,000.

We employ our assets and partner with other institutional resources to accomplish the following specific aims:

1. Solicit and select the most meritorious research proposals for PESC funding.
2. Identify opportunities for co-sponsorship of PESC studies.
3. Provide PESC investigators with access to resources from other OAIC cores and institutional research facilities/centers.
4. Monitor the progress of PESC studies.
5. Ensure regulatory compliance, safety and protection of human subjects enrolled in PESC studies.
6. Provide assistance and mentorship to develop PESC studies into independently funded grant applications.

The PESC is an inherently innovative core because it is designed to spearhead new research. However, innovation of our PESC also originates from our novel approach to its activities, which are guided by the following principles:

- The PESC is proactive in stimulating and generating ideas for proposals.
- The PESC partners with other centers, institutes, departments and related sources to increase the pool of funds available for pilot research in the OAIC’s theme area.
- Pilot project recipients are associated with Multidisciplinary Translational Teams (MTT).
- Priority is given to projects that build new collaborations, apply innovative methodologies or emerging new technologies to the study of sarcopenia, physical function and recovery from illness.
- The PESC actively encourages and recruits faculty from underrepresented minority groups to participate in OAIC research.

We consider the PESC process as broader than simply awarding funds for OAIC pilot research. The goal is to support aging research at the institutional level. The most important outcome is new external funding resulting from work supported by the PESC.
B. Research

UTMB Pepper investigators hold a number of externally funded grants that support interdisciplinary translational research on muscle function in older persons. These are listed below:

PI: James Goodwin, MD  
**Source:** CPRIT  
**Period:** 08/01/10 – 02/28/16  
**Grant #:** RP101207  
**Title:** Comparative Effectiveness Research on Cancer in Texas, (CERCIT)  
**Goal:** CERCIT is a multidisciplinary consortium of investigators at the University of Texas Medical Branch (UTMB), MD Anderson Cancer Center, the University of Texas School of Public Health, Rice University, Baylor College of Medicine and the Texas Cancer Registry. The overall goal of CERCIT is to create a statewide resource for outcomes and comparative effectiveness research in cancer for Texas.

PI: James Goodwin, MD  
**Source:** AHRQ  
**Period:** 05/01/13 – 04/30/18  
**Grant #:** R24 HS022134  
**Title:** Patient-Centered Outcomes Research in the Elderly  
**Goal:** The goal of the project is to build infrastructure within UTMB to support research into patient-centered care and to educate investigators in the methodology of patient centered outcomes research (PCOR).

PI: James Goodwin, MD (site)  
**Source:** NIA  
**Period:** 05/01/11 – 04/30/16  
**Grant #:** T35 AG038048  
**Title:** Medical Student Training in Aging Research (MSTAR)  
**Goal:** The Medical student Training in Aging Research Program (MSTAR), a collaborative effort between the University of Texas Health Science Center at San Antonio and University of Texas Medical Branch, offers an 8-12 week intensive experience in translational aging research for first-year medical students. Training plans are developed for each student to reflect their individual research interest and progress is monitored by mentors chosen specifically with expertise to match the student’s research topic.

PI: Elizabeth Lyons, PhD  
**Source:** NCI  
**Period:** 09/01/14-8/31/18  
**Grant #:** 1 K07CA175141-01  
**Title:** LEVEL UP: Video Games for Activity in Breast Cancer Survivors  
**Goal:** The goal of this project is to develop and test an intervention that uses video games to motivate postmenopausal breast cancer survivors to increase their physical activity.

PI: Elizabeth Lyons, PhD  
**Source:** American Cancer Society  
**Period:** 01/01/15-12/31/19  
**Grant #:** MRSG-14-165-01-CPPB  
**Title:** Self-Monitoring Activity: A Randomized Trial of Game-Oriented Applications  
**Goal:** This study will test the feasibility and acceptability of mobile video games for physical activity promotion among postmenopausal breast cancer survivors. Two narrative-based walking games will be used to increase self-monitoring and autonomous motivation for walking.

PI: Kyriakos Markides, PhD  
**Source:** NIA  
**Period:** 04/01/09 – 08/31/19  
**Grant #:** R01 AG10939  
**Title:** Longitudinal Study of Mexican American Elderly Health
**Goal:** A longitudinal study of at least 3,952 elderly Mexican Americans in the Southwest. Estimate prevalence and incidence of major conditions and disabilities and compare with other populations. Study predictors of mortality and change in health over time.

**PI:** Kyriakos Markides, PhD  
**Source:** NIH  
**Grant #:** T32 AG051131  
**Period:** 07/01/15 – 06/30/20

**Title:** Clinical and Behavioral Science Training in Aging and Health Disparities

**Goal:** The proposed MD-PhD program in clinical and behavioral sciences on health disparities in aging will focus on core areas of strengths in minority aging and health disparities research at UTMB, including: Hispanic and Hispanic/Latino health and aging, and disparities in health outcomes in older adults. These are areas in which the University has committed substantial resources toward creating new faculty positions and has demonstrated significant success in obtaining peer-reviewed (R01) support. In concert with the recently accredited graduate program in Population Health Sciences, we are proposing an integrated curriculum throughout medical school and the graduate years that will address both clinical aspects and cutting edge research on health disparities in older adults.

**PI:** Kenneth Ottenbacher, PhD  
**Source:** NIH  
**Grant #:** K12 HD055929  
**Period:** 09/25/07 – 08/31/17

**Title:** Rehabilitation Research Career Development Program

**Goal:** The RRCD Program will recruit and train rehabilitation scientists who are occupational and physical therapists. Program activities will provide trainees with the skills necessary to become independent investigators and future leaders and mentors in rehabilitation.

**PI:** Kenneth Ottenbacher, PhD  
**Source:** DOE  
**Grant #:** H133G140127  
**Period:** 10/01/14 – 09/30/17

**Title:** Hospital readmission following post acute care

**Goal:** Examine hospital readmission for persons in high volume, high cost impairment groups who receive post-acute care services including inpatient rehabilitation, skilled nursing facilities, and care from home health agencies.

**PI:** Kenneth Ottenbacher, PhD  
**Source:** NIH  
**Grant #:** R24 HD065702  
**Period:** 07/03/10 – 05/31/16

**Title:** Center for Rehabilitation Research using Large Datasets

**Goal:** Provide training and funding opportunities in the use of large administrative and research datasets to increase the quantity and quality of rehabilitation research.

**PI:** Kenneth Ottenbacher, PhD  
**Source:** DOE  
**Grant #:** H133P110012  
**Period:** 10/01/11 – 09/30/16

**Title:** Interdisciplinary Rehabilitation Research Postdoctoral Training

**Goal:** Provide support for postdoctoral fellows participating in rehabilitation and disability research.

**PI:** Kenneth Ottenbacher, PhD  
**Source:** NIH  
**Grant #:** R01HD069443  
**Period:** 07/05/12 – 04/30/16

**Title:** Hospital Readmission and Inpatient Medical Rehabilitation

**Goal:** Examine rates and reasons for hospital readmission using CMS files in high volume and high cost patients, such as those with stroke or hip fracture, who receive inpatient medical rehabilitation.

**PI:** Douglas Paddon-Jones, PhD  
**Period:** 02/15/12-12/31/16
Source: NINR  
Grant #: R01 NR01297301  
Title: Preserving muscle mass and function in bedridden older adults  
Goal: The goal of this study is to reduce the negative consequences of inactivity and promote rehabilitation in aging muscle.

PI: Douglas Paddon-Jones, PhD  
Period: 08/01/12-12/31/16  
Source: Dairy Research Institute  
Title: Whey protein, aging and physical inactivity  
Goal: The goal is to assess the ability of whey protein to protect muscle mass and function during inactivity.

PI: Douglas Paddon-Jones, PhD  
Period: 08/01/12-12/31/16  
Source: Dairy Research Institute  
Title: Whey protein, aging and physical inactivity  
Goal: The goal is to assess the ability of whey protein to protect muscle mass and function during inactivity.

PI: Blake Rasmussen, PhD  
Period: 09/01/13-06/01/16  
Source: Solae, LLC.  
Title: A Randomized, Controlled Double Blind Acute Study: Effects of Protein Blend Supplementation Following Resistance Exercise in Older Men  
Goal: The major goals are to determine whether a blend of high quality proteins consumed as a nutritional supplement following an acute bout of resistance exercise will improve muscle mTORC1 signaling and protein synthesis as compared to a single protein source.

PI: Blake Rasmussen, PhD  
Period: 10/15/14-10/15/15  
Source: Navitor Pharmaceuticals, Inc.  
Title: Effect of Specific Amino Acids on Human Muscle Protein Synthesis  
Goal: The major goals are to determine which specific amino acids induce the largest increase in translation initiation, protein synthesis and mTORC1 signaling in human skeletal muscle.

PI: Timothy Reistetter, PhD, OTR  
Period: 04/01/11-08/31/15  
Source: NICHD  
Grant #: K01 HD068513  
Title: Regional Variability in Inpatient Rehabilitation Facilities among Medicare Beneficiaries  
Goal: The Specific Aims of this project are to: 1) Describe the differences in rehabilitation outcomes (length of stay, functional status, community discharge, re-hospitalization, and mortality) across Hospital Referral Regions (HRR) for older adults who have experienced a stroke or hip fracture; 2) Determine how much variation in these outcomes is attributed to the patient, facilities and regions; and 3) Identify patient, facility, and geographic characteristics that independently contribute to variation in these rehabilitation outcomes.

PI: Timothy Reistetter, PhD, OTR  
Period: 05/01/13-04/30/18  
Source: AHRQ  
Grant #: R24 HS022134  
Title: Comparative Effectiveness of Patient Centered Outcomes Following IRF and SNF Stroke Rehabilitation  
Goal: The study will enhance the understanding and application of clinical and patient-oriented rehabilitation outcome decisions. The findings will inform rehabilitation professions, health services researchers, and policy makers in developing guidelines and practices that improve patient outcomes and the quality of stroke rehabilitation.
**Title:** Patient Centered Decision Support in Cancer  
**Goal:** The goal of the Patient-Centered Decision Support in the Elderly multidisciplinary translational team is to translate comparative effectiveness research (CER) into clinical practice by developing patient-centered decision support tools for older patients, physicians, and their families. The risks and benefits of different treatment options must be assessed in the context of an individual’s disease, unrelated chronic medical conditions, overall functional status, and personal preferences. This proposal uses mixed methods (qualitative and quantitative) to improve the delivery of patient-centered care with the goal of identifying the right treatment, for the right patient, in the right setting.

**Title:** Quality of Post Treatment Surveillance of Cancer Patients in Texas  
**Goal:** The grant supports the linkage of Texas Cancer Registry data to Medicare and Medicaid data, in order to support population-based analyses of screening for, and diagnosis, treatment, and post-treatment surveillance of cancer patients in Texas, with a particular emphasis on disparities in cancer care associated with race/ethnicity and rural residence.

**Title:** The University of Texas System Chancellor’s Health Fellow for Health Information Technology Grant  
**Goal:** This study aims to implement CDSS to manage patient hospitalized with COPD or CHF exacerbation and improve care coordination during care transition period by using Health IT.

**Title:** The University of Texas System Chancellor’s Health Fellow for Systems Engineering Grant  
**Goal:** This study aims for systems engineering is to provide integrated care for patients with Chronic Obstructive Pulmonary Disease (COPD).

**Title:** Growth hormone or sildenafil as a novel function-promoting therapy for fatigue, cognition and neuroplasticity in mTBI  
**Goal:** The goal of this pilot grant is to assess whether growth hormone therapy can reduce symptoms of fatigue (performance and cognitive) and improve neuroplasticity as measured by fMRI and DTI in military fighters with mild traumatic brain injuries.

**Title:** Amino Acids and Inflammatory Burden in Chronic Traumatic Brain Injury  
**Goal:** The purpose of this project is to assess the inflammatory burden and amino acid profile in institutionalized patients with traumatic brain injury.
Title: Amino Acid and Inflammatory Profiles in an Animal Model of Traumatic Brain Injury (TBI)

Goal: The purpose of this project is to assess the inflammatory burden and amino acid profile in rats with traumatic brain injury.

PI: Labros Sidossis, PhD
Source: ADA
Grant #: 1 14 TS 35
Period: 01/01/14-12/31/16

Title: Effect of Brown Adipose Tissue activation on insulin sensitivity in humans

Goal: To determine the effects of brown adipose tissue, activated by mild cold exposure, on carbohydrate and lipid metabolism and insulin sensitivity in overweight and obese humans.

PI: Labros Sidossis, PhD
Source: Shriners Hospitals for Children
Grant #: 84090
Period: 01/01/09-12/31/16

Title: Special Shared Facility -- Mass Spectrometry Core

Goal: To maintain a mass spectrometry facility that enables the continued application of stable isotope methodology to the study of the response of humans to severe injury, stress, and rehabilitation. This includes service (routine sample analysis), method development (both analytical and theoretical), and education regarding stable isotope techniques.

PI: Labros Sidossis, PhD
Source: Shriners Hospitals for Children
Grant #: 85310
Period: 01/01/14-12/31/16

Title: Effect of severe burn injury and propranolol on adipose tissue metabolism

Goal: To determine the effects of severe burn injury on brown and white adipose tissue metabolism and the role of adrenergic stimulation on whole body and tissue metabolism in children 6-17 yr.

PI: Elena Volpi, MD, PhD (site)
Source: NIA
Grant #: U01 AG029824
Period: 09/15/09-01/31/17

Title: Aspirin in Reducing Events in the Elderly (ASPREE)

Goal: The major goals are to determine if the potential benefits of aspirin outweigh the risks for people over age 65.

PI: Elena Volpi, MD, PhD (site)
Source: NIA/PCORI
Grant #: U01 AG048270
Period: 05/03/14-04/30/19

Title: A Randomized Trial of a Multifactorial Fall Injury Prevention Strategy

Goal: The major goal of this patient-centered intervention is to reduce the risk of serious fall injuries among non-institutionalized older persons using an adaptive design.

PI: Elena Volpi, MD, PhD
Source: DRI
Grant #: 1229
Period: 01/01/14-12/31/16

Title: Whey protein and exercise to accelerate recovery of muscle mass and function after acute hospitalization in previously independent older adults
**Goals:** The goal of this project is to collect preliminary and feasibility data to determine if a 30-day nutritional and/or in-home exercise intervention can accelerate functional recovery in older adults discharged from the hospital.

**PI:** Elena Volpi, MD, PhD (site)  
**Source:** NIMHD  
**Period:** 09/20/11 - 06/30/16  
**Grant #:** U24 MD006941  
**Title:** A Randomized Recruitment Intervention (RECRUIT)  
**Goals:** Our goal is to develop and implement a randomized trial of a recruitment intervention to increase racial/ethnic diversity.

**PI:** Rebeca Wong, PhD  
**Source:** NIA  
**Period:** 09/30/14 – 05/31/16  
**Grant #:** R03 AG048809  
**Title:** Dynamic of Economic Well-Being and Health in a Rapidly-Aging Developing Economy: the Case of Mexico  
**Goal:** The immediate project goal is to identify how various dimensions of health affect economic well-being for different groups in a rapidly aging country, Mexico.

**PI:** Rebeca Wong, PhD  
**Source:** NIA  
**Period:** 05/01/04 – 04/30/16  
**Grant #:** T32 AG002070  
**Title:** Health of Older Minorities – Training Grant  
**Goal:** The goal of this pre and postdoctoral training program is to recruit academically promising candidates into the study of health of older minorities and comparative effectiveness research.

**PI:** Rebeca Wong, PhD  
**Source:** NIA  
**Period:** 04/15/11 – 03/31/16  
**Grant #:** R01 AG018016  
**Title:** The Mexican Health and Aging Study II (MHAS)  
**Goal:** The proposed study aims to design and field the 3rd and 4th waves of data collection in Mexico. This is a longitudinal prospective study of Mexican aging starting with a national sample of persons aged 50 and older, with the first two waves fielded in 2001 and 2003. Funds are requested also to archive and disseminate the 3rd and 4th rounds as well as the resulting integrated database containing all four waves.

**C. Pilot Projects**

**Recently Announced Pilot Awards (Funding Period: 09/01/15-08/31/16)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Department</th>
<th>Title of Research</th>
<th>Amount Awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. Lichar Dillon, PhD</td>
<td>Internal Medicine - Endocrinology</td>
<td>Cycled Testosterone Therapy to Improve Physical Function in Frail Nursing Home Residents</td>
<td>$25,000</td>
</tr>
<tr>
<td>Christopher Fry, PhD</td>
<td>Nutrition &amp; Metabolism</td>
<td>Satellite Cell Regulation of Fibrogenic/Adipogenic Progenitor Cell Activity in the Development of Skeletal Muscle Fibrosis during Aging</td>
<td>$10,000</td>
</tr>
<tr>
<td>Jean Gutierrez, PhD, RD</td>
<td>Nutrition &amp; Metabolism</td>
<td>Predicting Hyperglycemia in Bedridden Older Adults Using Diabetes Risk Scores</td>
<td>$10,000</td>
</tr>
</tbody>
</table>
Currently funded pilot projects
In the budget year 2014-2015, seven pilot/developmental projects were selected for funding. They are displayed in Table 2 below.

Table 2. Current Pilot Projects (05/01/14-08/31/15)

<table>
<thead>
<tr>
<th>Name</th>
<th>Department</th>
<th>Title of Research</th>
<th>Amount Awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celeste Finnerty, PhD</td>
<td>Surgery</td>
<td>Burns and the Elderly</td>
<td>$30,000</td>
</tr>
<tr>
<td>Steven Fisher, PT, PhD</td>
<td>Physical Therapy</td>
<td>Fall Risk Reduction in the Elderly Through the Physical Therapy Management of Incontinence: A Pilot Study</td>
<td>$20,000</td>
</tr>
<tr>
<td>Nisha Garg, PhD</td>
<td>Microbiology &amp; Immunology</td>
<td>Mitochondrial Biomarkers of Cardiac Disease in Older Adults</td>
<td>$10,000</td>
</tr>
<tr>
<td>Roberto Garofalo, MD</td>
<td>Pediatrics</td>
<td>Oxidative Determinants of Acute Respiratory Tract Infections (ARI) in Older Adults*</td>
<td>$30,000</td>
</tr>
<tr>
<td>Amol Karmarkar, PhD</td>
<td>Rehabilitation Sciences</td>
<td>Hospital Readmission in Patients after Hip Fracture with Sarcopenia**</td>
<td>$20,000</td>
</tr>
<tr>
<td>Demidmaa Tuvdendorj, MD, PhD</td>
<td>Internal Medicine – Endocrinology</td>
<td>The Mechanism of Intramuscular Accumulation of Acyl-CoA in Aging*</td>
<td>$20,000</td>
</tr>
</tbody>
</table>

*Co-funded by the Institute for Translational Sciences
**Co-funded by the Division of Rehabilitation Sciences

Section III. Career Development

Activities and accomplishments:
The UTMB Pepper OAIC provides a vigorous program in which all RCDC scholars participate. This program includes regularly in multiple training and career development activities including:

- Attending monthly Pepper Investigators seminars
- Attending weekly Translational Research in Aging and Metabolism (TRAM) meetings
- Activities held in collaboration with the Institute for Translational Sciences (ITS) as part the ITS Career Development Program including the Translational Scholars and offers the Translational Research Scholars Program (TRSP), a biweekly series of 1-hour seminars held every other Thursday focusing on Topics in career development presented by UTMB campus faculty and senior investigators as well as external special invited speakers
- Addition of 2 new RCDC Scholars: Christopher Fry, PhD & Monique Pappadis, PhD.
- Blending of activities associated with the Rehabilitation Research Career Development (RRCD) Program designed to educate and train future rehabilitation scientists and encourage development through K12 awards.
• Continue partnerships with K12 training programs and Institute for Translational Science to support scholars (e.g., Elizabeth Lyons)

• Continue to explore opportunities to recruit clinician investigators (MSTAR, presentations and meetings with clinical chairs and division directors).

• RCDC mentors participate in activities of the UTMB Academy of Research Mentors

• Collaborated in education and training activities with AHRQ R24 grant on Patient-Centered Outcomes Research in the Elderly.

**RCDC Scholars**

a) **Current Junior Faculty Scholars being supported by RCDC:**

<table>
<thead>
<tr>
<th>Trainee</th>
<th>Mentors</th>
<th>Period of support</th>
<th>Role during support</th>
<th>Department</th>
<th>Research focus</th>
<th>Current status &amp; [Funding history]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christopher Fry, PhD</td>
<td>Papaconstantinou</td>
<td>2014- present</td>
<td>Assistant Professor</td>
<td>Nutrition &amp; Metabolism</td>
<td>Role of satellite cells in skeletal muscle plasticity</td>
<td>Assistant Professor, UTMB</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[Searle Scholar Program]</td>
</tr>
<tr>
<td>Elizabeth Jaramillo, MD</td>
<td>Goodwin</td>
<td>2013- present</td>
<td>Assistant Professor</td>
<td>Institute for Translational Sciences</td>
<td>Over-diagnosis &amp; treatment, cancer</td>
<td>Assistant Professor, UTMB</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td>[KL2]</td>
</tr>
<tr>
<td>Monique Pappadis, PhD</td>
<td>Ottenbacher</td>
<td>2015- present</td>
<td>Assistant Professor</td>
<td>Rehabilitation Sciences</td>
<td>Rehabilitation following TBI, qualitative methods</td>
<td>Assistant Professor, UTMB</td>
</tr>
</tbody>
</table>

Trainees supported by the UTMB OAIC Research Career Development Core 2000-present

<table>
<thead>
<tr>
<th>Trainee</th>
<th>Mentors</th>
<th>Period of support</th>
<th>Role during support</th>
<th>Department</th>
<th>Research focus</th>
<th>Current status &amp; Funding history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elena Volpi, MD, PhD</td>
<td>Goodwin/Wolfe</td>
<td>2000</td>
<td>Asst. Prof</td>
<td>Geriatrics</td>
<td>Nutrition and muscle metabolism</td>
<td>Professor &amp; Director, UTMB, R03, 3 R01s, S10, 2 P30s</td>
</tr>
<tr>
<td>Glenn Ostir, PhD</td>
<td>Goodwin/Markides</td>
<td>2002-2005</td>
<td>Asst. Prof</td>
<td>Epidemiology &amp; Public Health</td>
<td>Positive affect, recovery from illness</td>
<td>Professor and Chief, University Maryland, K01, 2 R01s</td>
</tr>
<tr>
<td>Name</td>
<td>Institution</td>
<td>Years</td>
<td>Position</td>
<td>Field</td>
<td>Title</td>
<td>Institution/funding</td>
</tr>
<tr>
<td>-----------------------------</td>
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</tr>
<tr>
<td>Melinda Moore, PhD</td>
<td>Wolfe/Urban</td>
<td>2000-2002</td>
<td>Post-doctoral</td>
<td>Endocrinology</td>
<td>Exercise, muscle metabolism</td>
<td>Professor, UTMB, 2 R01s</td>
</tr>
<tr>
<td>Kristen Peek, PhD</td>
<td>Ottenbacher/Markides</td>
<td>2001-2003</td>
<td>Asst. Prof</td>
<td>Prev Med &amp; Comm Health</td>
<td>Strength &amp; disability in older Hispanics</td>
<td>Professor, UTMB, R01</td>
</tr>
<tr>
<td>Lois Killewich, MD, PhD</td>
<td>Wolfe/Goodwin</td>
<td>2001-2004</td>
<td>Assoc. Prof</td>
<td>Surgery</td>
<td>Peripheral vascular and muscle function</td>
<td>Professor, UTMB, K08</td>
</tr>
<tr>
<td>Sylvette Ajala-Torres, PhD</td>
<td>Papaconstantinou/Van Houten</td>
<td>2000-2001</td>
<td>Post-doctoral</td>
<td>Biochemistry &amp; Structural Biology</td>
<td>Reactive oxygen mitochondrial function and aging</td>
<td>Assistant Prof., Univ. Central de Caribe, Puerto Rico R03,S06</td>
</tr>
<tr>
<td>Quynh Bui, MD, MPH</td>
<td>Goodwin/Markides</td>
<td>2003-2005</td>
<td>Geriatric Fellow</td>
<td>Internal Med. Geriatrics</td>
<td>Diabetes and liver function</td>
<td>Physician, Private practice, Houston, TX</td>
</tr>
<tr>
<td>Bartoz Szczesny, PhD</td>
<td>Papaconstantinou/Mitra</td>
<td>2005-2007</td>
<td>Post-doctoral</td>
<td>Biochemistry &amp; Molecular Biology</td>
<td>Age-dependent change in DNA base repair proteins</td>
<td>Assistant Professor, UTMB, R21</td>
</tr>
<tr>
<td>Elisabet Borsheim, PhD</td>
<td>Wolfe/Urban</td>
<td>2005-2008</td>
<td>Asst. Prof</td>
<td>Surgery</td>
<td>Transcapillary Insulin Transport and Aging</td>
<td>Associate Professor, U of Arkansas, R01</td>
</tr>
<tr>
<td>Mukaila Raji, MD</td>
<td>Goodwin/Markides</td>
<td>2005-2007</td>
<td>Asst. Prof</td>
<td>Internal Med. Geriatrics</td>
<td>Muscle function and cognitive process in the elderly</td>
<td>Professor and Chief, UTMB. GACA, Diversity Suppl.to R01</td>
</tr>
<tr>
<td>Hans Dreyer, PhD, PT</td>
<td>Volpi/Rasmussen</td>
<td>2006-2008</td>
<td>Asst. Prof</td>
<td>Human Physiology</td>
<td>Nutritional and Regulation of Muscle Growth</td>
<td>Associate Professor, University of Oregon, K12, K01, R01</td>
</tr>
<tr>
<td>Douglas Paddon-Jones, PhD</td>
<td>Wolfe/Goodwin</td>
<td>2006-2008</td>
<td>Asst. Prof</td>
<td>Nutrition &amp; Metabolism</td>
<td>Muscle protein catabolism during inactivity and</td>
<td>Professor, UTMB, NSBRI, R01, Abbot, Dairy Institute,</td>
</tr>
</tbody>
</table>

**P30-AG024832: 2005-2010**

- **Bartoz Szczesny, PhD**
  - Position: Asst. Prof
  - Institution: University of Oregon
  - Funding: K01, R01

- **Elisabet Borsheim, PhD**
  - Position: Asst. Prof
  - Institution: UTMB
  - Funding: K12, R01

- **Mukaila Raji, MD**
  - Position: Asst. Prof
  - Institution: UTMB
  - Funding: GACA, Diversity Suppl.to R01

- **Hans Dreyer, PhD, PT**
  - Position: Asst. Prof
  - Institution: University of Oregon
  - Funding: K12, K01, R01

- **Douglas Paddon-Jones, PhD**
  - Position: Asst. Prof
  - Institution: UTMB
  - Funding: NSBRI, R01, Abbot, Dairy Institute,
<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Years</th>
<th>Title</th>
<th>Research Area</th>
<th>Funding/Position</th>
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<tr>
<td>Felipe Amador, MD</td>
<td>Goodwin/Ottenbacher</td>
<td>2006-2007</td>
<td>Asst. Prof</td>
<td>Internal Med. Geriatrics</td>
<td>Social Factors and function ACE Unit Clinical Asst Prof, University of Colorado</td>
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<tr>
<td>Micah Drummond, PhD</td>
<td>Rasmussen/Volpi</td>
<td>2009-2011</td>
<td>Asst. Prof</td>
<td>Physical Therapy</td>
<td>MicroRNA’s and Sarcopenia Assist Professor, U of Utah, K01, AFAR, R03, R01</td>
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<tr>
<td>William Durham, PhD</td>
<td>Sheffield-Moore</td>
<td>2009-2012</td>
<td>Asst. Prof</td>
<td>Internal Med. Endocrinology</td>
<td>Changes in muscle perfusion on muscle protein metabolism. Assistant Professor, UTMB, R44</td>
</tr>
<tr>
<td>Soham Al Snih, MD, PhD</td>
<td>Ottenbacher/Markides</td>
<td>2011-2014</td>
<td>Asst. Prof</td>
<td>Rehabilitation Sciences</td>
<td>Obesity, frailty, disability, diabetes in older Mexican Americans Assistant Professor, UTMB, K12 scholar R03</td>
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<tr>
<td>Jose Barral, MD, PhD</td>
<td>Epstein/Volpi</td>
<td>2010-2013</td>
<td>Asst. Prof</td>
<td>Neuroscience &amp; cell biology</td>
<td>Chaperone function in sarcopenia Associate Professor, Assistant Dean, UTMB</td>
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<td>Steve Fisher, PT, PhD</td>
<td>Ottenbacher/Goodwin</td>
<td>2010-2013</td>
<td>Asst. Prof</td>
<td>Physical Therapy</td>
<td>Activity in hospitalized older adults Associate Professor, UTMB, K12 scholar</td>
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<tr>
<td>Elizabeth Jaramillo, MD</td>
<td>Goodwin/Riall</td>
<td>2013-present</td>
<td>Instructor/Asst. Prof</td>
<td>Geriatrics &amp; ITS</td>
<td>Over-diagnosis &amp; treatment, cancer Assistant Professor, UTMB</td>
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<tr>
<td>Michael Kinsky, MD</td>
<td>Sheffield-Moore/Urban</td>
<td>2010-2012</td>
<td>Asst. Prof</td>
<td>Anesthesiology Perioperative fluid management</td>
<td>Associate Professor, UTMB, DOD</td>
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<tr>
<td>Elizabeth Lyons, PhD</td>
<td>Volpi/Berenson; Goodwin</td>
<td>2011-present</td>
<td>Asst. Prof</td>
<td>Institute for Translational Sciences Video games and energy balance in older women</td>
<td>Assistant Professor, UTMB, K12 scholar, AHA, K07</td>
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<td>Rene Przkora, MD, PhD</td>
<td>Volpi/Ottenbacher</td>
<td>2013-2015</td>
<td>Asst. Prof</td>
<td>Anesthesiology Improving outcomes of hip replacement</td>
<td>Assistant Professor, UTMB, KL2, IARS</td>
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**P30-AG024832: 2010-Present**

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<tr>
<th>Name</th>
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<th>Years</th>
<th>Title</th>
<th>Research Area</th>
<th>Funding/Position</th>
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Section IV. Publications
Year 15 (2014-2015)


**Section V.** External Advisory Board Members Names, Institutions and Years of service

<table>
<thead>
<tr>
<th><strong>External Advisory Committee</strong></th>
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<tbody>
<tr>
<td><strong>Neil Alexander, MD,</strong> University of Michigan - 8 years of service</td>
</tr>
<tr>
<td><strong>Stephen B. Kritchevsky, PhD,</strong> Wake Forest – 4 years of service</td>
</tr>
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Minority Research:

Markides, Kyriakos (PESC Co-Leader): Continues to work on as Principal Investigator of the Hispanic EPESE (Established Population for the Epidemiological Study of the Elderly)

Pappadis, Monique (RCDC Scholar): Qualitative analysis of the perceptions of African-American women over the age of 70 regarding when to stop breast cancer screening

Volpi, Elena (Principal Investigator, CR-RC1 Core Leader): Minority recruiting site Principal Investigator for the ASPREE clinical trial

Wong, Rebeca (RCDC Co-Leader): Principal Investigator of the following NIA grants:
   1) The Mexican Health and Aging Study II (MHAS)
   2) Health of Older Minorities Training Grant
   3) Dynamic of Economic Well-Being and Health in a Rapidly-Aging Developing Economy: the Case of Mexico
Recognition and Awards:

**Fry, Christopher (RCDC Scholar):** Accepted to the National Institutes for Aging Buck Institute 2015 Annual Summer Training Course in Aging

**Markides, Kyriakos (PESC Co-Leader):** Recipient of the 2015 Robert W. Kleemeier Award

**Volpi, Elena (Principal Investigator, CR-RC1 Core Leader):** Selected as the Chairperson of the Aging Systems and Geriatrics Study Section of the NIH
I. Description of Center

The Wake Forest University Claude D. Pepper Older Americans Independence Center (OAIC) was established in 1991. The Wake Forest University OAIC consists of twenty-eight faculty members from twelve departments (Internal Medicine, Biomedical Engineering, Cardiology, Human Genomics, Infectious Disease, Molecular Medicine, Neurology, Pathology, Public Health Sciences, Physiology/Pharmacology, Surgical Sciences and Health & Exercise Sciences at Wake Forest University).

Over the past twenty-three years, we have developed specific competencies to advance our mission to assess risk factors for physical disability in older adults, develop and test effective prevention therapies, and train new leaders in research on aging and disability. We propose to utilize the new findings and subsequent hypotheses generated during this cycle to extend our current skeletal muscle-based disability model to integrate adipose tissue mass and distribution into multiple disability-related pathways according to the theme: Integrating pathways affecting physical function for new approaches to disability prevention.

The leading research hypotheses are the following:

1. Discover new common pathways contributing to age-related declines in physical function and disability;
2. Develop, evaluate and refine strategies for disability treatment and prevention;
3. Translate proven strategies beyond the traditional academic research environment; and
4. Train the next generation of research leaders focused on disability treatment and prevention.

The operational objectives are the following:

- To provide the investigators, infrastructure, environment, and services necessary to support the accomplishment of the above-mentioned research and educational objectives.

To address these objectives our OAIC is composed of seven cores, which currently supports 6 junior investigators, 15 clinical studies (all which are funded by the NIH), 2 research development projects, and 7 pilot studies.

II. Research, Resources and Activities

A. Cores

Leadership and Administrative Core (LAC)
Stephen Kritchevsky, PhD 336/713-8548
Dalane Kitzman, MD 336/716-3274

The Leadership and Administrative Core is responsible for scientific leadership, strategic planning, organization, administrative operations, review, evaluation, tracking and monitoring of the OAIC research and training program. It is supported by the OAIC Executive Committee, the Joint Scientific Review Panel, and the External Advisory Committee. The core communicates with other OAICs and the NIA and fosters collaborations with other OAICs including UTMB, University of Maryland and Duke. Maintains the OAIC web-based tracking and monitoring system and promotes the use of uniform assessment batteries in all OAIC
The Research Career Development Core (RCDC) seeks to promote and augment the development of future research leaders in the area of focus of this OAIC application, i.e., a muscular approach to disability and its prevention. The core emphasizes development of skills for translating basic findings into clinical research, and clinical findings into basic research. Resources of this core are integrated with other sources for career support, such as NIH and other source career development and research awards. It employs structured education and a formal mentoring process for junior faculty, who are stringently selected to join the core. To date, 43 junior faculty members have been supported.

The current junior faculty members are:

Anthony Molina, PhD amolina@wakehealth.edu
Assistant Professor, Department of Internal Medicine, Geriatrics

D. Clark Files, MD dfiles@wakehealth.edu
Assistant Professor, Infectious Diseases

Tan Zhang, MD, PhD tzhang@wakehealth.edu
Assistant Professor, Gerontology and Geriatric Medicine

Snezana Petrovic, MD, PhD snpetrov@wakehealth.edu
Assistant Professor, Phys Pharm / Internal Med Nephrology

Kristen Beavers, PhD kbeavers@wakehealth.edu
Assistant Professor, Gerontology and Geriatric Medicine

Kathryn Callahan, MD kcallahan@wakehealth.edu
Assistant Professor, Gerontology and Geriatric Medicine, (Emerging Scholar)

The pilot and exploratory studies core supports research to acquire information needed to select or design future crucial studies in the OAIC areas of focus. Over the past 20 years, through support from the OAIC grants, Wake Forest University has been very active in efforts to enhance aging related research activities. These activities have focused on the mechanism, treatment and outcomes associated with functional decline and disability and have had a profound impact on the research culture at our institution with greater awareness and interest in addressing these important yet understudied issues of geriatric research. We have initiated 82 aging pilot projects and exploratory studies during the previous 20 years of OAIC funding.

The Clinical Research Core provides infrastructure and investigators for conducting research in human subjects, including controlled trials, observational studies, pilot projects, and research development studies in externally supported studies, research development projects and pilot studies. The primary goal of the Clinical Research Core...
Core is to test innovative hypotheses aimed at the prevention of physical disability, primarily by targeting the skeletal muscle. This core performs and develops physical and behavioral function assessments, and conducts pharmacological and behavioral intervention studies. This core currently supports 10 independently funded studies, 1 RCDC junior faculty project, and 3 Pilot and Exploratory Study projects.

**Biostatistics and Research Information Systems Core (BIC)**

Michael Miller, PhD 336/716-6837
Edward Ip, PhD 336/713-9833

The Biostatistics and Research Information Systems core supports all research activities in the planning, implementation and analytical phases, and develops novel analytical methodologies. This Core devises analytical strategies, which take advantage of the uniform measures of physical function, biomarkers and body composition assessed across all OAIC studies. This core will also provide assistance with methodological, statistical, quality control and computational issues, including study design, data collection, computer networking, database management, data analysis, and presentation of results for publication.

**Integrative Biology Core (IBC)**

Barbara Nicklas, PhD 336/713-8504
Osvaldo Delbono, PhD 336/713-8504

The Integrative Biology Core supports the measurement of biomarkers and genetic variation related to adiposity, sarcopenia, physical function and disability. This core supports "reverse translation" through techniques to identify the mechanistic bases of novel clinical and epidemiological findings. During the period of funding, the Core primarily focused on inflammatory processes and muscle metabolism. The markers of interest included those with direct anabolic or catabolic effects on skeletal muscle, and those that may indirectly affect physical disability through incident diseases. The Core provided laboratory space, trained personnel, consultative and collaborative scientific expertise, and a wide spectrum of established methodologies (enzyme-linked immunosorbent assays, radioimmunoassays, an automated continuous random-access immunoassay system, and high-throughput detection of DNA variability and nucleotide sequence) to assess a uniform battery of biological and genetic factors in several research protocols. Data analyses and publication of the findings is on-going.

**Bioimaging Resource Core (BIRC)**

Greg Hundley, MD 336/716-0607

The Bioimaging Resource Core supports the use of DXA, CT, MRI and PET to document body composition and to obtain functional measures relevant to disability pathways, and develops and supports studies that use imaging technology to enhance the translational research opportunities available through the use of imaging. This core supports independently funded studies, pilot studies, and research development studies in the accurate *in vivo* measurement of body composition, specifically focusing on skeletal muscle mass and composition, fat mass and distribution, and bone mineral density. This core collaborates with other OAIC cores in the development of new, multidisciplinary, and translation research projects directed at elucidating the etiology, consequences, prevention and treatment of sarcopenia and its sequelae.

**B. Research:**

**Pepper Supported Independently Funded Studies**

**Current during this cycle:**

**Project 1.**

**Project Title:** Study of the Effects of Caloric Restriction and Exercise Training (SECRET 2)
**Leader:** Dalane Kitzman, MD
**Professor, Department of Internal Medicine Section on Cardiology**
**NIA 2R01 AG018915 / 2015-2020**
The primary aim of the study is to conduct a randomized, controlled, single-blinded, 2x2 design trial to examine weight loss via caloric restriction, aerobic exercise training, a combination of caloric restriction and exercise training, and attention control in 100 patients with heart failure and normal ejection fraction (HFNEF) and body mass index >30 in order to test the following hypotheses: 1) Both weight loss and exercise training will improve exercise intolerance and quality of life in older, obese patients with HFNEF. 2) Weight loss and exercise training combined will produce complementary effects on body and thigh muscle composition and additive improvements in exercise intolerance in patients with HFNEF. 3) Improvements in exercise tolerance will correlate with improvements in lean body mass, reversal of adverse thigh muscle remodeling, and increased thigh muscle capillarity.

Following baseline assessments, 100 patients with HFNEF aged > 60 years will be randomly assigned to 1 of the 4 arms: aerobic exercise training; caloric restriction; combined aerobic exercise training and caloric restriction; or attention control. Outcomes assessments will be performed at baseline and following the 20-week intervention. The primary outcomes will be peak exercise oxygen consumption (VO2peak) by expired gas analysis during graded treadmill exercise to exhaustion and quality of life by the Minnesota Living with Heart Failure Questionnaire (MLFH). Secondary, mechanistic outcomes, will include: total and regional lean and fat mass by DEXA; thigh skeletal muscle / intramuscular fat (SM/IMF) by MRI; skeletal muscle capillarity ratio, fiber type, and enzyme activity, on samples obtained by vastus lateralis needle biopsy; and circulating IL-6, CRP, and adiponectin. Personnel performing outcomes assessments will be blinded to treatment group. Clinical status, weight, and function will be checked at 12 month follow-up.

LAC supports this study as Dr. Kitzman is the PI. CRC will perform the standard battery of physical performance assessments for the follow up visits. BIC is supporting the collection and data entry of the core battery data into the common database. IBC is collecting blood and muscle for storage into the biospecimen repository. The core will also perform measures of mitochondrial quality control. BRC is supporting the acquisition and storage of DEXA and MRI scans.

Study Status: Protocol development underway.

Project 2.
Project Title: Early Supported Discharge for Improving Functional Outcomes After Stroke
Leader: Pamela Duncan, PhD, PT
Professor, Department of Neurology
PCS-11403-14531 / 2015-2020
We are planning a randomized trial of 50 North Carolina hospitals, in partnership with the North Carolina Stroke Care Collaborative (NCSCC) registry, to compare approaches to care for stroke patients. We are asking whether Comprehensive Post-Acute Stroke Services (COMPASS), which combines transitional care and early supported discharge for stroke patients who go home directly from the hospital, improves patients’ daily function compared with usual care. We will also consider caregiver strain, hospital readmission rates, and mortality, use of health care, consistency of physician care, use of transitional care services, and death. We will also compare outcomes in some subgroups (race, sex, age, stroke severity, and insured versus uninsured). Participating hospitals will be assigned randomly to receive COMPASS or usual care. Phase 1 compares COMPASS with usual care. In Phase 2, the usual-care hospitals will also receive COMPASS, while the other hospitals continue the intervention. In addition to COMPASS, which combines Medicare-approved transitional care services from advanced practice providers (APPs; nurse practitioners or physician assistants) and early supported discharge services coordinated by the APPs, our intervention includes a community coordinator, who will work with local organizations to improve services for stroke survivors and their caregivers, and a stroke scorecard report, so hospital and primary care providers can see how they are doing in improving care for patients after a stroke. Together with the patient and caregiver, the APPs will develop an individualized care plan for each patient. Trained post-acute-care coordinators will help organize community groups to improve and continue care for recovering stroke patients.

We will assess 90-day and 1-year health outcomes. The primary outcome of our study is function as reported by the patients. Secondary outcomes at 90 days include caregiver stress, all-cause readmissions 30 and 90 days after discharge (assessed via insurance data), cognitive status, taking medicines as needed, blood pressure
control, depression, continuity of care, and use of community resources. One year after stroke, outcomes will include death, recurrent stroke, utilization of transitional care management billing codes, proportion of patients re-hospitalized within 7 or 14 days after their first stroke hospitalization, physician follow-up, and use of health care.

Our Patient and Stakeholder Engagement Committee will work with our community coalitions to advise and support the implementation of COMPASS, provide feedback to the researchers, and recommend ways to continue COMPASS in the future. These coalitions will help us tell others about the COMPASS results and (if merited) how to begin similar programs across the United States to improve life for stroke survivors and their caregivers.

CRC is providing intellectual support and training on the assessments.

Study Status: Protocol development is underway.

Project 3.
Project Title: REHAB-HF: A Trial of Rehabilitation Therapy in Older Acute Heart Failure Patients
Leader: Dalane Kitzman, MD, Professor, Department of Internal Medicine Section on Cardiology
R01 AG045551 / 2014-2019

Acute decompensated heart failure (ADHF) is the leading cause of hospitalizations in older persons, which markedly worsen quality-of-life, increase mortality and health care costs, and have been declared a national priority by CMS. However, current management strategies have had only modest impact on rehospitalizations for ADHF, and recent trials have been negative, suggesting a need for a new approach. Multiple lines of evidence suggest that severe impairments in physical function strongly contribute to adverse outcomes in older ADHF patients. Even when stable and well-compensated, older patients with chronic HF have severe impairments in physical function, which markedly worsen as they transition to ADHF. These are further exacerbated by hospital-related factors, including forced bed rest. After discharge, patients continue to have marked impairments in strength, balance, mobility, and endurance. Most patients meet formal definitions of frailty, and some never recover baseline function. This occurs during the highest risk period for early rehospitalization and adverse outcomes. We hypothesize that this cascade of events resulting in persistent, severe physical dysfunction contributes to the high rates of rehospitalization in older HF patients. However, current HF management paradigms do not address the marked impairments in physical function, and neither chronic nor acute HF are approved indications for cardiac rehabilitation. Furthermore, exercise training trials have excluded ADHF, and have also not included the domains of balance, strength and mobility which are important for preventing injuries in frail, older patients. To address this critical evidence gap, we developed a novel, tailored, progressive, multidisciplinary 12-week rehabilitation intervention beginning during hospitalization and designed to address the specific deficits in physical function of older ADHF patients. In our pilot study, this intervention was safe and produced a 17.9% improvement in the Short Physical Performance Battery (SPPB) score and a 29.3% reduction in all-cause rehospitalizations. The change in the SPPB score explained 90% of the reduction in all-cause rehospitalizations. The primary aim of the proposed study (REHAB-HF) is to conduct a multi-center, randomized, controlled, single-blind trial in 360 older patients with ADHF to test the primary specific hypothesis that the REHAB-HF intervention will improve physical function, as measured by the SPPB. The secondary aim is to collect clinical outcomes data during 6-month follow-up to test the hypothesis that the REHAB-HF intervention group will have a reduced 6-month all-cause rehospitalization rate. The investigators are a cohesive, highly experienced multidisciplinary team from three well-established sites. By testing a novel intervention supported by multiple levels of evidence, the REHAB-HF trial will address a critical evidence gap in the care of older patients with ADHF, the most common Medicare discharge diagnosis. The REHAB-HF results could shift clinical management paradigms, improve function, reduce costs, and change health care policy for the 1 million older patients per year with hospitalized ADHF.

LAC supports this study as Dr. Kitzman is the PI.

CRC will perform the standard battery of physical performance assessments for the follow up visits. BIC is supporting the collection and data entry of the core battery data into the common database.

Study Status: Recruitment and intervention are ongoing.
Project 4.
**Project Title: Epigenetic Roles in Regulation of Cholesterol Metabolism and CVD Risk**
**Leader: Yongmei Liu, PhD**
**Associate Professor, Department of Epidemiology and Prevention**
**R01 HL126477 / 2014-2018**

Several lines of experimental evidence indicate that disruption of certain aspects of intra-cellular cholesterol homeostasis in various cell types (e.g. macrophage, ß-cell) can lead to pathological processes preceding type 2 diabetes mellitus (T2DM) and atherosclerotic vascular disease (ASCVD). Our recent transcriptomic study of purified human monocytes corroborates these findings, and specifically identifies a co-expressed cholesterol metabolism transcriptional network (CMTN) whose alteration is significantly associated with T2DM and coronary artery calcification (CAC, a subclinical ASCVD measure). This network includes 11 genes involved in coordinated up-regulation of cholesterol uptake and synthesis, and down-regulation of cholesterol efflux - a molecular profile expected to increase intracellular cholesterol. To translate these intriguing observations into meaningful improvements in human health, our goal is to comprehensively characterize the epigenetic regulators of this network of genes in human monocytes, and to investigate how this network and its regulatory factors relate to intra-cellular cholesterol in the monocytes and to the development of T2DM and ASCVD. Our principle focus will be on epigenetic regulation of this network by microRNAs (miRNAs). It is already well established via in vitro and animal models that one specific miRNA (miR-33) plays a critical role in cholesterol homeostasis in concert with its co-transcribed host gene, SREBP2. Our pilot data from 373 human monocyte samples indicate that intra-cellular levels of miR-33a is associated with expression of the entire gene network of interest in this proposal and with prevalent T2DM in the cell donors. We also identified several other promising miRNA candidates associated with expression of the gene network. Based on these preliminary data, and taking advantage of the well-phenotyped Multi-Ethnic Study of Atherosclerosis (MESA) cohort with existing genomic data, DNA methylomic and transcriptomic data on 1,264 monocyte samples, and miRNA sequencing data in a subset of 373 monocyte samples, we now proposes to additionally quantify miRNAs in the remaining 891 monocyte samples using next generation sequencing to achieve the following specific aims: 1) To characterize the relationship between miRNAs and the CMTN in 1,264 MESA monocyte samples; 2) To establish the association of miRNAs with T2DM and CAC in the 1,264 MESA participants; 3) To replicate miRNA associations with the most compelling evidence in an independent set of 562 MESA participants; and 4) To validate the functional consequences of the CMTN alterations and associated-miRNAs, using ex-vivo cultured human monocytes. The integration of genetic, epigenetic, transcriptional, and clinical data along with the ex-vivo experimental studies may provide novel mechanistic insights concerning the regulation of cholesterol metabolism and susceptibility to T2DM and ASCVD and lead to new strategies for prevention and treatment of T2DM and ASCVD.

**IBC** is providing intellectual support.

**Study Status:** Analyses are underway.

Project 5.
**Project Title: Tropin T and Excitation-Contraction Coupling in Aging Skeletal Muscle**
**Leader: Osvaldo Delbono, MD, PhD, Professor, Dept of Internal Medicine Section on Gerontology and Geriatric Medicine**
**R01 AG013934 / 2013-2018**

In aging rodents and humans, decreased muscle mass does not fully account for the decrease in strength, indicating that atrophy only partially explains muscle weakness. Publications from our laboratory and others support the concept that aging impairs muscle activation-contraction efficiency. Altered transmittal of membrane depolarization to SR Ca2+ release decreases specific force in a process termed excitation contraction uncoupling (ECU). Previous works from our laboratory identified the mouse specific Cav1.1 subunit gene 5’-flanking sequences necessary for basal transcription and control of Cav1.1 expression. However, the mechanism leading to impaired Cav1.1 transcription with aging and its treatment is unknown. Troponin T (TnT) is known to mediate the interaction between the Tn complex and tropomyosin (Tm) in the myoplasm, which is essential for calcium-activated striated muscle contraction. We have preliminary evidence of a nontraditional role for...
TnT3, the TnT isoform expressed in fast-twitch muscle fibers. We found full-length (FL)-TnT3 and its fragments in both the nuclear and cytosolic fractions of myofibers isolated from mouse skeletal muscle. More important, the myonuclei from old FVB mice had less of the full-length protein and more of the COOH-terminal (CT) fragment than those of young mice. When we knocked down endogenous TnT3 by shRNA in muscle in vivo, the calcium channel \( \alpha_1 \) subunit, essential molecule for muscle contraction, was downregulated at both the RNA and protein levels. The following specific aims will test the hypotheses that: (1) TnT3 regulates voltage-gated Ca\(^{2+} \) channel \( \alpha_1 \) subunit (Cav1.1) expression in fast adult myofibers, and (2) decreased nuclear FL-TnT3 and increased CT-TnT3 fraction result in decreased Cacna1 expression and impaired excitation-contraction coupling with aging. These hypotheses will be tested by the following specific aims. (1) To establish that TnT3 regulates Cav1.1 expression and excitation-contraction coupling. (2) To determine that TnT3 is enzymatically cleaved in aging skeletal muscle and (3) To determine whether inhibiting skeletal muscle \( \mu \)-calpain prevents age-dependent increase in TnT3 fragmentation and reduced Cacna1 expression and sarcoplasmic reticulum Ca\(^{2+} \) release. The proposed studies will define a novel role for TnT3 as a regulator of Cav1.1 and a tool to ameliorate or prevent muscle weakness with aging.

IBC ELISA measures of fTnT and sTnT will be validated by the IBC and their role in aging-related loss of muscle function and their response to exercise will be examined in stored samples.

**Study Status:** Analyses are underway.

**Project 6.**
**Project Title:** Exploring VItamin D’s Effects on NeuromusCular Endpoints Study (EVIDENCE Study)
**Leader:** Denise Houston, PhD, RD
**Associate Professor, Dept of Internal Medicine**
**Section on Gerontology and Geriatric Medicine**
**R01 AG042411 / 2013-2018**
Growing evidence indicates that vitamin D’s effect on reducing falls is mediated by improvements in neuromuscular function. We and others have shown associations between 25(OH)D concentrations and muscle strength and physical performance measures associated with fall risk (e.g., gait, balance) in observational studies. Yet trials of vitamin D supplementation on changes in muscle strength and physical performance are equivocal, likely due to inadequate trial duration, small sample sizes, insufficient vitamin D dose, and sample heterogeneity. Moreover, vitamin D’s effects on the mechanisms underlying neuromuscular function are not well understood. Determining whether increasing 25(OH)D concentrations to \( \geq 30 \) ng/mL will improve neuromuscular deficits that are risk factors for falls and elucidating the underlying physiological mechanisms linking vitamin D and neuromuscular function could change clinical practice by providing evidence to guide vitamin D supplementation recommendations for neuromuscular-related outcomes in older adults. We plan to conduct a 12-month, double-blind randomized placebo controlled trial in 200 older (65-89 yrs) men and women with initial 25(OH)D concentrations of 20-<30 ng/mL to determine the effect of vitamin D3 supplementation on 1) change in neuromuscular functions that are established risk-factors for falls in older adults; and 2) changes in the underlying physiological mechanisms over 4 months in a subset of up to 66 randomly selected participants. Participants will be randomized to 2000 IU/d of vitamin D3 or placebo. Lower extremity muscle strength and power, physical performance, and postural sway will be assessed at baseline, 4 months and 12 months and falls assessed monthly. Muscle biopsies of the vastus lateralis will be taken at baseline and 4 months to assess muscle fiber type, contractility, and denervation, and number and differentiation stage of satellite cells.

**RCDC** supports this study as Dr. Houston is the PI and Dr Molina (RCDC fellow) has a pilot project as an ancillary to this study.
**CRC** will perform the standard battery of physical performance assessments for the visits.
**BIC** is supporting the collection and data entry of the core battery data into the common database.
**IBC** is collecting blood and muscle for storage into the biospecimen repository.

**Study Status:** Recruitment and intervention is ongoing.

**Project 7.**
**Project Title:** Cooperative Lifestyle Intervention Program (CLIP) II
**Leaders:** Jack Rejeski, PhD and Anthony Marsh, PhD, Professors, Health and Exercise Sciences, WFU
We recently completed a successful translational study funded by NHLBI, the Cooperative Lifestyle Intervention Program (CLIP), an intervention co-delivered with agents from three North Carolina Cooperative Extension county centers. In this investigation, 288 obese, older adults with CVD or MetS were randomized to a successful aging control treatment (SA), aerobic exercise training (AT), or AT+ diet-induced weight loss (WL) for 18-months. Building on the CLIP experience, we now propose to have community partners deliver a similar program with our staff serving as trainers and advisers for healthful behavior change. In addition, this study will provide the first large scale randomized controlled clinical trial to evaluate the effects of WL on mobility in obese, older adults with CVD or the MetS as compared to WL combined with physical activity. The primary outcomes will be the 400M walk test and muscle strength. Because uncertainty exists about the best approach for promoting WL in older adults due to concerns with the loss of lean mass, the design will also permit a contrast between AT+WL and resistance exercise training (RT)+WL on muscle strength while targeting a protein intake of 0.8 g·kg body mass⁻¹·d⁻¹. To accomplish our goals, we have created a community partnership with the YMCA using 4 sites in Forsyth County, NC instead of the Cooperative Extension centers because the latter have neither the equipment nor the personnel necessary to independently train and monitor RT or AT. We will recruit 252 older (60-79 yrs), obese adults who either have CVD or MetS who will be randomized into one of three interventions: WL alone, AT+WL or RT+WL. Participants in AT+WL or RT+WL will exercise 4 times per week. The dual primary outcomes for this study will be changes in mobility disability and strength using both the 400 m Walk and knee extensor strength tests. The secondary aims include stair-climb time, body composition, changes in CVD risk factors including blood lipids, high sensitivity C-reactive protein, IL-6, fasting glucose, and resting blood pressure; disease-specific and health-related quality of life (HRQL), and self-reported physical function.

CRC trained the staff and oversees the physical performance testing and core battery
BIC is supporting the collection and data entry of the core battery data into the common database.
BRC is supporting the acquisition of DEXA scans.
IBC is collecting blood for storage into the biospecimen repository.

Study Status: Recruitment is complete and intervention and follow up continues.

Project 8.
Project: Northwest Triad Care Transitions Program (NTCTP)
Leader: Pamela Duncan, PhD, Professor; Neurology
Centers for Medicare and Medicaid Services, OMB No. 0938-1124 / 2012-2017
Northwest Triad Care Transitions Community leaders propose the expansion of Forsyth Medical Center’s Hospital to Home Program for Medicare fee-for-service patients who have heart failure, pneumonia, or heart attack. The goal of this program is to reduce re-hospitalization in high risk patients. The program will involve 1000 patients who will receive 1) examination by a patient navigator who provides both hospital and home visits, teaches proper self-management by the participant and family on medical issues, arranges for non-reimbursable in-home care services such as transportation, housekeeping, laundry and light meal preparation, and connects the participant to appropriate community resources for expanded supports to remain safe at home; 2) short-term funds for immediate home care services; and 3) enhanced communication and collaboration with community agencies that provide longer term senior services.

Project 9.
Project Title: Strength Training for ARthritis Trial (START)
Leader: Steve Messier, PhD, Professor, Health and Exercise Sciences, WFU
R01 AR059105 / 2011-2016
This is an 18-month, high-intensity strength-training intervention for older adults with knee OA, focused on improving thigh composition. We hypothesize that in addition to short-term clinical benefits, combining greater duration with high intensity will alter thigh composition sufficiently to attain long-term changes in knee-joint forces, decrease inflammation, lower pain levels, and slow progression.
Participants (age ≥ 55 yrs; BMI ≥ 25 kg/m2 and ≤ 40 kg/m2) will be randomized to one of 3 groups: high-intensity strength training (75-90% 1RM); low-intensity strength training (30-40% 1RM); or attention control. The study sample will consist of 372 ambulatory, community-dwelling persons with: (1) mild-to-moderate medial tibiofemoral OA (KL = 2-3); (2) knee varus malalignment (varus angle ≥ 2 degrees and ≤ 10 degrees); and (3) no participation in a formal strength-training program for more than 30 minutes per week within the past 6 months. The primary clinical aim is to compare the interventions’ effects on knee pain, and the primary mechanistic aim is to compare their effects on knee-joint compressive forces during walking, a mechanism that affects the OA disease pathway. Secondary aims will compare intervention effects on additional clinical measures of disease severity; disease progression, measured by MRI; thigh muscle and fat volume, measured by CT; components of thigh muscle function, including hip abductor strength and quadriceps strength, power, and proprioception; additional measures of knee-joint loading; and inflammatory and OA biomarkers.

CRC is training the staff and overseeing the physical performance testing and core battery and will also assist with recruitment.

BIC is supporting the collection and data entry of the core battery data into the common database.

BRC is supporting the acquisition, image analysis, and storage of DEXA and CT scans.

IBC is collecting blood for storage into the biospecimen repository.

Study Status: Recruitment and intervention is ongoing.

Project 10.

Project Title: Prosocial Behavior and Volunteerism to Promote Physical Activity in Older Adults (PACE)
Leader: Capri Foy PhD, Assistant Professor, Department of Social Sciences and Health Policy
R01HL109429-01 / 2011-2016

This is a randomized controlled trial to assess the effect of a physical activity intervention that incorporates prosocial behavior upon physical activity at 12 months post-randomization as compared to a healthy aging education program. We will randomize 300 participants, aged 55 to 80 years, into either a prosocial behavior physical activity (PBPA; n=150), or a healthy aging (HA; n=150) intervention. Our primary aim is to determine the efficacy of the PBPA and HA interventions on physical activity at 12 months in men and women aged 55 to 80 years. We will also determine the impact of the two interventions upon physical function and HRQL. In this project, we will continue our successful collaborations from our previous pilot project with the William G. White Family YMCA and Lowe’s Foods. In addition, we will use both qualitative and quantitative approaches in our development and implementation of the PBPA intervention. The PBPA intervention itself is based upon Social Cognitive Theory, a well-established theory of behavioral change. If successful, this study may suggest that prosocial behavior is associated with constructs in Social Cognitive Theory, which would be a novel finding. Moreover, this intervention may have public health significance, and could serve as a model for dissemination across the country to enhance physical activity, physical and psychological wellness, and social benefit.

CRC is training the staff and overseeing the physical performance testing and core battery and assisting with recruitment.

Study Status: Recruitment and intervention continues.

Project 11.

Project Title: Minimizing Physical Function Decline in Older Adults Receiving Chemotherapy (PA AML)
Leader: Heidi Klepin, MD, Assistant Professor, Hematology/ Oncology
K23 AG038361/ 2011-2013

The focus of this research project is to develop a tailored physical activity program during cancer treatment to maximize functional independence for older cancer survivors with acute myelogenous leukemia. The objectives are to 1) evaluate the feasibility of conducting a symptom-adapted, randomized behavioral intervention designed to improve physical function in older adults receiving chemotherapy for AML; estimate the effect size of the physical activity intervention on change in an objective measure of physical function, SPPB (short physical performance battery); 3) estimate the effects of the physical activity intervention on self-reported physical function, health-related quality of life, and symptoms (depression, distress, fatigue).
Patients will be recruited for participation and administered informed consent within 4 days of hospital admission. Subjects will undergo a baseline assessment performed by the SN, and then will be randomized to the physical activity protocol or usual care in a 1:1 ratio. For those in the physical activity group, sessions will be offered 5 days per week (adherence is defined as participation in an average of 3 or more offered weekly sessions). Each session will be tailored to the patient's daily condition to maximize participation and benefit. Participants randomized to physical activity will also receive a 20-30 minute lifestyle counseling session weekly during hospitalization with post-discharge phone follow-up. Participants in the control group will receive usual care, which may include physical therapy (PT) at the discretion of the attending physician. Assessments will be done weekly in each group until discharge.

**Study status:** Recruitment is complete and follow up continues.

**Project 12.**
**Project Title:** Systolic Blood Pressure Intervention Trial (SPRINT HEART)
**Leader:** Dalane Kitzman, MD
**Professor, Department of Internal Medicine Section on Cardiology**
**NIH R01 HL107257/ 2010-2015**
The parent trial to this proposed ancillary study is an NHLBI-funded two-arm, multicenter, randomized clinical trial designed to determine whether intensive systolic BP reduction to a lower goal than currently recommended will reduce CV risk. SPRINT-HEART is proposed as a prospective ancillary study to SPRINT. A protocol-specific cardiac magnetic resonance imaging (CMR) and echocardiographic exam will be performed at baseline and at 18-month follow-up. A total of 340 participants will be recruited from among 800 SPRINT enrollees at 5 clinics in the Southeastern (SE) Clinical Network. Recruitment of CKD patients will be capped at 45%, equal to SPRINT.

We will use established operational protocols for communication, coordination, and patient flow that were successful in ACCORD-MIND and have been reported. After completing a checklist verifying absence of contraindications to MRI, written, informed consent will be obtained at the clinic during the same time as for the parent study. The baseline CMR exam visit will be performed at the WFUSM CMR suite within 7-10 days of the regular SPRINT study baseline clinic visit. The 18-month follow-up CMR exam will likewise be performed in-line with the regular 18-month SPRINT clinic visit, which is a key ‘milestone’ visit for SPRINT.

**CRC** is training the staff and overseeing the physical performance testing.

**BRC** is supporting the acquisition, storage, and analysis of MRI scans.

**Study Status:** The 18 month follow up scans are complete and data analysis is underway.

**Project 13.**
**Project Title:** Cardiac Imaging of Thoracic Fat and Aortic Stiffness in older High Risk Patients
**Leader:** Tina Brinkley, PhD Dept of Internal Medicine, Section on Gerontology and Geriatric Medicine
**K01 AG033652/ 2010-2015**
Recent evidence highlights the potentially detrimental effects of localized fat depots on cardiovascular health. PCAT and PVAT are in close proximity to the heart and aorta and likely have local effects on the myocardium and vasculature. However, no studies have specifically examined the relationship of these fat depots with either aortic stiffness or risk for cardiac events. Evaluating the cross-sectional and longitudinal associations between PCAT and PVAT and aortic stiffness and future cardiac events, respectively, is necessary to determine the importance of these localized fat depots in assessing obesity-related CVD risk. As such, this study can potentially have a significant public health impact, as it will help to refine the relationship between obesity and CVD risk by determining the relative importance of various visceral fat depots in older high risk patients. Ultimately, our results could advance the clinical treatment of obesity and help to reduce the morbidity, mortality, and health care costs associated with obesity-related CVD. This will be an ancillary study to the Vascular Stiffness and Pulmonary Congestion (PREDICT) Study. The primary and secondary aims of the parent study are to determine if dobutamine stress-induced changes in aortic stiffness independently predicts the
future occurrence of flash pulmonary edema warranting hospital admission, and whether the predictive ability of changes in aortic stiffness is independent of changes in LV stroke volume reserve. PREDICT is currently in the process of enrolling 600 participants and obtaining MRI scans for the assessment of aortic stiffness and various measures of cardiac function, as well as follow-up data on the future occurrence of cardiac events, including pulmonary edema, myocardial infarction, and cardiac death. This ancillary study will measure PCAT and PVAT from existing scans and circulating adiponectin and insulin in stored blood samples.

RCDC supported Dr. Brinkley as an RCDC scholar.
IBC is supporting the collection in the PREDICT study and will be performing adiponectin and insulin measures on the stored samples.
BRC is supporting this project and Dr. Brinkley by assisting in the training of analyzing the MRIs.

Study Status: Completed most of the quantification of pericardial and periaortic fat on the MRIs.

Project 14.
Project Title: Lifestyle Interventions and Independence for Elders (LIFE)
Leader: Stephen Kritchevsky, PhD, Professor, Dept of Internal Medicine, Section on Gerontology and Geriatric Medicine
U01 AG022376 /2010-2016

Based upon promising results from a pilot study among 424 sedentary older adults who were randomized to a physical activity intervention or a successful aging health education intervention, a Phase 3 multi-center randomized controlled trial is being conducted to compare a moderate-intensity physical activity program to a successful aging health education program in 1,600 sedentary older adults who are followed for an average of 2.7 years. The primary aim is to assess the long-term effects of the proposed interventions on the primary outcome of major mobility disability, defined as inability to walk 400 m. Secondary aims focus on assessing the relative effects of the interventions on the following outcomes: cognitive function; serious fall injuries; persistent mobility disability; the combined outcome of major mobility disability or death; disability in activities of daily living; cardiovascular and pulmonary events; and cost-effectiveness. Tertiary aims relate to assessing the relative effects of the interventions on (a) the combined outcome of mild cognitive impairment or dementia and (b) physical performance within pre-specified subgroups defined on the basis of race, gender and baseline physical performance. The proposed trial will provide definitive evidence regarding whether lifestyle modification interventions are effective and practical for preventing major mobility disability. Eight sites around the country participate in the LIFE study. Wake Forest University Health Sciences will serve as a Field Center for the overall Lifestyle Interventions and Independence for Elders (LIFE) study. We will track, assess, and deliver the LIFE study intervention to participants enrolled at our sites. The investigators and staff will participate in study management activities such as conference calls and site visits as required.

LAC supports this study as Dr. Kritchevsky is the PI.
CRC will perform the standard battery of physical performance assessments for the follow up visits.
BIC is supporting the collection and data entry of the core battery data into the common database.
IBC is collecting blood for storage into the biospecimen repository.

Study Status: Recruitment and intervention is complete.

Project 15.
Project Title: Exceptional Survival: Trajectories to Functional Aging (CHS Allstars)
Leader: Stephen Kritchevsky, PhD, Dept of Internal Medicine Section on Gerontology and Geriatric Medicine
R01 AG023629/ 2009-2016

The Functional Aging Study is an ancillary study of the Cardiovascular Health Study (CHS). CHS began in 1988 as longitudinal, observational, population-based study of the onset, progression, and course of heart disease and stroke in the elderly. Specifically, CHS was designed to address four main issues: 1) the majority of morbidity and mortality from cardiovascular disease occurs in the elderly; 2) this age group is growing in both absolute and proportional terms; 3) the characteristics, treatment, and course of cardiovascular disease may differ with increasing age; and 4) little information has been collected to date in this age group. Furthermore,
because asymptomatic atherosclerosis is common in this age group (arbitrarily defined here as age 65 and older), the study will be able to investigate factors precipitating the onset of clinically evident disease, as well as factors associated with underlying atherosclerosis. Through this observational study of CHS participants, the Functional Aging Study is designed to meet the following objectives:

1. To identify and characterize surviving CHS participants (mean age 84) who have remained functional, comparing them to those who have died or become disabled.
2. To determine the baseline and cumulative trajectories of CVD risk factors and behavioral factors, especially physical activity and CVD treatment that lead to functional aging in the oldest survivors.
3. To determine whether other age-related biological factors will be long-term predictors of functional aging in a nested case-control design focusing on the oldest survivors.
4. To identify individuals who have maintained functional aging in the presence of a large atherosclerotic burden and to examine factors that may promote function in spite of CVD.

LAC is supporting this study as Dr. Kritchevsky is leading a metabolomic investigation of unintentional weight loss.

BIC will help Dr. Kritchevsky analyze the metabolomic data this project will generate.

IBC is providing OAIC specimens from participants in weight loss studies to compare to unintentional weight losers in the Allstars cohort.

**Completed Projects in previous cycles:**

**Investigating Fitness Interventions in the Elderly (INFINITE)**
Barbara Nicklas, PhD, Professor, Dept of Internal Medicine, Section on Gerontology and Geriatric Medicine  
R01 HL093713/ 2009-2014  
The main goal of this study is to determine whether the amount of fat loss (achieved through controlled underfeeding) affects the magnitude of improvement in aerobic function (maximal aerobic capacity and endurance) in response to a standardized exercise training stimulus that follows current recommendations for older persons. Secondary goals are to examine whether fat loss is necessary to elicit improvement in specific cardiovascular disease (CVD) risk factors, and to examine whether improvements in functional and CVD risk factor outcomes are related to the degree of total fat loss, as well as to reductions in fat accumulation in skeletal muscle (inter-muscular fat) and surrounding visceral organs (abdominal visceral and pericardial fat). We will accomplish these goals by conducting a 3-arm, 5-month randomized, clinical trial in 180 older (65-79 yrs), obese (BMI=30-34.9 kg/m2), sedentary men and women. Participants will be randomized to an exercise training intervention (moderate-intensity treadmill walking, 4 d/wk) alone (EX Only), exercise with moderate caloric restriction (-250 kcal/d deficit) designed for low weight loss (EX+Low CR; ∼4.5 kg weight loss), or exercise with intensive caloric restriction (-600 kcal/d deficit) designed for high weight loss (EX+High CR; ∼10.9 kg weight loss)

**Loss of Fat Tissue and Functional Response to Exercise in Older, Obese Adults (IM FIT)**
Barbara Nicklas, PhD, Professor, Dept of Internal Medicine, Section on Gerontology and Geriatric Medicine  
R01 AG020583/ 2009-2014  
This study is a randomized, clinical trial in 130 older (65-79 yrs), obese (BMI=30-34.9 kg/m2), sedentary women and men with low physical function designed to determine whether addition of caloric restriction (CR) to a standardized, progressive resistance training (RT) program enhances improvements in skeletal muscle and overall physical function. We will also examine the effects of the two interventions on in vitro characteristics of skeletal muscle and on systemic and abdominal adipose tissue levels of inflammation. Subjects will be randomized to 5 months of RT alone (RT) or RT with caloric restriction (RT+CR; -600 kcal/day deficit) designed to elicit considerable loss of body fat (∼8.7 kg fat loss). The Specific Aims are to determine the effect of adding CR to RT on: 1) clinical measures of skeletal muscle function and overall physical function; 2) in vitro characteristics of skeletal muscle (single-fiber contractile force and power, intramyocellular lipid, and...
muscle gene & protein expression of interleukin-6 and tumor necrosis factor alpha); and 3) inflammatory activity of abdominal adipose tissue and circulating adipokines. Our primary hypothesis is: Compared to RT only, RT+CR will result in greater improvement in muscle function, assessed by knee extensor force per unit of muscle tissue (muscle quality) and leg press muscle power, and in overall physical function, assessed by Short Physical Performance Battery (SPPB) score. Confirmation of this hypothesis will provide persuasive evidence that addition of CR to a RT intervention in older, obese women and men may be a more effective treatment than RT alone for prevention or delay of disability.

Standardized Rehabilitation Therapy for ICU Patients with Acute Respiratory Failure (TARGETT)
Peter Morris, MD, Professor, Pulmonary, Critical Care, Allergy and Immunologic Diseases
R01NR011186/2009-2014
This study will test the following hypotheses: 1) Standardized Rehabilitation Therapy will shorten hospital stay in patients with Acute Respiratory Failure (ARF); 2) Standardized Rehabilitation Therapy will improve objective functional measures and quality of life at 6 months post-enrollment; 3) Standardized Rehabilitation Therapy will reduce biomarkers of inflammation; 4) Standardized Rehabilitation Therapy will decrease hospital costs. We will conduct a two-arm, randomized trial in 326 patients with ARF to compare Standardized Rehabilitation Therapy, initiated in the ICU and administered throughout the hospitalization, vs. Usual Care (control). Standardized Rehabilitation Therapy will consist of: passive range of motion, physical therapy and progressive resistance exercise (strength training). Our unique environment provides a hospital-funded, experienced Mobility Team (7 days/week) consisting of a critical care nurse, physical therapist and nursing assistant to administer this protocol. The proposed study is a natural extension of our prior work, is multidisciplinary (Exercise Physiology, Physical Therapy, Nursing, Medicine, Basic Science, Health Economics), is supported by extensive preliminary studies, is innovative, and is responsive to recent critical care society consensus statements. For patients with ARF, no national standard for the administration of in-hospital rehabilitation exists. Patients with ARF suffer for months after hospital discharge with weakness and decreased quality of life. This study will provide the information for US hospitals to prioritize and budget for the rehabilitation needs of patients with ARF by demonstrating that Standardized Rehabilitation Therapy, initiated in the ICU, reduces hospital stay with immediate and sustained improvement in function and quality of life for patients with ARF.

Study of the Effects of Caloric Restriction and Exercise Training (SECRET)
Dalane Kitzman, MD, Professor, Department of Internal Medicine Section on Cardiology
NIH R37 AG018915/2009-2014
The primary aim of the study is to conduct a randomized, controlled, single-blinded, 2x2 design trial to examine weight loss via caloric restriction, aerobic exercise training, a combination of caloric restriction and exercise training, and attention control in 100 patients with heart failure and normal ejection fraction (HFNEF) and body mass index >30 in order to test the following hypotheses: 1) Both weight loss and exercise training will improve exercise intolerance and quality of life in older, obese patients with HFNEF. 2) Weight loss and exercise training combined will produce complementary effects on body and thigh muscle composition and additive improvements in exercise intolerance in patients with HFNEF. 3) Improvements in exercise tolerance will correlate with improvements in lean body mass, reversal of adverse thigh muscle remodeling, and increased thigh muscle capillarity.
Following baseline assessments, 100 patients with HFNEF aged > 60 years will be randomly assigned to 1 of the 4 arms: aerobic exercise training; caloric restriction; combined aerobic exercise training and caloric restriction; or attention control. Outcomes assessments will be performed at baseline and following the 20-week intervention. The primary outcomes will be peak exercise oxygen consumption (VO2peak) by expired gas analysis during graded treadmill exercise to exhaustion and quality of life by the Minnesota Living with Heart Failure Questionnaire (MLFH). Secondary, mechanistic outcomes, will include: total and regional lean and fat mass by DEXA; thigh skeletal muscle / intramuscular fat (SM/IMF) by MRI; skeletal muscle capillarity ratio, fiber type, and enzyme activity, on samples obtained by vastus lateralis needle biopsy; and circulating IL-6,
CRP, and adiponectin. Personnel performing outcomes assessments will be blinded to treatment group. Clinical status, weight, and function will be checked at 12 month follow-up.

**Intentional weight reduction and physical and cognitive function (Look AHEAD Movement and Memory Study)**

*Steve Kritchevsky, PhD, Professor, Dept of Internal Medicine, Section on Gerontology and Geriatric Medicine*

**R01 AG033087 / 2009-2014**

An ancillary study to the Look AHEAD (Action for Health in Diabetes) trial will evaluate the role of intentional weight loss on physical and cognitive function. Look AHEAD is a multi-center, randomized clinical trial to examine the cardiovascular effects of a 4-year lifestyle intervention, designed to achieve and maintain weight loss over the long term through decreased caloric intake and exercise in overweight/obese men and women aged 45-74 years of age with type 2 Diabetes.

To test our hypothesis that intentional weight loss is associated with better physical and cognitive function, we will add validated and well-established measures of physical and cognitive function at either the Year 8 or Year 9 follow-up visit – during the trial’s weight maintenance phase – at four Look AHEAD field centers (Colorado, Memphis, Pennington, Pittsburgh) in approximately 1,000 individuals.

**Physical Activity and Total Health (PATH)**

*Leader: Capri Foy, PhD, Assistant Professor, Division of Public Health Sciences*

**R21 AG027413/ 2008-2011 (no-cost extension)**

This study was funded based on data from a Pepper pilot study that Dr. Foy completed in 2003. This study will explore different programs to help adults between the ages of 55-80 improve their physical activity and quality of life. We are conducting this study to learn more about the factors that influence older adults to engage in regular, long-term, independent physical activity so that we can design safe and effective physical activity programs. There are two facets to this study. One program will work through the Central YMCA to provide participants with help on how to be more physically active, including fitness, strength, and how to set goals. The other program will include help on how to become more active, while also providing opportunities through a cooperative effort with Lowes Foods to provide food to those in need based on how active they are. Both groups will be supervised by trained staff at no cost to the participants. Dr. Foy received R01 funding for a proposal based on this pilot study in 2011. Findings from the pilot study were presented at the American Heart Association's Conference in March 2011.

**Investigating the Relationship between Physical Function, Comorbidity, Cytogenetic Risk Group and Prognosis in Older Adults with Acute Myelogenous Leukemia**

*Leader: Heidi Klepin, MD, Assistant Professor, Section on Hematology and Oncology*

**American Society of Hematology / Association of Subspecialty Professors (ASH/ASP) / 2008-2010**

The goal of this project is to investigate the predictive value of pretreatment self-report physical function and objective performance assessment on treatment related mortality in older adults with acute leukemia and to evaluate interactions between cytogenetic risk groups and physical function. Acute myelogenous leukemia (AML) is a disease of older adults characterized by disproportionately worse survival associated at older ages leaving optimal therapy for older adults unclear. Standard treatment includes aggressive chemotherapy administered in the hospital setting. This study aims to evaluate the predictive value of self-report and objective physical function on treatment related mortality and overall survival. Improved risk stratification for older adults is critical to inform patient decision making as well as the development of elderly specific clinical trials to improve outcomes for this disease. Outcomes from this research lead to Dr. Klepin’s recent Beeson award.

**Vitamin D, falls, fractures, and function in the community-dwelling older adult (Vitamin –D)**

*Leader: Stephen Kritchevsky, PhD, Professor, Dept of Internal Medicine Section on Gerontology and Geriatric Medicine*

**R01 AG029364**
To advance our understanding of the role of vitamin D in function and bone health, the investigators propose to measure circulating 25(OH)D and parathyroid hormone (PTH) levels in archived samples from the Health, Aging and Body Composition (Health ABC) Study, a cohort of 3,075 black and white well-functioning community-dwelling men and women aged 70-79 yrs at baseline. Three specific aims will be addressed: Specific Aim 1. Determine whether vitamin D status as determined by circulating 25(OH)D and PTH affects the rate of incident mobility limitation over 6 years; Specific Aim 2. Determine whether vitamin D status affects the rate of falls over 6 years; Specific Aim 3. Determine the role of vitamin D status in fracture risk over 6 years. We will also examine vitamin D's role in trajectories of proximal mediators of these important outcomes (i.e., strength, balance, walking speed and bone mineral density). As secondary aims, we will evaluate: 1) alternative cut-points to inform the debate on vitamin D adequacy in older adults; 2) the role of PTH independent from vitamin D; and 3) the effects of dietary and supplementary vitamin D intake on function and bone. We will specifically examine the associations in African-Americans, a group at high risk for vitamin D insufficiency. Health ABC, with longitudinal data on important functional outcomes (mobility limitation, falls and fractures) and proximal mediators (strength, balance, walking speed and bone mineral density) is the ideal study to advance scientific knowledge in this area of high priority in a cost-effective and efficient manner. To date five manuscripts have been published.

Vascular Stiffness and Pulmonary Congestion (PREDICT)
Gregory Hundley, MD, Assistant Professor, Dept of Internal Medicine Cardiology and Radiology
NIH R01 HL076468 / 2007-2012
608 subjects aged 55 to 85 with 60% women and 13% black. They must have either hypertension, diabetes, or coronary artery disease. Participants with contraindication to MRI (i.e. pacemaker or defibrillator) are not included. The LVEF at rest must be >40%. They will receive a MRI stress test and undergo rest and stress measures of LV and RV volumes and wall motion, myocardial perfusion, aortic stiffness (distensibility and pulse wave velocity), and quantization of prior infarction. Serum measures of CRP and BNP will be obtained. Serum will be stored and cells for future genetic analyses. They receive a single MRI and are followed by questionnaire 3x per year for 4 years. Hospitalizations are reviewed and an adjudication committee determines presence or absence of CHF. The aim of the study is to determine if stress induced change in LV performance or aortic stiffness predict future admission to the hospital for CHF in elderly patients at high risk for the development of CHF. This has recruited 579 people to date. Intervention and participant contact is ongoing. The study is currently on hold as they wait for funding for a piece of equipment and once the equipment is received they can complete the study.

Exercise Training and Inflammatory Risk Factors for Disability (LIFE-Time)
Barbara Nicklas, PhD, Professor, Dept of Internal Medicine, Section on Gerontology and Geriatric Medicine
NIH R01 AG027529 / 2006-2010
The LIFETIME study is an ancillary study to the on-going Lifestyle Interventions and Independence for Elders (LIFE) study, which is a four-site, single-blind randomized, controlled clinical trial in 424 elderly men and women at risk for physical disability. The primary aim is to measure plasma concentrations of a panel of 12 inflammatory biomarkers (CRP, in fasting blood samples collected from LIFE participants at baseline, and at 6-mos and 12-mos following randomization to the interventions to test two primary hypotheses that: 1) compared to a non-exercise health education intervention, a 12-month exercise training intervention will decrease concentrations of inflammatory biomarkers (specifically CRP and IL-6) in elderly men and women at high risk for physical disability, and 2) 12-mo changes in measures of physical function (400m walk time, 4m walking speed, and chair rise time) will be inversely related to changes in the biomarkers. The results will provide new knowledge regarding the effects of exercise training on several indicators of chronic inflammation and will yield valuable empirical data about which individual or combination of inflammatory markers are better predictors of poor physical function in the elderly. Research from this project has lead to many published journal articles.
Pericardial fat and subclinical and clinical measures of coronary heart disease
Jingzhong Ding, MD, PhD, Assistant Professor, Dept of Internal Medicine, Section on Gerontology and Geriatric Medicine
R01 HL085323 / 2006-2012 (no cost extension)
We are investigating the association of pericardial fat with subclinical and clinical measures of coronary heart disease. Visceral fat is more detrimental than subcutaneous fat with regard to coronary heart disease. Pericardial fat, a novel fat depot around the heart with properties like visceral fat, may be especially detrimental due to local lipotoxicity and inflammation in coronary arteries. We hypothesize that increased amounts of pericardial fat accelerates the atherosclerotic process in coronary arteries and that pericardial fat is the primary contributor to the development of coronary heart disease among commonly assessed regional fat depots. The proposed study is an ancillary study to the Multi-Ethnic Study of Atherosclerosis (MESA). We will examine 1) the association of pericardial fat with subclinical coronary heart disease (calcified coronary plaque measured by computed tomography (CT)) at baseline, 2) the association of baseline and changes in pericardial fat with changes in calcified coronary plaque over three years, and 3) the risk of clinical coronary heart disease associated with pericardial fat in a 6 year follow-up among 6,814 white, black, Hispanic, and Asian American men and women, age 45-84. The measures of calcified coronary plaque and clinical coronary heart disease will be obtained from the existing MESA database. We will measure the volume of pericardial fat using the existing CT scans in MESA, from which calcified coronary plaque was quantified, at baseline (N=6,814) and a follow-up exam (N=6,000) three years later. All CT scans have now been analyzed and the data have been submitted to the database of Genotypes and Phenotypes (dbGaP). A total of 8 manuscripts have been published. These reports extend the previously found association of pericardial fat with coronary calcified plaque to the multi-ethnic MESA population, and for the first time demonstrate that pericardial fat predicts incidental coronary heart disease events.

Impact of an exercise program on physical function and quality of life in aged candidates for renal transplantation (PART)
Erica Hartmann, MD, Assistant Professor, Dept of Internal Medicine Section on Nephrology
ASN /ASP / 2006-2008
The goal of this pilot study is to determine the feasibility of an exercise intervention in dialysis-dependent patients aged 60 and older awaiting kidney transplantation, assessing its effect on maintaining transplant candidacy. Forty patients on the wait list will be randomized to an exercise intervention or no intervention. The exercise intervention will include both center and home-based components tailored to the unique needs of this patient population. After an initial evaluation, participants will receive 3-weeks of center based instruction regarding technique and self-monitoring of exercise intensity and provided with a home-based exercise plan. In the 4th week of the study, participants will receive a home visit to observe the participant at home and help plan exercises that accommodate the home environment. The goal of the intervention is to increase moderate intensity physical activity to a goal of 150 minutes per week. Participants will be then be contacted weekly to monitor and motivate for the following 2 months and then monthly thereafter. Participants in both groups will be evaluated at 3 and 6 months and after 1 year. The clinical research core will provide advice on the structure and goals of the exercise intervention and on adherence and retention and will assist in the assessment of functional outcomes including the PAT-D, the SPPB, grip and knee extensor strength, 400m walk. The core will also provide transportation for these participants. The bioimaging core will support body composition measured by DXA measured annually. This project is supported in part by Dr. Hartmann’s American Society of Nephrology-ASP Junior Development Award in Geriatric Nephrology.

Intensive Dietary Restriction with Exercise in Arthritis (IDEA) & IEAD Follow up
Leader: Stephen Messier, PhD, Professor, Department of Health and Exercise Sciences
Wake Forest University
NIH R01 AR052528 / 2006-2011
The IDEA study is a randomized, controlled trial in 450 older (>60 yrs), overweight/obese (BMI=27-40 kg/m²) men and women with knee OA randomized to either 18 months of a Diet only, Exercise only, or Diet+Exercise intervention. Both the Diet only and Diet+Exercise groups receive the same dietary therapy (based on partial meal replacements) designed to achieve a weight loss of 10% of initial body weight. The exercise intervention is identical for both exercise groups and involves 60-minute sessions conducted 3 d/wk of aerobic (primarily walking) and resistance exercise. The primary aim is to compare the effects of the interventions on the primary outcomes of inflammatory biomarkers (CRP, IL-6, TNFa) and knee joint loads and on the secondary outcomes of body composition (via DXA), self-reported physical function, pain, and mobility, and on disease progression measured by changes in quantitative MRI. The study will also determine whether inflammatory biomarkers and knee joint loads are mediators of the interventions, with significant effects on function, pain, and mobility.

**Follow Up:** We propose to conduct the first follow-up study of older adults with knee OA who participated in long-term (18 month) intensive diet and/or exercise interventions. They will be scheduled for 1 clinic visit to determine body weight, health related quality of life, physical activity level, pain, function, mobility, the need for joint replacement, co-morbid diseases, and the number of hospitalizations. We hypothesize that participants randomized to the intensive dietary groups, with and without exercise, will maintain more of the benefits derived from the intervention than participants randomized to the non-weight loss group. This proposal is designed to initiate the follow-up data collection process with this clinically important cohort, and provide information 2-3 years after the interventions were terminated. The study reported enrollment of 97 participants. Recruitment and participant contact are complete.

**Age-Related inflammatory changes: The role of genes and body composition changes**

**Leader:** Yongmei Lui, PhD, Assistant Professor, Division of Public Health Sciences

**Biostatistical Sciences**

**NIH R01 AG028288 / 2006-2009**

We postulate that age-related changes in adiposity and inflammatory gene polymorphisms underlie age-related changes in inflammatory mediators. Furthermore, we believe these age-related changes may be an important risk factor for subsequent ASCVD, a condition linked with substantial morbidity and mortality in older persons. We propose a series of longitudinal data analyses using the Health Aging and Body Composition (Health ABC) Study, a prospective study of 3,075 70-79 year old, black and white, men and women (42% blacks, 52% females) who have been followed annually since 1997-98, to achieve the following aims:

**Specific Aim 1:** Measure serum inflammatory markers, C-reactive protein (CRP) and interleukin-6 (IL-6), and determine their changes with age across 7 years of follow-up. Hypothesis 1: Levels of inflammatory markers in older adults increase with age during the 7 year follow-up. The increase is similar across gender and race.

**Specific Aim 2:** Use existing measures collected by Health ABC and newly identified sequence variants of ~29 genes related to the inflammatory process to examine the following hypotheses: Hypothesis 2.1 Increase in fat mass or visceral fat area is associated with increases in inflammatory marker levels. Hypothesis 2.2 Selected genetic polymorphisms are associated with increases in inflammatory marker levels. We will consider the role of changes in physical activity and intervening health events in changes in inflammatory markers as important confounders of the adipose related changes. We will also explore interactions between gene polymorphisms and changes in fat mass or visceral fat. Specific Aim 3: Determine the ability of age-related changes in inflammatory markers to predict subsequent ASCVD events. Hypothesis 3: Rising levels of CRP or IL-6, particularly the combination of both, predicts higher risk of ASCVD events independent of known cardiovascular risk factors. Because of the exploratory nature of the genetic associations with multiple tests it is imperative that the results be confirmed in an independent sample. Therefore, we propose a two-stage design for the genetic association study with a minimal loss of power. In the first stage, we will perform exploratory tests evaluating all genes of interest on a subset of 1500 randomly selected individuals from the Health ABC cohort. In the second stage, we will perform confirmatory tests of the most promising genes identified from the first stage using the remaining cohort. The Health ABC study, the only large cohort of community-dwelling older adults with long term follow-up and annually detailed measures of body composition, along with a wide range
of functional, clinical, and laboratory data, provides a unique opportunity for studying this area of high
scientific priority.

Cooperative Lifestyle Intervention Program (CLIP)
Jack Rejeski, PhD, Professor, Department of Health and Exercise Sciences, Wake Forest University
NIH M01-RR07122 / 2005-2010
The CLIP study is a 3-arm 18-month randomized, controlled trial of the effectiveness of physical activity, with
and without weight loss, in the treatment of mobility disability in 288 older (60-79 years), overweight/obese
men and women who have evidence of CVD or the metabolic syndrome. Participants are randomized to one of
the 3 intervention groups: 1) a successful aging education control condition; 2) a group treatment program for
physical activity; and 3) a lifestyle intervention that is designed to promote weight loss and increase physical
activity. The primary aim of the study is to compare the effects of the three treatments on 18-month change in
mobility disability, as assessed by the distance walked during a 400M walk test. A secondary aim is to test the
effects of the interventions on change in: CVD risk factors (high-sensitivity C-reactive protein; lipid profiles;
glucose and insulin; blood pressure), physical activity and dietary intake, body composition, and on health-
related quality of life (HRQL). The public health relevance of the trial lies in the fact that the interventions will
be delivered in conjunction with Cooperative Extension Centers.

Pharmacological Intervention in the Elderly Phase 2 (PIE 2)
Dalane Kitzman, MD, Professor, Department of Internal Medicine Section on Cardiology
NIH 2R01 AG18915 / 2004-2008
The PIE study investigated the effects of 12-months of ACE inhibitor use on aortic distensibility and wall
thickness, left ventricular mass, exercise tolerance, and quality of life in 80 (40 placebo and 40 treatment)
elderly (>60 yrs) patients with diastolic heart failure.
The PIE II study investigated the use of Spironolactone (an aldosterone antagonist) on these same outcomes in
80 (40 placebo and 40 treatment) elderly (>60 yrs) patients with diastolic heart failure. All PIE and PIE II
participants also had measures of physical function and body composition measured by DXA.

Intervening on spontaneous physical activity to prevent weight regain in women (INFINITE SPA)
Barbara Nicklas, PhD, Professor, Dept of Internal Medicine, Section on Gerontology and Geriatric
Medicine
R21HL097252
The main goal of this pilot is to provide preliminary data and effect estimates to begin to test our overall
hypothesis that prevention of weight loss-induced reductions in SPA will be more beneficial for long-term
maintenance of weight loss in women than in men. We propose to conduct a pilot study using a 2-arm, 10-
month design in 72 obese, middle-aged/older (55-70 yrs) men and women (n=36 per group). Participants will be
randomized to a 5-month standardized weight loss intervention involving a hypocaloric diet and aerobic
exercise (DIET+EX) or to the same weight loss intervention with addition of a behavioral component that
targets self-monitoring (SM) of SPA (SM+DIET+EX), and then followed for another 5 months
following weight loss. The detailed, specific aims of this R21 exploratory/developmental proposal are:
Primary Aim: To examine whether SPA self-monitoring results in less body weight regain in the follow-up
phase in both men and women. Secondary Aims: To examine whether: 1) women regain more weight than men
in the follow-up phase; 2) SPA self-monitoring and gender have an effect on change in weight in the intensive
weight loss phase; 3) SPA self-monitoring and gender have an effect on change in SPA in the intensive weight
loss phase; 4) there is an association between SPA changes in the weight loss phase and weight regain in the
follow-up phase. We anticipate that the results will lead to a larger and longer trial to definitively test our
hypothesis, which could potentially provide evidence against the current standard of care (i.e., exclusive
prescription of structured moderate-intensity exercise) for obesity therapy in women and may lead to sex-
specific treatment guidelines.

Rehabilitation and Exercise Training After Hospitalization: Assessing Benefit in Acute Heart Failure
Pilot Study (REHAB-HF Pilot)
Rehabilitation and Exercise Training after Hospitalization: Assessing Benefit in Acute Heart Failure (REHAB-HF) pilot study is a multicenter, randomized trial designed to establish the feasibility of conducting a larger clinical trial to address the hypothesis that, in addition to standard care, a novel, progressive, multi-domain rehabilitation intervention administered to elderly patients with acute decompensated heart failure (ADHF) beginning early during hospitalization and continuing for 3 months will improve key clinical outcomes, including the rate of rehospitalization and death, physical function, and quality of life.

Three centers will recruit a total of 60 consenting patients ≥ 60 years old hospitalized with ADHF. Once identified and screened, the participants will be randomized in a 1:1 fashion to receive a 3 month novel rehabilitation and exercise training intervention or usual care. This multi-domain intervention will include endurance, mobility, strength, and balance training and be tailored based on participant performance in each of these domains. It will begin early during the hospitalization and continue three times per week in an outpatient facility. Patients who after hospital discharge are initially too debilitated, in particular those with significant balance deficits, to participate in the facility-based cardiac rehabilitation program, which will focus primarily on increasing endurance and strength, will be given a short-term transitional intervention at a specialized, comprehensive rehabilitation outpatient facility, and will then transition to the outpatient facility when functional performance improves adequately. All patients will undergo measures of endurance, physical function, and quality of life at baseline, 1 week, 1 month, and 3 months. Clinical events will be monitored throughout the study. The results of this study will be used to help inform a larger clinical trial powered to assess a composite clinical endpoint and with the potential to impact many of the approximately one million patients hospitalized with ADHF each year. The overarching goal of this project is to test the novel hypothesis that in elderly patients with ADHF and multiple comorbidities, a progressive, tailored, multi-domain rehabilitation intervention that begins early during hospitalization and continues for 3 months following discharge will improve physical function and quality of life, reduce rehospitalizations, and improve a composite clinical endpoint. The purpose of this 3-site pilot study is to provide key pieces of information that will be required for designing a larger study to definitively test this important hypothesis.

Predicting Pulmonary Function Decline in the Elderly
Stephen B. Kritchevsky, PhD, Professor, Dept of Internal Medicine, Section on Gerontology and Geriatric Medicine
NIH R01 HL074104 / 2004-2009
Our studies using cDNA microarray technology, have established associations between COPD and two chemokine receptors, CXCR-2 and CXCR-5 using cellular constituents of bronchoalveolar fluid in COPD patients. We propose to evaluate whether peripheral blood mononuclear cell expression of these and related biomarkers predict accelerated FEV1 decline in an established community-based cohort over a 5-year period, the Health ABC study. Spirometry was performed on 2075 participants in Year 5 of the study. COPD has increasingly been seen to be a systemic disease characterized by loss of lower extremity lean body mass, loss of strength, and poor endurance. We propose to test the additional hypothesis that inflammatory biomarkers will predict the accelerated loss of lean body mass, loss of strength and loss of endurance over a 5-year period.

Diet, Exercise and Metabolism in Older Women (DEMO)
Leader: Barbara Nicklas, PhD, Professor, Dept of Internal Medicine, Section on Gerontology and Geriatric Medicine
NIH 1RO1 AG20583 / 2002-2007
The DEMO study was a randomized trial in 112 overweight and obese (BMI=25–40 kg/m2; waist >88 cm), postmenopausal women (50-70 yrs) assigned to one of three 20-week interventions of equal energy deficit: caloric restriction (CR Only), CR plus moderate-intensity aerobic exercise (CR+Moderate-intensity), or CR plus vigorous-intensity exercise (CR+Vigorous-intensity). The diet was a controlled program of underfeeding during which meals were provided at individual calorie levels (~400 kcal/day). Exercise (3 days/week) involved treadmill walking at an intensity of 45-50% (Moderate-intensity) or 70-75% (Vigorous-intensity) of heart rate reserve. The primary outcome was abdominal visceral fat volume. Average weight loss for the 95
women who completed the study was 12.1(4.5) kg and was not different across groups. VO2max increased more in the CR+Vigorous-intensity group than either of the other groups (P<0.05). All groups showed similar decreases in abdominal visceral fat (approximately 25%, P<0.001 for all). Changes in lipids, fasting glucose/insulin, and 2-hr glucose and insulin areas during the OGTT were similar across treatment groups. Analysis of abdominal and gluteal subcutaneous adipose tissue metabolism, including gene expression, lipolysis, and cytokine release, is on-going. In addition, the study has measures of resting metabolic rate and physical activity energy expenditure, as well as a 1-year follow-up of weight regain following the interventions.

Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF Action)
Leader: Dalane Kitzman, MD, Professor, Department of Internal Medicine, Section on Cardiology
NIH-U01HL63747A2 / 2002-2009
HF-ACTION is a multi-center randomized controlled trial investigating outcomes of aerobic exercise training. The primary outcomes of the trial are to see if long-term exercise training can decrease morbidity and mortality among patients with congestive heart failure. The secondary outcomes are to see the effects of exercise training on physical function and quality of life. Those patients randomized to the exercise training group will receive three months of supervised exercise training, consisting of 30-40 minutes of exercise three times per week at a prescribed intensity between 60-75% of Heart Rate Reserve. Once the supervised sessions are complete, the patient’s transition to a home based exercise program using exercise equipment provided by the study until study completion. Those patients randomized to the usual care group follow standard of care practices and receive periodic telephone follow-up. Patients are screened for qualification for the study, and then complete a full baseline assessment before randomization. After randomized, all patients are asked to return every three months for follow-up and re-testing for the first two years. After the initial two years, annual follow-up will continue until study completion. Maximum follow-up for any patient is four years.

Other Development Projects Supported by WFU Pepper OAIC

Ongoing:

Project Title: Physical Function and Transitions of Care
Leaders: Pamela Duncan, MD and Jeff Williamson, MD
OAIC investigators have developed reliable and valid measures of physical function and evidence-based interventions to improve physical function and promote healthy aging in numerous studies. However, these tools are rarely tested or implemented in clinical programs to assess clinical and policy-relevant outcomes (e.g. 30-day readmissions). This development project will join the OAIC’s expertise in this area with infrastructure recently developed for our proposed Center for Medicare and Medicaid (CMS) Innovations project, including newly implemented data systems, materials and procedures to support patient identification, enrollment, tracking and outcomes assessment. These activities build upon WFU OAIC strengths in physical function assessment and intervention and extend our efforts into patient-oriented comparative effectiveness research in acutely ill older adults.

Project Title: Development of Methylomic and Transcriptomic Approaches to Pathways to Disability
Leaders: Liu/McCall/Nicklas
This project is being supported by the BRC (RC4) and the IBC. DNA methylation is a key factor in regulating transcription and cell phenotypes, and thus may be important in the disability pathway. The objective of this is to develop the infrastructure and process, including the biological and biostatistical analyses, for expanding our Center’s capability to assess specific epigenetic and transcriptional profiles, particularly in cell types with high relevance to known disability pathways. This potential is buttressed by Dr. Liu’s on-going research (HL101250) where monocytes purified from blood samples of the initial 700 subjects in the Multi-Ethnic Study of Atherosclerosis study display aging-specific epigenetic and transcriptional profiles implicating metabolic regulatory genes that increase glycolysis and reduce glucose oxidation and mitochondrial oxidative phosphorylation. A central finding emerging from the collective prior work of our OAIC is that adiposity, with
inflammatory and metabolic lipotoxicity, likely plays a crucial role in disability;2,40,41 however the precise mechanisms by which excess fat contributes to functional decline remain unknown. Adipose-associated inflammation is primarily due to local monocyte-derived macrophages and other immune cells which are recruited in response to weight gain.42,43 DNA methylation and transcriptional profiles in these cells likely influence adiposity-associated inflammation, metabolic dysregulation, and ultimately physical function in the elderly; yet to our knowledge there are no studies which directly and simultaneously address these issues. This project will develop our Center’s capabilities for investigating gene reprogramming of cells involved in obesity-related physical disability and to eventually expand to age-related muscle atrophy. We hypothesize that there will be shifts in these profiles in response to fat loss which will signal reprogramming of pathways that involve inflammation, metabolism, and mitochondrial biogenesis and function. Approach: In this project, we will examine DNA methylome and transcriptome changes in adipocytes and blood monocytes in 40 older, obese adults undergoing the 5-mo diet intervention in the IFINITE trial. Subcutaneous abdominal fat (obtained via suction biopsy) will be processed by collagenase digestion to isolate adipocytes. We will also collect blood using CPTTM tubes to separate peripheral blood mononuclear cells. Subsequently, monocytes will be isolated with anti-CD14 coated magnetic beads using an automated magnetic separation unit (AutoMAC, Miltenyi Biotec). Methylocimic (using Illumina’s Infinium Human Methylation 450 BeadChip) and transcriptomic (using Illumina’s HumanHT-12 v4 Beadchip) profiles will be evaluated and assessed in relation to weight loss and physical function. Pathway enrichment and network analyses will be performed. Tissue collection and cell purification/storage will occur in years 1-2 of the proposed cycle. Methylocimic and transcriptional profiling will be performed in year 2, with data analysis and interpretation taking place in year 3. Expected outcomes: Completion of this project will enhance our Center’s capability for assessing epigenomic-transcriptomic mechanisms underlying age-related functional decline. This will provide us with a new tool for discovering novel factors that contribute to disability and expand our ability to design future intervention studies that incorporate examination of these pathways.

Completed Development Projects in past cycles:

Project Title: DEMO Maintain
Leader: Barbara Nicklas, PhD, Professor, Dept of Internal Medicine Section on Gerontology and Geriatric Medicine
The DEMO study currently is not funded to follow the women who complete the study to determine the extent or composition of weight regain. Thus, we do not know how successful DEMO participants will be in maintaining their lifestyle changes and weight loss. In those who regain their weight, little is known about the relative pattern of fat and lean body mass distribution. If initial weight reduction and reduction in abdominal fat are followed by regain of even more abdominal fat or replacement of lean body mass by fat, what are the overall CVD and disability consequences? If weight is maintained or further reduced at the expense of reduction in lean body mass, the desired reduction in CVD risk factors may not ensue. In that case, participants may be at higher risk for physical disability. DEMO MAINTAIN will allow 2 additional assessments in all 112 women which will take place 6 months and 12 months following the last day of weight loss intervention. It will assess body composition, physical activity and food intake, fasting lipoprotein lipids, glucose, and insulin, blood pressure, and physical performance, including walking distance, grip and knee extensor strength, and self-reported physical function at these time-points. The GCRC has approved ancillary funding for the additional DXA scans, for assessment of fasting lipoprotein lipids, glucose, and insulin, and blood pressure, and for measurement of dietary intake.

Project Title: Properties of the disability measure FAST 23
Leader: Edward Ip, PhD, Associate Professor, Dept of Public Health Sciences Section on Biostatistics
This research development project is to validate and expand the use of the WFU-FAST 23 disability questionnaire. This project will examine the factor structure of FAST 23 data across a variety of Pepper Center supported studies to identify potential weaknesses in the questionnaire and to validate its use across a range of disabled populations.
Project Title: Preclinical, noninvasive assessment of aging skeletal muscle denervation/reinnervation with PET scanning
Leader: Osvaldo Delbono, MD, PhD, Professor, Dept of Physiology and Pharmacology, Section on Gerontology and Geriatric Medicine
This project tests the hypothesis that the noninvasive imaging procedure (flurobenzytrozamicol)-Positron Emission Tomography (FBT-PET) can be used to assess skeletal muscle innervation throughout the aging process in rodents in the first phase of studies to determine its role in human sarcopenia. Recently started experiments (02/01/09) examine (1) hindlimb muscle innervation using FBT-PET, (2) the relationship between FBT-PET and mouse skeletal muscle function in vivo and in vitro, and (3) mouse muscle VACHT density using in vitro determinations and to establish a relationship with FBT-PET uptake. Validation of FBT-PET as a novel, accurate, noninvasive measure of skeletal muscle innervation in rodents will provide valuable data that can be rapidly translated into an effective research tool in animals and humans. Clinically, it can be used to evaluate interventions aimed at preventing and/or ameliorating the contribution of muscle denervation to sarcopenia and subsequent physical disability in the elderly. Manuscript in preparation.

Project Title: Optimizing Body Composition for Function in Older Adults (OPTIMA)
Leader: Stephen Kritchevsky, PhD Professor, Dept of Internal Medicine, Section on Gerontology and Geriatric Medicine
The purpose of this study is to refine the measurement of ectopic adiposity in the context of a pilot-trial. The trial compares two strategies intended to improve the health of overweight older adults by improving body composition. One strategy, resistance training, is designed to preserve skeletal muscle mass. The other strategy, the use of a PPAR-γ agonist, is designed to enhance the loss of fat from visceral and skeletal depots. These strategies will be used in conjunction with a hypocaloric diet and will be compared to a hypocaloric diet alone to determine if either of these strategies are superior in reducing visceral fat and preserving muscle mass. We plan to recruit 88 older (65 - 79 yrs) men (n=48) and women (n=40) at risk for disability and with indications for weight loss according to NIH guidelines. Adiposity and skeletal muscle changes were measured using CT and DXA. Manuscript in preparation.

Project Title: Adaptive Assessment Methodologies to Evaluate Physical Functioning in Older Adults
Leader: J. Rejeski, Professor, Health & Exercise Science
This study proposes to create and validate an innovative infrastructure that provides the capacity to assess mobility function and disability in a multimedia enhanced, and Computerized Adaptive Testing (CAT) environment, a measure we call M-CAT. The enhanced multimedia component makes extensive use of animation video clips. Animation serves three purposes: First, it removes potential biases in judgments that may arise from characteristics such as the sex, race, age or experience of the actor. Second, it standardizes item interpretation. Respondents view the actual demands of the task and are no longer required to make implicit judgments regarding item content. This research development project will accomplish four specific aims:
1. Create an animation-based system that allows the implementation of CAT technology for assessing mobility in older adults (the M-CAT).
2. Broaden the item pool for the mobility domain beyond traditional item content in this area.
3. Recruit participants (n=300, in two phases) and collect pilot data for item calibration.
4. Assess the efficacy of the M-CAT through rigorous psychometric evaluation.
Data has been collected on the full MCAT which involves 129 items on 253 older adults. There is also data on the SPPB, the 400-M walk, and a traditional self-report measure of disability—the PAT-D. This past year we completed development of a short form of the MCAT that is called the Mobility Assessment Tool—Short Form (MAT-sf) and now have a psychometric paper under review (revision) at the Journals of Gerontology: Medical Sciences. In addition, we have a second conceptual paper on our technology nearly ready for submission. The
MAT-sf has now been accepted by the LIFE steering committee as an outcome measure in that multi-center NIA funded trial.

**Project Title:** A Computational Biology Approach to Reverse Translation: Tools for identification of mechanisms underlying clinical observations  
Project Leader: Richard Loeser, Professor, Department of Molecular Medicine  
During the past year, the Affymetrix gene microarrays (total of 24) were run on 12 pairs (pre/post intervention) of RNA samples that had been isolated from muscle biopsy specimens collected from community-dwelling older (65-79 yrs) overweight/obese (BMI>27 kg/m2) adults who completed the OPTIMA trial. The raw expression data from the arrays was normalized using the Systematic Variation Normalization (SVN) method. Genes with significant detection p-values were evaluated for significant changes in expression between the pre and post-intervention time points. A total of 107 genes were up-regulated and 119 genes were down-regulated. Next a computational analysis was performed using the Extracting Gene Expression Patterns and Identifying Co-expressed Genes (EPIG) method. For this subjects in the two pioglitazone treated groups (pio power, n=5 and pio no power, n=4 training) were evaluated. Four patterns were extracted. A second analysis was performed using a new clustering method developed by Dr. Fetrow’s group. Twenty gene clusters were created to compare the pio power, pio no power, and placebo groups. Genes of interest from the two computational analyses were then chosen for quantization by real-time PCR which is currently on-going and should be completed in about a month.

**Project Title:** Molecular, Cellular, and Histologic Characterization of Non-invasively Imaged Adipose Infiltration and Accumulation in Nonhuman Primates  
Leaders: Thomas Register, PhD and Carol Shively, PhD, Professor, Dept of Pathology / Comparative Medicine  
Subproject 1: Imaging Fat Heterogeneity in Female Cynomolgus Monkeys (X9817, n=28): RNA has been isolated from subcutaneous, and visceral fat and quantitative RTPCR has been performed for key targets related to cell populations, adipose tissue, and inflammation. CT scans have been assessed for fat attenuation employing recently developed software and protocols using 2 sampling strategies. Work is underway to finalize this dataset. We have modified the software for assessing muscle characteristics in these same CT scans.  
Subproject 2: In a longitudinal study of imaging fat metabolism in aging female cynomolgus monkeys (X0721, n=45), we have acquired baseline and 18 month CT and DEXA exams and will be measuring fat volumes and attenuation in the abdomen and thigh. Biopsies of liver, subcutaneous fat, visceral fat, and muscle were collected at baseline, and biopsies of subcutaneous fat, visceral fat, and muscle as well as an iliac artery were obtained at 18 months, along with blood for measures of adipocytokines and other markers. Behavior, ovarian function, and plasma responses to an atherogenic typical American diet are currently being assessed. Physical function data are being continuously collected during behavioral observations (e.g. walking speed, frequency and duration of climbing leaping, slips, falls).  
Progress Summary includes:  
VFat had a lower level of leptin mRNA expression than subcutaneous fat (p=0.002); VFat tended to have a greater level of IL-6 (p=0.14) and TNF-α (p=0.06) mRNA expression than did subcutaneous fat; Expression of CD68, a macrophage marker, was lower in visceral than subcutaneous fat (p=0.05), while CD3, a T cell marker, was higher (p=0.01); VFat CT attenuation was inversely associated with serum leptin and VFat leptin mRNA expression, and positively associated with serum adiponectin (all p<0.05); Walking speed among 3 species of primates (cynomolgus and bonnet macaques, and vervets) was significantly reduced in aged animals compared to younger animals; VFat and SQFat CT attenuation tended to be higher (p=0.1) in older vervets; Pilot studies of muscle strength were initiated in collaboration with Dr. K.C. Childers; Pilot studies of isolations of primate adipose inflammatory cell populations were initiated.

C. Pilots  

*Pilots Just Initiated – Protocols are being developed*
Role of Skeletal Muscle in Heart Failure Patients Bob Kraft, PhD (Biomedical Engineering)

Heart Failure (HF) is a major contributor to morbidity, mortality and healthcare burden in US. HF with Preserved Ejection Fraction (HFPEF) accounts for approximately 50% of all HF cases. Unfortunately, HFPEF pathophysiology is poorly understood. Exercise intolerance, the predominant and chronic symptom of HFPEF patients, has a dramatic effect on quality of life. Exercise intolerance can be measured objectively during whole body exercise as a decrease in peak exercise pulmonary oxygen uptake (peak VO2). Recent findings by Kitzman and Haykowsky suggesting that reduced skeletal muscle blood flow and metabolism may play an important role in limiting exercise tolerance in HFPEF patients. The long-term goal of this project is to examine the potential contribution of abnormal skeletal muscle perfusion and oxygen utilization to the severe physical disability experienced by the large and growing population of older HFPEF patients and potential interventions to improve it. Blood flow (BF) and oxygen consumption (mVO2) of skeletal muscle will be measured in response to a submaximal plantar exercise using two innovative and complementary Magnetic Resonance Imaging (MRI) methods: 1) by inferring skeletal muscle BF and mVO2 for assessing peak and post-exercise kinetics by measuring blood in the large veins that is returning from the skeletal muscle, and 2) by a complementary method to directly measure BF in individual skeletal muscles with Arterial Spin Labeling. Dr. Kraft proposes to use both methods to determine the role of skeletal muscle metabolism and blood flow in HFPEF patients (n=10) and healthy controls (n=10). Successful completion of this pilot study will provide the first direct evidence that exercise intolerance is related to skeletal muscle metabolism and blood flow. To complement the functional data acquired in this pilot study, structural data (intramuscular fat fraction and muscle volume) will also be collected. Both types of data may serve as additional preliminary data for other projects and for an R01 proposal to examine the effectiveness of interventions that may improve the quality of life of HFPEF patients.

Rehabilitation & Exercise Training after Hospitalization: Assessing Benefit in Patients Undergoing Transcatheter Aortic Valve Replacement for Aortic Stenosis- Bharathi Upadhya, MD (Cardiology)

Calcific aortic stenosis (AS) is the most frequent heart valve disease in Western countries, where its prevalence steadily increases with age. Symptomatic severe AS is associated with severe physical dysfunction, hospitalizations, and increased mortality. In view of the natural course of the disease (survival usually does not exceed 3 years after the onset of symptoms), the recommendation since 1968 has been to perform surgical aortic valve replacement (AVR) promptly after the onset of even minor symptoms. However, many very elderly patients are not good surgical candidates due to multiple co morbidities. Transcatheter aortic valve replacement (TAVR) has become an alternative treatment option for patients with severe symptomatic AS considered being at high or prohibitive surgical risk. TAVR was approved by the US Food and Drug Administration for the treatment of severe, symptomatic AS and inoperable status (in 2011) and high-risk but operable status (starting in 2012). However, despite procedural success, many patients continue to have significant or even severe physical dysfunction and significant mortality. Patients in this cohort had a high burden of advanced heart failure (HF) with severe functional limitations as more than 81.3% had New York Heart Association class (NYHA) III/IV HF symptoms, 72% had a slow gait speed, 26% were extremely limited in their ability to shower or bathe. Aging, cardio-vascular dysfunction, impaired skeletal muscle function and chronic valve disease with associated multiple comorbidities resulting in severe impairment in physical function in these patients, which leads to poor outcomes, poor quality of life, and increased re-hospitalization after successful TAVR. This is further exacerbated by the hospital processes, including forced bed rest which markedly accelerates physical dysfunction. Dr. Uphadya proposes to address this problem with a novel, multi-domain rehabilitation intervention. Multiple studies have reported that early physical rehabilitation care can be safely executed in acutely hospitalized old adults and lead to functional benefits. The primary aims are to assess the feasibility of recruitment, retention, and compliance of a 12-week trial of physical function rehabilitation intervention in older patients hospitalized for TAVR procedure, to assess the feasibility of performing measurements of physical function and quality of life at baseline and during.
3-month follow-up, and to collect data on clinical outcomes for a composite clinical endpoint. The data generated will be useful for developing new grant applications to address this important problem.

**Mediterranean vs. Western Diet Effects on NHP Mitochondrial Bioenergetics & Physical Function**- Carol Shively, PhD (Pathology/CompMed), and Anthony Molina, PhD.

Gait speed is an integrated measure of physical ability that predicts morbidity, disability, and mortality in older adults. Our understanding of the factors that contribute to this measure of overall function is poor. In order to understand declines in physical function with age in general, and gait speed in particular, we developed a nonhuman primate (NHP) model of aging and physical function in which gait speed and other measures of physical performance declined with age, and are associated with age-related degenerative changes of the shoulder joint, and muscle fiber force and power generation. Energy demands associated with walking increase with age, suggesting that age-related bioenergetic decline may play a role in the slowing of gait speed with increasing age. Recently, we observed that the bioenergetic profile of mitochondria isolated from skeletal muscle is associated with gait speed in community dwelling older adults. Our studies, and others, further suggest that respirometric profiling of circulating cells may reflect systemic bioenergetic capacity. Our data indicate that numerous measures of physical ability including gait speed are positively associated with peripheral blood mononuclear cell (PBMC) bioenergetic capacity. Recent observations suggest that adherence to a Mediterranean diet results in faster gait speed at follow-up in community-dwelling older adults. High levels of monounsaturated fat (olive oil) and omega-3 fatty acids are characteristic of Mediterranean diet patterns, and both appear to enhance physical function and increase resting metabolic rates suggesting beneficial effects of a Mediterranean diet on mitochondrial function. However, observational studies are dependent upon self-report of diet, and other variables that may affect bioenergetics may be difficult to either control or accurately quantify in clinical studies. Dr. Shively is assessing the effects of long term consumption of a Western versus Mediterranean diet on body composition, carbohydrate and lipid metabolism, and cardiovascular health in 42 NHPs through her funded RO1. In this pilot project collaboration with Anthony Molina, she proposes to leverage this time limited resource to address the hypothesis that compared to a Western diet, a Mediterranean diet pattern will have beneficial effects on mitochondrial bioenergetics and physical function. To test this hypothesis mitochondrial bioenergetics will be evaluated in PBMCs, platelets, and muscle. Physical function (gait speed, time spent jumping, climbing, hanging, or locomoting, and activity levels) will also be quantified. These data will be used to support grant applications for external funds to evaluate dietary influences on bioenergetics, health, and physical function.

**Pathways to Improving Functional Capacity in Older Patients with Chronic Kidney Disease and Cardiovascular Disease**- Killian Robinson, MD

We propose a double-blind, placebo-controlled, randomized, 2x2 factorial design, pilot study of n-3 PUFA and/or oral bicarbonate use in older (age >60 years) CAD patients with concomitant CKD enrolling in a standard, 3-month CR program. We will assess the effects of this intervention on exercise capacity, markers of inflammation and serum bicarbonate concentration. Our goal is to obtain 8 evaluable patients per group. Exercise capacity will be measured by VO2 peak. Response to bicarbonate will be monitored by serum bicarbonate concentration. Since CKD may adversely affect muscle function both by acidosis and/or mitochondrial function, we propose that these may be mechanisms for the poorer exercise capacity in these patients. Our overarching hypothesis is that exercise capacity response to CR in older patients with CKD may be modifiable by concomitant n-3 PUFA and/or bicarbonate use to suppress acidosis.

**aSPIRE: Study Promoting Critical Illness Recovery in the Elderly**- Rita Bakhru, MD, MS

Older Americans constitute a high percentage of those hospitalized with critical illness. Despite increasing survivorship and multiple studies demonstrating long-term physical and cognitive impairment, little attention is being paid to outpatient practices that could optimize outcomes after
critical illness. There is no literature on patients recovering from critical illness in regards to (1) assessment of post-ICU recovery or (2) optimal outpatient healthcare delivery to facilitate recovery. Objective: To investigate interrelationships between elderly ICU survivors' subjective concerns and objectively measured function in the immediate post-hospital discharge time frame. The association of these factors with 6-month outcomes will guide future studies of interventions. Hypothesis: Objective measures of physical and cognitive impairment and subjective reports of inadequate patient-healthcare system interactions are independently associated with adverse outcomes in the post-hospital discharge window. Specific Aims: Aim 1: To investigate the association between short-term objective measures of physical and cognitive dysfunction and outcomes in elderly ICU survivors. Aim 2: To investigate the association between short-term subjective reports of physical and cognitive dysfunction and outcomes in elderly ICU survivors. Methods: We will perform a prospective cohort study of older survivors of critical illness. This study will characterize their physical and cognitive function in depth immediately following hospital discharge for critical illness. These data will be examined in relation to post-hospitalization outcome measures of quality of life, healthcare utilization, and mortality. Impairments will be explored both objectively (with the Short Performance Physical Battery, dynamometry, and Montreal Cognitive Assessment) and subjectively (through semi-structured interviews), which will be novel to the existing literature. No other study has examined how short-term physical and cognitive impairments are associated with outcomes. Future Studies: This pilot study will provide important preliminary data to inform interventions to improve care for elderly patients who have survived critical illness.

Cardiac Troponin T and Skeletal Muscle Dysfunction in older adults with Obesity and Heart Failure - Tan Zhang, PhD

Our preliminary data suggest that loss of muscle mass and strength and gain of body fat are associated with increased circulating levels of cTnT in obese older adults without any cardiac diseases. Elucidating sources of the elevated circulating cTnT and the mechanisms through which cTnT regulates muscle function in older obese adults will help to develop treatments for HFPEF, characterized by skeletal muscle abnormality (fat infiltration and fiber type switch) and severely reduced exercise intolerance. Our hypothesis is that older HFPEF patients will have higher levels of skeletal muscle cTnT than age-matched obese and lean controls and will be associated with reduced skeletal muscle function. We will test this hypothesis using specimens previously obtained from 30 subjects with age >60 year: 10 HFPEF older patients; 10 age- and gender-matched obese adults; and 10 age- and gender-matched lean older adults without any known cardiovascular diseases as controls. Laboratory and clinical assessments, together with vastus lateralis muscle tissue have already been collected in prior clinical trials (SECRET and IM FIT). This proof-of-concept pilot study will (1) determine if there is higher cTnT level (mRNA and protein) in older HFPEF patients compared to age-matched obese or lean control without HFPEF, (2) establish the association between skeletal muscle cTnT and skeletal muscle dysfunction in the older obese and HFPEF patients and (3) determine if skeletal muscle cTnT plays a role in regulation skeletal muscle innervation/denervation. In addition to the previously well-known role as diagnostic marker for acute cardiac infarction, the proposed study may establish cTnT as a novel biomarker as well as therapeutic target that can be readily applied in aging, HFPEF, and other obesity related diseases.

The current pilot projects are:

Imaging Brain Structure and Function to Predict Physical Performance in Obese Older Adults-Christina Hugenschmidt, PhD (prior RCDC scholar, in collaboration with Paul Laurienti, MD, PhD). Older adults with better physical function have better cognitive function, and poor cognitive function raises the risk for physical decline. Cardiovascular exercise may improve
physical and neural function. However, the neural basis for the link between exercise, cognition, and physical function is not known. Network science approaches to examine physical function-cognition relationships may provide unique insights into the functional architecture of brain networks. Recent WFU findings highlight the importance of brain networks in poor physical function, and the potential for reversibility through exercise. Individuals with poorer physical function (by SPPB performance) had more disorganized brain networks (Fig. 1). Sedentary older adults randomized to a 4-month cardiovascular exercise intervention showed greater connectivity between cingulate cortex and the hippocampus, brain regions important for higher cognitive function, than controls, suggesting neural networks may be targets for exercise and other interventions. The overall hypothesis is that neural connectivity is increased by exercise and physical activity to improve physical function in older adults, and that brain network patterns may be useful in identifying participants most likely to benefit from an exercise and diet intervention. The specific aim is to determine relationships between brain networks and physical function in 45 obese older adults before and after diet-exercise interventions in the INFINITE study (EP9; PI: B. Nicklas), a 5-month aerobic exercise intervention in older adults. Outcomes include aerobic capacity (VO2Max), endurance (400m walk), fat mass/distribution, glucose, inflammatory markers, SPPB, 1 repetition maximum test (1RM), Pepper Assessment Tool for Disability (PAT-D), global cognitive performance, processing speed, memory, and MRI evaluation of brain structure and neural activity. The results will provide novel insights exercise-brain-body interaction and critical data for grant applications targeting these interactions to improve physical function.

**Study Status:** Data collection is complete for this pilot, including additional scans that we were able to collect using additional funding. Currently, data are being cleaned and processed. Errors in lab data entry were caught and should be corrected within the next month, and final analysis of the data should begin then.

**Weight loss strategy designed to protect bones, muscle and kidney function in elderly subjects** – Snezana Petrovic, PhD

Obesity in older adults is associated with a burden of comorbidities that decrease quality of life and life expectancy. Intentional weight loss however results in reductions of both fat and lean tissue, with lean mass loss ranging from 15-35% of total weight lost. The severity and duration of caloric restriction, initial body mass, and concomitant exercise training determine relative loss of lean mass during weight loss. Mechanisms of these effects are incompletely understood. We hypothesize that subtle changes in acid-base status during weight loss contribute to the loss of muscle mass and propose that these can be reversed by bicarbonate supplementation during weight loss interventions. This hypothesis is based on the fact that metabolic acidosis causes sarcopenia in patients with chronic kidney disease, whereas oral bicarbonate supplementation reduces urinary nitrogen wasting and improves lean body mass. Moreover, subtle changes of acid-base status can affect nitrogen balance in postmenopausal women; alkaline producing diets favor lean mass retention in older adults, and lower serum bicarbonate associates with slower gait speed and reduced quadriceps strength. Fasting results in metabolic ketoacidosis, however studies examining acid-base status during moderate or mild calorie restriction and whether this affects loss of muscle- are lacking. The goal of this pilot study is to determine whether weight loss induced by moderate caloric restriction in older adults alters acid-base status sufficiently to affect the magnitude of muscle mass loss during weight loss. Two specific aims are proposed. In the first aim, we will determine acid-base status of participants of the Silver and Demo trials by analyzing serum bicarbonate in 136 participants, before and after the weight loss intervention. We expect that small, but significant, alterations of acid-base status accompany intentional weight loss in elderly, because otherwise healthy older adults exhibit a low-grade metabolic acidosis. This mild acidosis results from the age-related decline of kidney function and impaired capacity of the kidney to excrete acid. In the second aim, we will test for correlation between changes in acid-base status and the magnitude of muscle mass loss during weight loss. Both trials demonstrated a range of lean mass loss that accompanied weight loss, and in the Silver trial there was a trend toward lower muscle mass loss in the participants who consumed
soy-based protein meal replacement (MR) (lesser acid load) vs. non-soy based protein MR, as a part of the intervention. We expect that weight loss produces small, but significant change in serum bicarbonate and that this change negatively correlates with the percent of lean body mass loss. such that the lower the serum bicarbonate the greater the loss of lean mass. The acquired pilot data will provide necessary justification and rationale for a planned, future R21 application that will propose to test the use of bicarbonate supplementation to blunt or prevent muscle mass loss during weight loss.

**Study Status:** To this date, we completed all the analyses planned: tCO2 by spectrophotometry, Cystatin C, bone turnover markers (XLAPs, BLAL), and comprehensive metabolic profile. We have also completed tedious analysis of the food records available for the two studies and have calculated net dietary acid load for those participants for whom meal records were available. We have dietary acid load calculated for all the SILVER participants and for 30 participants in the DEMO trial. Unfortunately, the spectrophotometric analysis of serum bicarbonate levels did not perform well and have yielded unrealistically low values likely due to some technical issue during the analysis; none of these can be recovered, so we will have to rely on the tCO2 measurements reported by the CMP. We expect to start statistical analysis in May 2015 and complete the pilot this summer. Should the results be encouraging, we can proceed to prepare an R21 application for October deadline to test bicarbonate supplementation as a means to alleviate loss of lean mass during intentional weight loss.

The effects of vitamin D supplementation on mitochondrial bioenergetics in older adults – Anthony Molina, PhD

In the past two decades, the role of vitamin D has extended beyond bone health to encompass a wide range of biological activities important to muscle function in older adults. Low 25-hydroxyvitamin D (25(OH)D) concentrations are associated with lower extremity muscle weakness, reduced gait speed, and exhaustion/fatigue in older adults. Clinical findings of vitamin D deficiency include proximal muscle weakness and gait impairments which are often reversed with vitamin D supplementation. Although vitamin D insufficiency is common in older adults, ranging from approximately one-third to three-fourths of community-dwelling adults aged ≥70 years depending on the cut-point used, vitamin D's effects on the mechanisms underlying muscle function are not well understood. Recent evidence supports a role for vitamin D in skeletal muscle mitochondrial metabolism. We hypothesize that low muscle strength and slow walking speed in individuals with low 25(OH)D concentrations may in part be due to diminished OXPHOS activity and lower ATP generation in skeletal muscle mitochondria. The specific aims for this pilot are to examine the effects of vitamin D3 supplementation among older individuals with vitamin D insufficiency on: 1) the bioenergetic profiles of isolated skeletal muscle mitochondrial as well as muscle fibers; and 2) on skeletal muscle mitochondrial mass and biogenesis. We hypothesize that, compared to participants randomized to placebo, those randomized to vitamin D3 supplementation will exhibit improved bioenergetic capacity and respiratory control and increased expression of key mitochondrial proteins (VDAC and COX4) and regulators of mitochondria biogenesis (PGC1a, SIRT1, SIRT3, and TFAM). To achieve these aims, we will utilize muscle biopsy samples already being collected as part of the EVIDENCE (Exploring Vitamin D's Effects on Neuromuscular Endpoints) trial (R01 AG042411; Houston, PI). The EVIDENCE trial is a 12-month, double-blind randomized placebo controlled trial in 200 older (65-89 yrs) men and women with initial 25(OH)D concentrations of 20-<30 ng/mL to determine the effect of vitamin D3 supplementation (2000 IU/d of vitamin D3 or placebo) on change in neuromuscular functions that are established risk-factors for falls in older adults. A subset of randomly selected participants (n=40; 20 from each group) will undergo a muscle biopsy at baseline and 4 month follow-up to examine changes in underlying physiological mechanisms. For this pilot, we will assess the bioenergetic profile of isolated mitochondria and muscle fibers as well as the expression of mitochondrial proteins and regulators of mitochondria biogenesis in pre- and post-muscle biopsy samples from 20 participants (10 per intervention group). Understanding the association between vitamin D and mitochondrial bioenergetics can improve our understanding of the underlying mechanisms linking vitamin D and muscle function and the potential benefits of
remediating low 25(OH)D concentrations in older adults. Moreover, this work will open a new area of research focused on the role of nutritional interventions on mitochondrial bioenergetics.

**Study Status:** To date, we have completed assessments on 10 pre-intervention, and 4 post-intervention participants enrolled in the EVIDENCE clinical trial. In addition, we have recruited and profiled 4 participants in our pilot sub-study which is focused on older adults with initial 25(OH)D concentrations of 13-<18 ng/mL (cutoffs that are lower than used in the EVIDENCE trial).

Pilot Projects completed in prior years:

**Project 1. Development of a Human Retinal Research Bank for Aging Studies** (Johnson, Ph.D. and Tytell, Ph.D., 1992-1993). This study supported development of a human retinal research bank for the analysis of changing in the eyes associated with aging. Over 200 eyes have been collected and processed. This retinal bank was being used for a number of different studies, among others a study examining the effect of heat shock proteins on free radical damage in aging eyes. Two publications resulted from this pilot work.

**Project 2. Assay of Chronic Changes in Trabecular Bone to Determine Correlates with Osteoporosis** (Webber, Ph.D., 1992-1993) This pilot project was funded to develop a simple, non-invasive technology capable of correlating fractal analyses of radiographs of the spine with quantitative digital radiologic assay of bone density abstracted from related regions in individuals exhibiting varying amounts of osteoporotic deformity. The pilot project proved the feasibility of the technology and results were reported and led to further NIH funding (Variable aperture dental tomosynthetic X ray system, NIH-5R01DE12227-03, PI Webber)

**Project 3. Pepper Center Functional Status Index: Development and Validation** (Rejeski, Ph.D., 1992-1993). This pilot study funded methodological work to develop a performance-based measure of function. This index was used in the FAST study and has been and is currently being used in several other OAIC and NIH-funded trials (e.g. ADAPT, PARIS I&II, PIE, REACT I&II). The results of this work were published in two articles and the instrument has later been used as a primary outcome in many other publications from OAIC investigators.

**Project 4. Central Peptidergic Function in the Aging Female: Steroid Therapy** (Sundberg, Ph.D., 1992-1993). This study examined the effect of aging and caloric restriction on spinal cord oxytocin levels in rats. Results demonstrated that spinal cord oxytocin levels are generally higher in the male than the female rat and that aging was associated with a significant reduction of oxytocin. This project has lead to a successful grant application for follow-up research to the National Institute on Aging (NIH-R01AG10850, PI Sundberg) and several publications.

**Project 5. Caregiver and Patient Functioning in Dementia: The Role of Caregiver Skills** (Rapp, Ph.D., 1992-1993). This observational pilot study examined the caregiver skills associated with caregiver emotional and physical well-being and illustrated the stress and coping process in family caregivers of older adults with dementia. The study revealed the difficulty recruiting adequate samples of caregivers at this site and hence the need for multi-site studies. Since a large, multi-site study of caregivers was conducted by other investigators around the time of this study, it was judged to be infeasible to submit a trial proposal by WFUSM investigators. The results of this pilot study have been used to develop a social resourcefulness scale, which has been used in 5 different papers.

**Project 6. Targeted Inspiratory Muscle Training and General Exercise Reconditioning in Elderly Patients with COPD** (Berry, Ph.D.,1993-1994). This study tested the feasibility of exercise as a method to improve physical function and reduce health care utilization in older patients with COPD. The results have been reported in a manuscript and this project lead to the award of two R01 grants (1R01 HL053755-01A1, 2R01 HL053755-05A1, PI Berry) for a large clinical trial of exercise reconditioning in older COPD patients. The
latter of these two is the REACT II study, which is one of independently funded studies that just completed follow up.

**Project 7. Exercise and Congestive Heart Failure** (Kitzman, M.D. 1993-1995). This pilot study tested the feasibility of exercise as a mean to reduce disability in patients with congestive heart failure (CHF). It showed that exercise had potential preventive effects on physical function decline in CHF patients. The project has led to several publications and resulted in a total of three R01 grants funding full intervention studies on exercise and pharmaceutical intervention among older persons with congestive heart failure (NIH-5R01AG12257-03, NIH-5R01AG12257-07, R01AG18915, PI Kitzman). The latter of these three is the PIE2 study, which is one of the independently funded studies, that is supported through the present OAIC application. This pilot project formed the basis for Dr. Kitzman’s extremely productive and impressive research career in identifying and examining Diastolic Heart Failure and its physiology, treatment and implications in older persons.

**Project 8. Lifestyle Intervention Study in Seniors with Arthritis** (Messier, Ph.D., 1993-1994) This pilot study examined the feasibility of a diet and exercise intervention in older persons with osteoarthritis. The feasibility and the potential benefits of this intervention were demonstrated and published. This resulted in the decision to develop the Arthritis, Diet, and Activity Promotion Trial (ADAPT) as the main intervention study in the second OAIC grant (NIA P60AG10484) which has led to additional ancillary funding on gene polymorphisms and prevention of disability (R01 AG18702-01A1, PI Pahor) and a planning grant on exercise and the prevention of disability (NGA 1 R21AG19353-01, PI Pahor). Dr. Messier received funding for R01 AR052528 to examine the effect of diet and exercise intervention for preventing physical health decline in the general older population.

**Project 9. Enhancing Recovery from Breast Cancer** (Shumaker, Ph.D., 1994-1995) This pilot study tested the feasibility of exercise as a way to enhance recovery from breast cancer in older women. The results have resulted in a publication showing potential effects of exercise on the immune system and have served as pilot data for two full exercise intervention studies among breast cancer patients which are funded by NIH (NIH-1R55XA7818-01A1, PI Shumaker) and the Department of Defense (DOD grant, PI Anderson). The latter grant is for the RESTORE study, one of the independently funded studies that is supported through the current OAIC application.

**Project 10. MRI for Knee OA** (Carlson, Ph.D. 1994-1995). This pilot study examined the use of magnetic resonance imaging and traditional radiology as a mean for diagnosing knee OA in cynomolgus monkeys, an animal model of OA. The study confirmed that our current MRI scanners allow excellent visualization of the internal structures of the knee joint and that both MRI and x-ray can be used to grade OA. Results correlated well with histology and pathology. Results have been presented and published and resulted in one NIH grant (5R01 RR14099-09, PI Carlson).

**Project 11. The Role of Proteoglycans in Metabolism of Advanced Glycosylation End Products and Arterial Cells** (Edwards, 1994-1995). The focus of this pilot study is the evolvement of cell surface proteoglycans in the metabolism of glycated low-density lipoproteins. The study demonstrated enhanced transport of LDL-AGE compared to control LDL across endothelial cell monolayers. Two NIH grants (NIA-5P51RR00167-390046 PI Weindruch, NIA R03 AF14190-01A1, PI Edwards) and one grant from the American Diabetes Association (PI Edwards) have been awarded on the basis of the results of this pilot study and several manuscripts have been published.

**Project 12. Skeletal Muscle Maintenance and Repair in the Elderly** (Delbono, M.D. Ph.D., 1994-1995) This project examined alterations in membrane properties, intracellular signaling and contraction properties in single intact muscle fibers from aging humans and rodents. It concluded that type II muscle fibers exhibit marked alterations in membrane properties and intracellular signaling in humans older than 65 compared with a group younger than 35 years. The results have lead to several publications and the successful awarding of a special
emphasis career award (5K01AG00692-04, PI: Delbono) and two NIH grants (5R29AG13934-03, PI: Delbono and R01 AG15820-03, PI: Delbono).

Project 13. **IGF-1 and Matrix Repair in Articular Cartilage** (Loeser, M.D., 1994-1995). This pilot study examined the effect of articular condrocytes to IGF-1 stimulation. The results showed that IGF-1 stimulates chondrocyte cell surface expression of the alpha 3/alpha 5 integrin subunit band and stimulate adhesion of chondrocytes to fibronectin and type II collagen. This pilot study resulted in a published manuscript, two NIH study grants entitled 'Aging and IGF-1 in Cartilage' (NIH 1R01AG016697-01A1 2001-2005 and 2005-2010), and an award to Dr Loeser from the American Federation for Aging Research: A Paul Beeson Physician Faculty Scholar Research Award.

Project 14. **Effects of Caloric Restriction on Intracellular Mechanisms Regulating Glucose Transportation in Muscle** (Cefalu, M.D., 1994-1995). This project was designed to evaluate the role of caloric restriction in altering muscle morphology in non-human primates subjected to caloric restriction. The project demonstrated that insulin sensitivity in caloric restriction states is not secondary to changes in muscle morphology. Nor did caloric restriction appear to alter glucose transporter levels. Dr. Cefalu has published these results and received a NIH follow-up grant to further examine caloric restriction, aging and insulin action (R01 AG15823, PI: Cefalu).

Project 15. **Community Resources Advocate** (Moran, M.D., 1995-1996). This pilot study demonstrated the efficacy of a community resource advocate to improve the functioning and effectiveness of the Community Care Coordination Network. Results were published and Dr. Moran received a grant from the Kate B. Reynolds Foundation to set up a community volunteer program based on his previous work.

Project 16. **Shaping Active Living in the Elderly** (Rejeski, Ph.D., 1995-1996). This project examined a traditional exercise program versus a behavioral-based lifestyle intervention to determine the effects on long-term physical activity. The results of this project suggested that persons in a lifestyle intervention had higher levels of activity and caloric consumption than persons trained in a traditional exercise program. This favorable outcome resulted in the development of the Cardiovascular Health and Activity Maintenance Program (CHAMP study) funded through the second Wake Forest OAIC grant (3P60AG10484-07S10005). This data also led to the CLIP study (R01 HL076441) that is currently being supported in the current OAIC application.

Project 17. **Mature Adult Passport** (Cohen, Ph.D., 1995-1996). This project is designed to aid in the development of an interactive booklet to enhance compliance with health behaviors and to facilitate communication between patient and physician. Upon the successful development of this booklet, this pilot project has resulted in the development of other health guides (e.g. for Hispanic women, for older adults in general and for a Congestive Heart Failure Guide) which were funded by NIH, CDC and the American Association of Health Plans.

Project 18. **Increasing participation in cardiac rehabilitation** (Anderson, Ph.D., 1997-1998). This pilot project tests the effect of physician and health-educator practices to motivate older persons with a recent MI to participate in cardiac rehabilitation. Initiation of and short-term adherence to cardiac rehabilitation is compared among patients treated by a cardiologist and patients treated by specially trained physician and health-educator. The results of this project have been published several times. Results of this project were also used to develop an R01 grant proposal, which was not funded.

Project 19. **Priming and signaling in neutrophils from elderly individuals** (McPhail, Ph.D., 1997-1998). The project is characterizing the regulation of the respiratory burst by cytokines in neutrophils from healthy young, middle-aged and elderly individuals. Signaling pathways following cytokine priming appeared to be altered in neutrophils from elderly individuals. These results have resulted in a NIH-funded follow-up study that examines the regulation of oxygen metabolism blood neutrophils (5R01 AI22564-15, PI McPhail).
Project 20. Genetic epidemiology of diabetic cardiovascular disease (Bowden, M.D., 1997-1998). This pilot project examined the feasibility of providing the infrastructure for recruiting and clinical characterization of Type 2 Diabetes Mellitus sibling pairs. The pilot study proved that with the developed system, it was possible to recruit and phenotype 20 sibling pairs, demonstrating the feasibility of carrying out a larger study. This project resulted in several publications so far and in a grant from the American Diabetes Association, which was subsequently followed by a NIH-grant (1R01 HL67348, PI: Bowden). These subsequent grants allowed Dr. Bowden to set-up the 'Diabetic Heart Study', a study that will recruit and examine 300 Type 2 sibling pairs in the area of Wake Forest University.

Project 21. Cognition and estrogen in aged female monkeys (Voytko, Ph.D.,1998-1999). This pilot project compares memory function of old female rhesus monkeys with and without ovariectomy and examines the effect of estrogen replacement therapy (ERT) on cognitive function. Memory performance both on a delayed response tasks as well as visuospatial attention tasks were improved in ERT-treated monkeys compared to placebo treated monkeys. These findings have been published several times and a NIH-grant entitled ‘Cognition and Estrogen in Menopause: A Monkey Model’ was funded (NIA R01 AG13204-08).

Project 22. Memory improvement trial in seniors (Rapp, Ph.D. and Marsh, Ph.D.,1999-2000). This pilot study was a randomized trial of a 6-week skills training program in older adults with documented mild cognitive impairment. Four cognitive memory enhancement strategies were taught. Compared to untrained control subjects, trained participants had more positive perceptions of their memory ability following training and 6 months later. There were no differences between groups on laboratory memory measures following training but a trend emerged by the 6-month follow-up assessment favoring trained participants. A paper of these results has been published. A multi-center RCT grant was awarded based on these results that will examine the efficacy of a memory improvement program (Seniors Health and Activity Research Program Pilot - SHARP-P, R01AG029285).

Project 23. Arterial calcification: a significant problem in aging populations (Wallin, M.D., 1999-2000). This study seeks to elucidate mechanisms responsible for calcification of the arterial wall. Findings showed that a vitamin K-dependent protein in the vessel wall regulates the activity of bone morphogenetic proteins, which can turn on bone formation in the wall. The pilot data have resulted in two published articles. The data were also used for the NIH grant proposal 'Vitamin K, Bone, and Arterial Calcification' that was recently funded (NIH R01 HL069331, PI: Wallin).

Project 24. Long-term effects of enalapril on physical performance in aging rats (Carter, Ph.D., 2000-2001). This study explored the effect the ACE inhibitor enalapril in healthy older rats over a 6-month time period. Physical performance appeared to decline but this was influenced by treatment. Since a small dose of enalapril was used (10mg/kg), the work has contributed to our ability to acquire further funding to examine potential effects at higher doses of ACE inhibitors. In addition, the results have resulted in four other extramural grants that explore potential medication effects on physical performance outcomes (American Federation for Aging Research grant, PI Carter; NIH 3P60 AG10484-10S1, PI Pahor; NIH 1R03AG019936-01, PI Pahor), PI Carter, NIH R01 AG024526. Several manuscripts have been published.

Project 25. Efficacy of exercise with and without ACE inhibitors in improving physical function in older adults (Williamson, M.D., 2000-2001). This pilot project examined the effect of ACE inhibitors on physical function decline over 10 months in 36 frail older persons living in an assisted living or nursing home facility. All persons received initial 3-month exercise training. Preliminary data-analyses show that persons on ACE inhibitors had a slightly improved walking speed (-9.9%) after 10 months compared to persons without ACE inhibitors (+8.3%), but no difference was found on muscle strength or DXA measures of muscle mass. The latter may partly be explained by the fact that the follow-up period was rather short and the sample was so frail that occurring health events may have obscured the potential effect of ACE inhibitors on muscle strength and
mass. In addition, this pilot study had guided the selection of OAIC support to the EFIT study to examine the potential effect of use of ACE inhibitors on physical function measures over a 6-month period. That study ended in 2004.

**Project 26. Gene therapy of sarcopenia** (Delbono, Ph.D., 2001-2002). Through this pilot study, an IGF-1-rAAV gene was constructed and successfully injected intrathecally in rats. Expression of the virus construct was detected in spinal cord of adult (7 months) and senescent (28) rats. A NIH research grant has been obtained through this pilot study (R01AG13934 – Single skeletal muscle impairment with aging, PI Delbono).

**Project 27. Effects of spironolactone on exercise capacity and quality of life in older subjects with diastolic heart failure** (Kitzman, MD, 2001-2002) This open-label trial of spironolactone showed that in eleven women with isolated diastolic heart failure, aldosterone antagonism with spironolactone is well tolerated and appears to improve exercise capacity and symptoms. Several manuscripts have been published. This resulted in an R01 with funding from 7/1/05-6/30/09. NIH 2R01-AG18915. In addition this project received a Merit Award.

**Project 28. Frailty and intensive treatment of hypertension in the elderly** (Di Bari, M.D., Ph.D., 2001-2002). This pilot project aimed to evaluate the short-term feasibility and safety of intensive treatment of hypertension in frail older persons. Treatment was planned to follow Joint National Committee (JNC-VI) guidelines of a goal blood pressure of <140/90 mmHg. This project was stopped due to poor response to inclusion/exclusion criteria. Also, Dr. DiBari concluded that the study would have required a tremendous effort in terms of community based recruitment, which was unsustainable with the limited resources.

**Project 29. Cox 2 inhibitor NSAID in osteoarthritis** (Messier, Ph.D., 2001-2002) This randomized pilot project was planned to test the study hypothesis that the use of non-steroidal anti-inflammatory drugs (Cox-2 inhibitor) will improve disability, physical performance, inflammatory biomarkers and pain compared to the use of placebo (control condition). Sixty older persons with osteoarthritis will be enrolled. This project was stopped due to denial from the internal review board (IRB).

**Project 30. Antidepressants and physical exercise in older persons with minor depression** (Penninx / Brenes, Ph.D., 2001-2002) This project examines the feasibility and efficacy of antidepressant treatment and an aerobic exercise regimen (compared to a control condition with phone follow-ups) among 45 older persons with minor depression. Emotional health (depressive symptomatology) as well as physical health (performance, disability) are primary study outcomes. This study has finished recruitment and data analyses. Results were presented at a Pepper Center Investigator’s meeting and show that mildly depressed persons who received either exercise or medication, improved their emotional health more than those in the control group. It was especially the mildly depressed persons who received exercise who improved their physical health. These data have been published in *Aging and Mental Health* and an R01 was submitted in June 2006 but was not funded.

**Project 31. IGF1 in Aging and Cancer: Role of modulation of iron metabolism and oxidative stress** (Torti, Ph.D., 2001-2002). This pilot project examines whether normal processes of down regulations of IGF-1 during aging lead to a reduction in ferritin, a response that exacerbates oxidative stress and ultimately contributes to carcinogenesis. Funding for this pilot project comes from a combined initiative of the WFU Comprehensive Cancer Center (50%) and our current OAIC (50%). Investigators on the project are both from the Comprehensive Cancer Center (Torti) and from our OAIC (Delbono, Sonntag). This pilot project is one of the examples of an ongoing collaborative initiative with other WFU research centers that will stimulate established researchers who work in other areas of research to develop an interest in aging research and consequently develop and conduct aging-related research. Initial results suggest that in aged rats, there is a decrease in levels of ferritin protein in muscle, which is consistent with a model in which aging increases susceptibility to oxidative stress through a down regulation of proteins that are important to cellular protection from oxidative stress. Analyses of the effects on mRNA to determine whether this is a transcriptional or translations effect is
ongoing. The changes seen in these measures are relatively modest and without further pilot data, are difficult to interpret.

Project 32. Prosocial behavior as a motivational facilitator of exercise adherence among older adults: a preliminary study (Foy, PhD, 2002-2003). Of the 38 participants randomized into the study, 35 completed baseline and 3-month assessments, producing a retention rate of 92%. Results from this trial were used as preliminary data that was included in an R21 application that was awarded in 2008.

Project 33. Reliability of the 400 meter walk test as an assessment of mobility limitation in seniors (Cesari, MD, 2002-2003). Sixty participants (age ≥65 years) who reported ≥2 difficulties in 4 functional domains (mobility, upper extremity function, ADL and IADL tasks) were recruited from the community. The 400-meter test and a 4-meter test were retested within 7 days. The test-retest reliability for disability to complete the 400-meter test is excellent (kappa=1) and speed in the 4-meter test is highly predictive of ability to perform the 400-meter test. These data supported the LIFE Trial Application (U01 AG022376). Paper published in JAGS 52:972-976, 2004.

Project 34. Anti-inflammatory drugs and performance in aged rats (Carter 2001-2003) This study compared the effects of long-term ACE inhibition on physical performance and body composition in aged rats (24 to 30 months of age). These data show that age related declines in physical performance were moderately attenuated with ACE inhibition. These effects were most likely modulated changing body composition as animals receiving ACE inhibition treatment were lost significant amounts of fat mass, as measured by DXA, relative to the control group. This study resulted in 2 published manuscripts and a R01 AG024526-01.

Project 35. Potential contribution of inflammation and skeletal muscle loss to disability in diastolic heart failure and the potential role of ACE inhibitor therapy (Kitzman, MD, 2001-2004) Results to date suggest that stable, ambulatory elderly patients with diastolic heart failure have greater interstitial fat within the muscle compartment compared to healthy matched controls and this tended to be associated with lower exercise tolerance. In addition, 32 muscle biopsies were performed in 22 subjects (including 1 year follow up). This work was in conjunction with the Research Development Core, and supported the development of thigh muscle biopsy techniques. In addition, the scope has been expanded in order to add biopsies in older patients with systolic heart failure being enrolled in an NHLBI funded trial of exercise training for mortality reduction (HF-ACTION) in a collaborative effort with several other Pepper Centers. Competitive renewal of the parent study began 7/1/05 (RO1 AG 18915), including a Merit Award Extension.

Project 36. Relationships between biomarker of the systemic oxidative stress, 8-iso-PGF-M, systemic inflammatory markers, and muscular function (Ilyasova, PhD, 2002-2004). This is an ancillary study to the NIH-funded TRAIN study (PI: Pahor). The required 60 participants have been recruited and their baseline specimens, urine and plasma, are being collected. Follow-up data and specimens of all 60 participants are finished and laboratory measurements are complete. Data analyses are complete. Data was also used to support a R01 that was funded (R01 AG0265556) for a previous RCDC fellow (Cesari).

Project 37. Power training in older adults: mechanisms underlying change in muscle function (Marsh, PhD, 2002-2004). Data collection, entry and cleaning is complete. Results show power training is a feasible, safe, and efficacious intervention. The power group showed similar improvements in knee extension and leg press strength to the strength group. The power group showed significantly larger improvements in knee extension and leg press power compared to the strength group. The strength and power improvements for the power group were significantly different from control. Thus the effect of the intervention was considerable. An RO1 has been submitted twice and both times not scored. As a result two RO3’s have been submitted and both unfunded. Two manuscripts have been published and one accepted.
Project 38. Leg blood flow, sarcopenia and physical function, (Hundley, MD, 2002-2004). Thirty six individuals were enrolled with 26 completing all aspects of the study. This project resulted in development of a new, noninvasive method to measure blood flow in the aorta and peripheral arteries at rest and after submaximal exercise, as well as assess in a near-simultaneous fashion leg muscle mass and in vitro muscle composition. Methods and data from the project were incorporated into NIH RO1 HL076438-01A1 that was funded 2/1/07-12/31/11, and form the basis for the STTR application that was was awarded in 2008 and 3 publications have resulted from this data.

Project 39. Effect of muscle power on disability: analyses of the InChianti Study, (Marsh, 2002-2004). Data analyses are complete. Results show that muscle power is independently associated with poor physical function, as determined by walking speed and stair climb ability. The association between muscle power and performance measures appears to be curvilinear. A manuscript was published in the Journal of Gerontology.

Project 40. Effect of ACE inhibitors on skeletal muscle and physical disability in older adults (Onder, MD, 2002-2004). Preliminary findings show that ACE inhibitor users do not appear to differ from non-ACE inhibitor users in terms of fat mass and lean mass. Analyses on other outcomes such as muscle strength and onset of disability have been published in the Journal of Gerontology.

Project 41. Effects of caloric restriction on physical performance in aged rats: role of cytokine expression and release from visceral adipose tissue (You, Ph.D., 2004-2006). Animal housing, performance and body composition testing, and tissue collection have been completed. Completed biochemistry analyses include serum levels of lipids, oxidative stress marker (TBARS), and inflammatory marker (CRP), adipose tissue gene expression and release levels of inflammatory cytokines (IL-6 and TNFa). Data analyses are complete and a R21 award was submitted in June 08.

Project 42. Developing CT measures of Adiposity and Body Composition for application in population based and genomic research (Carr, MD, 2004-2005). This pilot project is performing body composition phenotyping of a subset of 400 DHS participants with CT assessments of abdominal adiposity, hepatic steatosis, and psoas muscle attenuation. Assays of inflammatory markers and for adiponectin and leptin have been completed. One manuscript has been published.

Project 43. Optical Imaging of Skeletal Muscle (Hamilton, MD, 2004-2005) A multidisciplinary team from Wake Forest Biomedical Engineering and NanoSonic Inc. has built a device that will allow in vivo assessment of skeletal muscle tissue. The prototype device now being tested utilizes optical fiber inside a standard 22 Ga. hypodermic needle, an infrared wavelength light source, coupled with a detector and a laptop PC. To date, we have been able to identify signatures within the IR spectrum that consistently match to specific fiber types. SBIR proposal “Minimally Invasive in vivo Muscle Biopsy with a Fiber Optic Probe” was submitted to NSF on December 1, 2005 with Nanosonic as our industrial partner as was not funded.

Project 44. Pericardial Fat and Subclinical and Clinical measures of Cardiovascular disease in a multi-ethnic sample of US adults. (2005-2006 PI: J. Ding) Investigators have developed a new method to measure the volume of pericardial fat in large epidemiologic studies. To examine the validity of this new method, they measured pericardial fat in a sample 10 Diabetes Heart Study participants. They also measured pericardial fat in a sample of 160 Multi-Ethnic Study of Atherosclerosis participants from Forsyth County, NC to examine the reproducibility of the new method. Finally, they assessed the association of pericardial fat with calcified coronary plaque. Using the preliminary data from this project, a R01 grant proposal was funded (R01 HL085323) and one paper has been published.

Project 45. Metabolic and Genetic Determinants of Non-Alcoholic Fatty Liver Disease in African-Americans and Hispanic Americans. (2005-2006 PI: L. Wagenknecht) This pilot will examine the epidemiology of fatty liver in a subset of 300 participants in the IRAS Family Study with specific attention
given to age-related differences in the risk factor profile for fatty liver, and the relationship of fatty liver to cytokines, muscle mass by DXA, and physical function. This preliminary analysis included 85 non-diabetic Hispanic Americans from 9 pedigrees. An important result was the high prevalence of fatty liver among persons with the Metabolic Syndrome (MetS). Overall, fatty liver (LS ratio < 1.0) was detected in 20% (17/85) of the subjects; 10% (7/70) among those without MetS and 67% (10/15) among those with MetS. An abstract has been published and the IRAS family study was funded for another 5 years.

Project 46. Impact of an Exercise Program on Physical Function, Body Composition, and Quality of Life in Aging Recipients of Renal Allografts. (2005-2007 PI: E. Hartmann) The aim of this pilot is to yield preliminary data to design a large scale intervention and prevention trial. This study has two components: an observational cohort consisting of 26 dialysis patients aged 60 years or greater awaiting transplantation, and a substudy of up to 20 transplanted patients randomized to either usual care or fitness training. This pilot is unique in that it focuses on the older renal transplant recipient controlling for prior physical state in a way that other studies have not. Data from this pilot lead to The American Society of Nephrology and the Association of Subspecialty Professors Grant (7/1/2006-6/30/2008).

Project 47. Effects of Sarcopenic Obesity on Recovery from a Trip. (2006-2007 PI: M. Madigan) This pilot will use an existing experimental model of trip recovery to evaluate the effect of obesity on the ability to recover from trip (Specific Aim 1), and to examine the role of muscle strength in the ability to recover from a trip (Specific Aim 2). The work will focus on trips because they are responsible for up to 53% of falls that older adults experience. The long-term goal of this research is to understand the biomechanical requisites of trip recovery that are specific to obese adults, and to develop an experimental basis for conducting and validating a fall prevention exercise intervention that targets these requisites. One manuscript has been published, 3 submitted papers and portions of these results were used for an R01 submission in 2008.

Project 48. Does Weight Loss Following Laparoscopic Roux-en-Y Gastric Bypass Improve Physical Function? (2005-2007 PI: G. Miller) The purpose of this observational pilot study is to examine physical function in obese individuals with a BMI > 35.0 kg/m2 following treatment for obesity using laparoscopic Roux-en-Y gastric bypass surgery. It is hypothesized that the intensive weight loss associated with bariatric surgery will improve physical function over a 12 month follow-up period. The primary aim to address this hypothesis is to determine self-reported physical function and performance on physical function tasks as a result of weight loss from obesity surgery. Patients saw a 21-35% improvement in physical function post surgery. Outcomes were presented to the NAASO.

Project 49. PPAR agonists and femoral blood flow. (2005-2008 PI: D. Eckman) This pilot project was designed to evaluate the vascular mechanisms that potentially contribute to progressive loss of endurance and skeletal muscle performance seen in aging. This age-associated loss of skeletal muscle function may be, at least in part, due to an inability to deliver adequate blood flow to the tissues during times of increased demand. It has recently been shown that peroxisome proliferators-activated receptor (PPAR) activators improve endothelium-dependent vasodilation, increase NO bioavailability and decrease oxidative stress; thus, these agents may improve femoral arteriolar reactivity in the aging animal. This proposal examined the hypothesis that treatment with PPAR activators improves physical performance measures in aged (24-mth old) Fisher 344/Brown Norway (F344XBN) rats. Results to date show improvement in physical performance measures in PPAR- treated animals compared to age-matched controls. In addition, there is an improvement in RTE times in both pioglitazone- and fenofibrate-treated aged rats. Furthermore, PPAR treatment is associated with weight gain whereas fenofibrate treatment is associated with weight loss in aged rats. Findings were presented at a WFU Medical Study Research Day, one manuscript and a NIH R01 submission is in preparation.

Project 50. Effect of Acute Inflammatory Mediators on Duration of Functional Limitations in Elderly Patients with Acute Respiratory Failure. (2006-2008 PI: P. Morris) This pilot hypothesize’s that it is the magnitude and duration of acute systemic inflammation seen with Acute Respiratory Failure (ARF) that
specifically contributes to the delay in mobility recovery for aged ARF patients. For the ARF patient, we suspect that Early ICU Mobility serves to reduce the magnitude or duration of the acute inflammation, in elderly patients, more so than in young patients. This pilot will analyze serum cytokines to determine whether a relationship exists between inflammatory cytokines on ICU days 0-7 and subsequent mobility limitations at hospital discharge. These data will seek to explore the role of Early Mobility as a moderator of cytokine-mediated muscle dysfunction. 78 of the planned 100 people have been enrolled into the study. Three manuscripts have been published and a NIH R01 NR011186 grant was funded in 2009. Five separate presentations at international meetings (1 podium, 1 abstract, and 3 invited talks at symposia), a NCBH-sponsored 1/2 day conference for Physical Therapists, two intramural grants funded (Cross Campus and Pepper Center), and an Innovation Profile, Four-Step Protocol Determines Therapy for Patients With Acute Respiratory Failure, Leading to Improved Mobility, Shorter Stays, appeared in the March 2009 issue of the AHRQ Health Care Innovations Exchange Web site (www.innovations.ahrq.gov).

**Project 51. Molecular Characterization of Adipose Density by Non-Invasive Imaging in Humans and Non-Human Primates (2009-2011 PI: H. Shi)** The aim of this study is to determine whether higher adipose density measured by CT imaging in nonhuman primates exposed to a high-fat diet is positively correlated with greater adipose inflammation and macrophage infiltration. This study is a joint effort between the PI (Hang Shi) and Dr. Thomas Register at primate Center. After discussing the collaboration with Dr. Register to split the workload of this project, the PI will use FACS analysis of adipose macrophage content and JNK activity/phosphorylation as two outcomes to determine the status of adipose inflammation. We recently succeeded in developing the methodology for FACS analysis of adipose macrophage content, a technology that can be broadly used in evaluating macrophage and other immune cell infiltration into adipose tissue in various model systems including mouse, primate, and human. We will now use this newly-developed analysis to examine the macrophage content in human adipose tissue. Study is completed and an AMPK NIH Grant was awarded.

**Project 52. Leptin and Cartilage Degradation: An Adiposity-Osteoarthritis Link. (2007-2010 PI: R. Yammani)** Decreased IGF-1 function in osteoarthritic cartilage results in loss of cartilage leading to the development of OA. Visfatin, has been recently found in the synovial fluid of OA patients and is hypothesized to have a local affect on the joint tissue. Here we demonstrate that the visfatin inhibited IGF-1 signaling and PG synthesis in human articular chondrocytes. Interestingly, stimulation of chondrocytes with visfatin activated the ERK/MAPK pathway independent of IGF-1 receptor. A recent study has shown that increased activation of ERK signaling pathway is inhibitory for IGF-1 mediated activation of IRS/AKT signaling pathway4. Taken together these findings suggest that the activation of ERK/MAPK pathway by visfatin in chondrocytes could contribute to loss of IGF-1 function and provide the possible mechanism for IGF-1 resistance in OA.

**Project 53. Vitamin D status, VDR polymorphisms, and physical function in older adults (2007-2011 PI: D. Houston)** The first aim to examine the association between vitamin D status, using circulating levels of 25(OH) D and PTH, and muscle strength and physical performance in the LIFE-P Study is underway. Approximately 50% of the LIFE-P cohort had 25(OH) D levels indicative of insufficiency (<50 nmol/L). Participants with insufficient 25(OH) D levels had significantly lower SPPB scores and slower 400-m walk speeds at baseline compared to those with sufficient levels. Participants who had insufficient 25(OH)D levels at baseline but sufficient levels at follow-up had significant improvements in SPPB scores after adjustment for demographics, intervention group, season, BMI, and physical activity (Mean change (SD): 0.57 (0.22), p=0.01). The results were presented (2008-American Geriatrics Society and Gerontological Society of America; 2009-Experimental Biology) and the manuscript is in press (J Gerontol A Biol Sci Med Sci. 2011; 66(4):430-6).

**Project 54. ACE gene polymorphisms and resistance training in COPD. (2007-2010 PI: M. Berry)**
This project, included in our competitive renewal for year 1 funding, also applied for and received funding through the WFU Translational Science Institute, resulting in significant ‘leveraging’ of OAIC funding. We have finished recruitment and the exercise intervention portions of our study. We enrolled 34 participants (goal of 32) and 26 participants completed all screening visits, the 12-week exercise intervention, and all follow-up visits. Data analysis is ongoing, and the project has arranged for Dr. Nicklas’ lab to measure serum CRP, IL6, and TNF-α.

Project 55.
Wake Seniors - Establishing a partnership with Senior Living Communities (2008-2010 PI: J. Williamson) This is an OAIC/TSI co-funded project that is a collaborative translational research project between Wake Forest University, Wake Forest University Baptist Medical Center, and Senior Living Communities. The long range objective is to implement and evaluate a variety of interventions that are designed to prevent, rehabilitate, or slow the loss of functional decline. Over the past year we have: (1) built a web-based data entry system for our research with SLC; (2) set-up computers in 6 facilities and now have the web-based entry system fully operational at these sites; and (3) tested and entered demographic, health, and disability related data on 189 participants at these 6 sites.

Project 56.
NORMALS – A Study to Develop a Database of Determinants of Physical Function in Healthy Older Persons Free of Co-Morbidities (2008-2009 PI: D. Kitzman) This is a competitively funded OAIC supplement study. The primary aim is to establish a shared, central database from a group of healthy, older male and female volunteers free of chronic medical diseases that includes detailed standardized assessments of physical performance and body composition. A majority of the data have been entered, cleaned, and made available to the Pepper Center database, thus fulfilling in part the primary aim of this grant. The muscle biopsy cores are being analyzed in Dr. Kraus’ lab at Duke University and the fresh single muscle fiber analyses were performed in Dr. Osvaldo Delbono’s lab here at Wake Forest Medical Center. The automated instrument allowed us to measure fiber specific force, contraction velocity and power in the same fiber in approximately 60 fibers. The data from of the Healthy NORMALS Study were also included as preliminary data for “I’m Fit” project application which was funded. (PI: Dr. Nicklas). Data clean-up has been completed, analyses are underway, and preliminary results will be presented at the National Pepper Investigators meeting in April 2011. Already, several requests for use of data have been received and approved, including from junior faculty and for pilot studies and RCDC scholars.

Project 57.
Age, Body Composition, Functional Status and Immune Function in African Green Monkeys (2010-2011 PI: J. Stehle) A recent WFU OAIC pilot project (PI: C. Shively, see below) demonstrated that aged monkeys walk slower and have other functional differences compared to younger counterparts. The objective of this proposal is to determine potential mechanisms in which chronic systemic inflammation influences age related declines in physical ability in young adult and aged African Green Monkeys. The project is evaluating interactions between dendritic cells (DCs) and T helper cells which may skew differentiation towards the inflammatory Th17 pathway. DC cytokine profiles in older subjects will be compared to those produced by younger subjects; and types of helper T cells present within the adipose tissue will be assessed in relation to age and body composition. Relationships between these immunological parameters, serum levels of inflammatory markers, and physical function as a surrogate for disability risk in the non-human primate population will provide mechanistic insights into the role of immune system dysfunction in physical decline.

Project 58.
Computed Tomography (CT) Imaging of Lingual Muscle/Fat Composition in Community-Dwelling Older Adult Aspirators and Non-Aspirators (2009-2011 PI: S. Butler)
Oropharyngeal aspiration plays an important role in the development of pneumonia in the elderly. The primary aim is to identify mechanisms underlying sub-clinical pulmonary aspiration so that interventions can be developed to prevent aspirational damage. Previous research has demonstrated that older adult swallow is weaker and slower. The primary hypothesis is that one of the contributors to the weaker and slower older adult swallow is a higher adipose or fat composition in the swallowing muscles, such as the tongue. The primary aim is assess for the first time tongue strength and fat composition as correlates of aspiration in community-dwelling adults greater than 65 years. Specific aim one will be to obtain data on tongue composition, via CT imaging, of 65 community-dwelling adults who aspirate versus those who do not aspirate as identified on an instrumental swallowing evaluation. The long-term goal is to advance the understanding and management of community-dwelling adults as well as patients with diagnosed aspiration and pneumonia risks.

**Project 59.**


Heat shock proteins (HSPs) decrease in muscle as people age, and prematurely reduce in insulin resistant and diabetic patients. Diabetes (DM) is a major cause of disability in aged individuals through complications that include neuropathy, amputation, diabetic ulceration, obesity and heart disease. Blood glucose is primarily metabolized by skeletal muscle and thus improvements in muscle metabolic capacity to cope with increased glucose should limit the development of disabling co-morbidities listed above. Increasing muscle chaperone proteins, particularly the HSP family, increase longevity and reverse obesity-associated DM in preclinical studies. One potential mechanism is by reducing inflammation associated with protein glycoxidation that occurs with normal aging or DM. Inflammation reduces insulin sensitivity, thus propagating a vicious cycle of declining insulin sensitivity. We hypothesize that increasing muscle HSP70 will improve glucose disposal, reduce inflammation and thus delay disabling co-morbidities seen in aging and DM. Currently it is unknown whether interventions that increase skeletal muscle HSPs will lead to improved skeletal muscle glucose metabolism. We plan to answer this gap in knowledge by assessing aged, glucose intolerant vervet monkeys before and after therapies aimed to increase muscle HSP70. Geranylgeranlyacetone, a prescription drug known to increase HSP70, will be administered in pilot clinical trial with insulin sensitivity, glucose metabolism and skeletal muscle HSP levels assessed before and after treatment. Heat is a known inducer of chaperone proteins. A second study will utilize heated hydrotherapy to increase muscle tissue temperature by 1-2°C and moderately increase the heart rate. Both feature as physiologic responses to exercise, which potently improves glucose metabolism but is rarely feasible in aged and disabled patients. The same study endpoints will be compared with the pharmacologic intervention. This assessment of aged, glucose intolerant primates will establish skeletal muscle HSPs role in glucose metabolism and provide proof of concept as a target for age-associated decline in muscle metabolic function.

**Project 60.**


This project has received funds from both the WFU Pepper Center and the WFU Translational Science Institute. The long term goal of the proposed translational research project is to provide key preliminary data for competitive grant applications to test hypotheses about mechanisms underlying variation in the decline in physical functioning with aging. To achieve this goal, we developed and validated a primate model of functional aging which included a battery of tests to evaluate physical mobility and function in old and young adult cynomolgus and vervet monkeys. Walking speed, activity levels and range of motion of old adult and young adult controls were measured. Although overall activity levels were the same between old and young animals, older animals were found to walk slower, and to climb and jump less frequently than the younger adult animals. Function is being assessed in relation to body composition (whole body lean and fat mass), bone density by DEXA, distribution of fat in subcutaneous and visceral compartments, muscle, and other organ systems by whole body CT, and circulating biomarkers relevant to adiposity and inflammation. Measurements are to be integrated with muscle assessments from biopsy tissue, cognitive and social behavioral assessments, and biomarkers of lipid and carbohydrate metabolism, and inflammation. These data is now available to the Pepper OAIC community and planned for use in subsequent interventional studies.
Project 61.
The impact of aging on the proliferation and differentiation potential of intramuscular adipose derived stem cells (2009-2011 PI: M. Van Dyke)
Preliminary experiments demonstrated that adipose derived stem cells (ADSC) from young and old rats display different proliferative and differentiation capacity. The primary hypothesis is that age-related changes in ADSC behavior may be responsible for a decreased capability of ADSC to serve as a regenerative cell reservoir for muscle tissue and may instead exacerbate the deposition of intramuscular fat observed in elderly patients. This pilot project examined ADSC characteristics in young and old cells. The first aim was to investigate the changes in proliferative capacity of ADSC during aging by studying the growth of cells from young and old rats. Specifically, signaling pathways involved in ADSC proliferation will be investigated through the analysis of gene and protein expression. One area of focus will be the role of the Wnt signaling pathway in ADSC proliferation as it has been shown to increase within aged muscle, and increased Wnt signaling renders ADSCs both more proliferative and less capable of adipogenic and osteogenic differentiation. In the second aim, the differentiation potential of ADSC relative to age was examined. Experiments were performed to compare the ability of young and old ADSCs to differentiate into the adipogenic, osteogenic, and myogenic cell lineages ex vivo. Differentiation is to be monitored by gene and protein expression analysis as well as histological characterization.

Project 62.
Reciprocal Influence Between Denervation and Progenitor Cells Depletion in Sarcopenia (2010-2011 PI: O. Delbono)
This pilot project tests the hypotheses that 1) NCAM is a biomarker of age-related human skeletal muscle denervation; 2) NCAM-positive myofibers exhibit fewer satellite cells (SC) than NCAM-negative myofibers; 3) fast fibers are predominantly NCAM-positive and exhibit greater SC depletion than slow fibers; and 4) vitamin D prevents myofiber denervation and SC depletion with aging. Studies were performed in the vastus lateralis of the quadriceps muscle obtained by needle biopsy in volunteers recruited for the vitamin D supplement pilot project. Muscle fiber innervation status, SC number, and fiber subtype were assessed in 14 biopsies (8 pre and 6 post vitamin D supplementation) so far. The project will recruit and randomize 13 men and women per treatment group (total n = 26). We quantified fiber grouping and number of NCAM positive fibers to assess muscle innervation status. Extensive fiber grouping plus NCAM+ cells in baseline samples indicate muscle denervation, which correlates with fiber atrophy. Loss of satellite cells associated with NCAM+ fibers may lead to impaired muscle regeneration with aging. RNA from 6 pre- and post-samples is being processed for transcriptional profiles by DNA microarray analysis.

Project 63.
Use of a Soy-Based Meal Replacement Weight Loss Intervention to Impact Ectopic Fat and Associated Cardio-Metabolic Risk in Obese, Older Adults: A Feasibility Study (2011) (PI: K. Beavers, PhD, MPH, RD & M. Vitolins, DrPH, MPH, RD)
Obesity is a common risk factor in the development and recurrence of a wide array of aging-related chronic diseases. Soy foods have been studied extensively for their health benefits, and recent data suggest that the consumption of soy products may favorably affect body composition by reducing body fat while preserving lean mass. This pilot study is designed collect preliminary data to test the hypothesis that a hypocaloric soy-based diet has advantages over animal protein based diets with respect to body composition, cardio-metabolic risk factors, and preserved physical function in obese, older adults.

Project 64.
Vitamin D and Vitamin K Status and Physical Function in Heart Failure (2011) (PI: K. Shea, PhD)
Heart failure with preserved ejection fraction (HFPEF) is the most common form of heart failure in older age. Patients with HFPEF are intolerant to exercise, which severely reduces their physical function and quality of life. A role for vitamins D and K in exercise capacity and disability in HFPEF is plausible because vitamin D
insufficiency is associated with skeletal muscle weakness and arterial thickening, which affect physical performance in older age, and vitamin K insufficiency is associated with reduced arterial distensibility and compliance, which themselves are highly correlated with exercise capacity. This small, ‘freezer’ pilot study will measure vitamin D and vitamin K status in 160 patients with HFPEF and 60 age-matched healthy controls, whose exercise capacity, physical performance, vascular function, and ventricular structure and function, and quality of life have been measured, to test the overall hypothesis that vitamin D and vitamin K insufficiencies are common in HFPEF patients and are associated with reduced exercise capacity and quality of life. Blood analyses have been partially completed.

Project 65.
Dietary Vitamin K Deficiency and Osteoarthritis (2011) (PI: R. Loeser, MD & K. Shea, PhD)
Osteoarthritis (OA) is the leading cause of physical disability in older age, afflicting nearly one-third of older adults, at an estimated annual cost burden of over $80 billion. Vitamin K-dependent processes are implicated in cartilage and bone health, and observational studies suggest vitamin K insufficiency is associated with greater risk for OA. However, the mechanisms underlying vitamin K’s role in OA are not well-understood. This study will determine the effect of dietary vitamin K deficiency on knee joint degradation and on the expression and function of vitamin K-dependent proteins found in knee cartilage of rats with surgically-induced knee OA, to test the overall hypothesis that dietary vitamin K deficiency effects the expression and function of vitamin K-dependent proteins implicated in joint health and leads to more severe knee OA.

Project 66.
Brain Transmitters as Markers of Autonomic Profiling in the Elderly (2010-2011 PI: D. Diz)
Brain imaging may provide a useful, non-invasive means to evaluate autonomic functioning in the elderly. The objective of this project is to determine the reactions of healthy, sedentary men and women, 20 to 75 yrs of age, to carefully selected environmental tests, in conjunction with resting continuous blood pressures for spectral and sequence analysis of sympathetic and parasympathetic balance, and to establish interrelationships between these findings and central transmitter/metabolite profiles using vivo 1H Magnetic Resonance Spectroscopy (MRS). The tests are intended to simulate a number of ordinary life stresses e.g., lifting and straining (isometric exercise), sudden increases in intrathoracic pressure (valsalva), and cold exposure (hand immersion). Stress responses will be monitored primarily by non-invasive methods such as impedance cardiography and continuous blood pressure monitoring. The overall goal is to establish one or more neurotransmitters or metabolites in dorsal medullary nuclei as indicators of centrally mediated disturbances in autonomic function, obviating the need for more extensive and invasive testing.

Projects completed in current cycle:

Project 67.
Preservation of Muscle Performance and Metabolism in Aging through HSP Induction (2012) (PI: Kylie Kavanagh, PhD)
Sarcopenia and insulin resistance are common co-morbidities seen in aging, and they set the clinical stage for diabetes and fall risk which are both conditions of great public health significance. In addition, aging is associated with significant loss of innervation in mixed fiber type skeletal muscle, and reductions in the protective chaperone proteins, heat shock protein (HSP)-70 and HSP90. This pilot is assessing the potential for induced increases in HSP70 and 90 to attenuate age-associated sarcopenia. The central hypothesis is that the protection of muscle mass and function through HSP induction will preserve glycemic control that typically deteriorates with aging.

Project 68.
Upper Limb Kinematics and Muscular Compensation during Activities of Daily Living in Older Adults with Rotator Cuff Impairment (2012) (PI: K. Saul, PhD)
Approximately 20-50% of older adults (≥65 yrs) live with a rotator cuff tear, which is associated with decreased shoulder strength, restricted range of motion, and limited upper limb function. These deficits compromise the performance of activities of daily living (ADLs), and ultimately can lead to loss of independence. Individuals with a torn rotator cuff use compensatory movements to complete upper limb tasks, with deviations from the desired movement and a reliance on unimpaired muscles for movement production. The muscles most responsible for the ability to perform important ADL tasks with and without compensation have not been identified. The objective of this study is to investigate the effect of rotator cuff tear on joint movement and muscular compensations in important upper limb ADL tasks, using subject assessment and musculoskeletal modeling. The primary hypothesis is that older adults with a rotator cuff tear will use a restricted range of motion and have altered muscle coordination when performing upper limb ADLs, and that compensatory movement will reduce the strength required to accomplish the ADL tasks.

**Project 69.**

Bioenergetics, Mitochondrial Quality Control, and Physical Ability in Older Adults- Anthony Molina, PhD (RCDC scholar) The primary accomplishment of this project was the generation of protocols that allow us to assess the bioenergetic profile of mitochondria isolated from skeletal muscle biopsies. The details of this methodology have been described in detail in a recent publication (JOVE 2015). Baseline data from this study have led to one published manuscript, two that are in review, and one in preparation. These detail the relationships of mitochondrial bioenergetics with physical function, obesity, adiposity, and inflammation in older adults. Methodologies developed as well as data generated have been used to support a number of external grant applications with investigators across multiple departments (including cardiology, molecular medicine, exercise physiology) and with other members of the Aging Center. These have resulted in 3 funded RO1’s thus far. The IM FIT parent study, and funds from this pilot, also allowed us to develop blood based bioenergetic profiling techniques. Development of this assay has led to two provisional patent applications with support from Wake Forest Innovations. Moreover, the Molina lab has proposed to utilize these techniques in three external grant applications currently under review with the NIA and the American Heart Association.

**Project 70.**

The Effect of Age on Recovery from Acute Lung Injury-Induced Skeletal Muscle Wasting in Mice-Dr. Daniel Clark Files, MD (RCDC scholar). This pilot grant has been instrumental in providing funds to complete critical experiments that led to publications and has been the foundation for a transition of my research into aging. Another publication was accepted which contains some data funded through this project. Another manuscript is in preparation regarding the role of MuRF1 in aging mice with acute lung injury.

**Project 71.**

Pericyte Subtype Balance Determines the Success of Muscle Repair with Aging – Osvaldo Delbono, MD, PhD
This pilot helped us to investigate the role of pericytes in the neuromuscular junction stability with aging. We collected monkey muscle to further characterize its pericyte subpopulations and examine their involvement in the NMJ composition with aging.

**Project 72.**

Impact of medical weight loss on physical function in severely obese older adults – Jamy Ard, MD
Participants completed the 24 week intervention and follow up. Of the 28 randomized participants, only 1 person dropped from study participation and follow up measurements. Program engagement was consistent throughout the 24 weeks of intervention for both study groups. We are currently conducting final analyses and this will provide overall direction of further research focus.

**Project 73.**

Health Outcomes after Participating in Exercise (HOPE): A Pilot Study – Denise Houston, PhD, RD
A random sample of participants (n=60) from 5 completed/ongoing exercise and weight loss studies (INFINITE, I’M FIT, SECRET, CLIP, IDEA) were recalled and interviewed (in clinic or by phone) from Oct
2013 thru May 2014. The response rate was excellent of 88% (42 participants completed a clinic visit; 10 completed a phone interview; 1 was deceased; 5 refused; and 2 unable to contact). Analyses of the complete data set is ongoing and manuscript in preparation. The mean follow-up time between the end of the original intervention trials and the HOPE follow-up visit was approximately 3.5 yrs. Among those attending a HOPE clinic visit (n=42), those in the exercise only group had lost 2% of their body weight while those in the exercise plus weight loss group had gained 6% of their body weight since the end of the original intervention, suggesting that most of the weight loss during the intervention was regained. For change in body composition since the end of the original intervention, there was a 5% increase in fat mass and 7% decrease in lean mass in the exercise only group; while in the exercise plus weight loss group there was a 25% increase in fat mass and 2% decrease in lean mass. SPPB summary score, repeated chair stand time, 4 m walk speed, and 400 m walk speed were similar in both groups at the HOPE follow-up visit suggesting that weight regain did not adversely affect physical function. An R01 AG051352 entitled “Long-term function and health effects of intentional weight loss in obese elders” was submitted to NIH/NIA 12/8/14 (reviewed 2/5/15; 35th percentile); Co-PIs, Houston & Nicklas; Co-Is: Kritchevsky, Miller, Kitzman, Rejeski, Messier. We plan to revise and resubmit for July 2015 deadline.

Project 74.
Prospective Randomized Intervention to Improve Exercise Intolerance (PRIORITIES) – Dalane Kitzman, MD
All patients have completed the study. Primary outcomes have been analyzed which showed a modest improvement in physical function. Results presented at the Nitrates conference at the Reynolda conference. Manuscript in preparation. The secondary outcome (perfusion) is undergoing image analyses.

Project 75.
Effect of dietary nitrate + protein supplementation on body composition and muscle function in older adults undergoing a resistance training program- Gary Miller, PhD
Data from this project is being used for 2 graduate thesis project and 1 undergraduate thesis project. Data analysis has just begun and once complete we hope that this will allow investigators to submit for a large external grant looking at the important issue of improving responses of resistance exercise training in older adults.

III. Career Development
Our Center has conducted several intervention studies supported partly or completely by the OAIC grant. We have listed independently funded peer-reviewed grants that resulted from OAIC pilots, studies and junior faculty mentoring:

Active Pepper Center Grants

<table>
<thead>
<tr>
<th>Project Dates by Years</th>
<th>Grant Number</th>
<th>Grant Name</th>
<th>Award PI</th>
<th>Funding Source</th>
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<tr>
<td>2015-2020</td>
<td>PCS-11403-145</td>
<td>Early Supported Discharge for Improving Functional Outcomes After Stroke</td>
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<td>2015-2020</td>
<td>R01AG018915</td>
<td>Study of the Effects Caloric Restriction and Exercise Training in patients</td>
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<td>R01 AG 045551</td>
<td>A Trial Of Rehabilitation Therapy In Older Acute HeartFailure (REHAB HF)</td>
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<td>NIA</td>
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<td>2014-2018</td>
<td>2R01AG018915</td>
<td>Exercise Intolerance in Older HFPEF Patients</td>
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<td>2013-2018</td>
<td>R01 AG013934</td>
<td>Tropin T and Excitation-Contraction Coupling in Aging Skeletal Muscle</td>
<td>Delbono</td>
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<td>2013-2018</td>
<td>R01 AG042411</td>
<td>Exploring Vitamin D’s Effects on Neuromuscular Endpoints Study (EVIDENCE)</td>
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<td>2013-2018</td>
<td>K01 AG043547</td>
<td>Cognitive/Brain Effects of Adding Weight Loss to Exercise in Obese Older Adults (INFINITE MIND)</td>
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<td>Project Title</td>
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<td>2012-16</td>
<td>K01 AR063167</td>
<td>Identifying Vitamin K Dependent Pathways in Osteoarthritis Progression</td>
<td>Shea</td>
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<td>2012-17</td>
<td>2T32AG033534</td>
<td>Training Program in Gerontological and Geriatric Medicine</td>
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<td>2012-17</td>
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<td>Cooperative Lifestyle Intervention Program (CLIP -II)</td>
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<td>2012-14</td>
<td>R21 AR062284</td>
<td>Vitamin K, Knee Osteoarthritis, and Physical Function in Older Adults</td>
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<td>R01HL109429</td>
<td>Rehabilitation and Exercise Training after Hospitalization: Assessing benefit in Acute Heart Failure Pilot Study (Rehab HF)</td>
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<td>Environmental Determinants of Cognitive Aging in the Women's Health Initiative Memory Study</td>
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<td>Women's Health Initiative Memory Study New contract</td>
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<td>N/a</td>
<td>Cardiac Imaging of Thoracic Fat and Aortic Stiffness in older High Risk Patients</td>
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<td>Action for Health in Diabetes Brain Magnetic Resonance Imaging Ancillary Study</td>
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<td>Systolic Blood Pressure Intervention Trial (SPRINT-HEART)</td>
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<td>ACCORDION MIND - main study</td>
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<td>2011-14</td>
<td>R03 AR06150</td>
<td>Invivo role of S100A4 in OA pathophysiology</td>
<td>Yamman</td>
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<td>2011-13</td>
<td>R21 ES01720</td>
<td>Pesticide Exposure and Age-Related Changes in Cognitive Function</td>
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<td>Vitamin K Nutritional Status and Osteoarthritis Progress</td>
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<td>2011-13</td>
<td>N/a</td>
<td>Epigenetic Regulation of Macrophage Polarization by Saturated Fat</td>
<td>Shi</td>
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<td>2011-12</td>
<td>U01 HL080295</td>
<td>CHS Events follow-up Study</td>
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<td>K23 AG038361</td>
<td>Minimizing Physical Function Decline in Older Adults Receiving Chemotherapy</td>
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<td>Minimizing Physical Function Decline in Older Adults Receiving Chemotherapy</td>
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<td>2010-16</td>
<td>HHSN268201100007C</td>
<td>New ARIC Study contract - Field Centers</td>
<td>Wagenknecht</td>
<td>NHLBI</td>
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<td>2010-16</td>
<td>U01AG029824</td>
<td>Aspirin in Reducing Events in the Elderly (ASPREE)</td>
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<td>R01 DK066358</td>
<td>Genetics of African American Type 2 Diabetes</td>
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<td>NIDDK</td>
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<td>2010-15</td>
<td>K01 AG033652</td>
<td>Cardiac Imaging of Thoracic Fat and Aortic Stiffness in older High Risk Patients</td>
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<td>2010-15</td>
<td>K01 HP020490</td>
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<td>WHI Southeast Regional Center</td>
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<td>R01 HL092301</td>
<td>Whole Genome Association Analysis of the Diabetes Heart Study</td>
<td>Bowden</td>
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<td>2010-14</td>
<td>K01 MH083664</td>
<td>An RCT of CBT-Telephone for Late-Life Generalized Anxiety Disorder</td>
<td>Brenes</td>
<td>NIMH</td>
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<td>2010-14</td>
<td>R01 HL098445</td>
<td>Longitudinal Changes in Pericardial Adiposity and Subclinical Atherosclerosis</td>
<td>Carr</td>
<td>NHLBI</td>
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<td>2010-14</td>
<td>R01 DK085175</td>
<td>GUARDIAN</td>
<td>Wagenknecht</td>
<td>NIDDK</td>
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<td>2010-14</td>
<td>U01 HL096814</td>
<td>Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study (NCS)</td>
<td>Wagenknecht</td>
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<tr>
<td>Year</td>
<td>Study Number</td>
<td>Title</td>
<td>Principal Investigator</td>
<td>Institute</td>
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<td>2010-2012</td>
<td>N/A</td>
<td>ASPREE clinic site</td>
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<td>N/A</td>
<td>Picker Institute/Gold Foundation</td>
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<td>Williamson</td>
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<td>2009-2018</td>
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<td>SPRINT Coordinating Center S.E. Network</td>
<td>Goff</td>
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<td>RFP HC0904</td>
<td>SPRINT MIND Memory in Decreased Hypertension</td>
<td>Williamson</td>
<td>NHLBI</td>
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<td>2009-2015</td>
<td>U01 AG022376</td>
<td>Physical Exercise to Prevent Disability Study (LIFE) WFU Field Center</td>
<td>Kritchevsky</td>
<td>NIA</td>
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<td>2009-2015</td>
<td>U01 AG022376</td>
<td>LIFE Data Management, Analysis and Quality Control Center</td>
<td>Miller</td>
<td>NIA</td>
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<td>2009-2015</td>
<td>R01 CA133483</td>
<td>Radiation -induced brain injury and cognitive dysfunction in aging rats</td>
<td>Riddle</td>
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<td>2009-2015</td>
<td>U01 AG022376</td>
<td>LIFE Cognition Study</td>
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<td>2009-2014</td>
<td>R01 AG015820</td>
<td>Age-dependent regulation of excitation-contraction coupling</td>
<td>Delbono</td>
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<td>2009-2014</td>
<td>T32 HL091824</td>
<td>Multi disciplinary Training in Cardiovascular Imaging</td>
<td>Hundley</td>
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<td>2009-2014</td>
<td>K01 AG33641</td>
<td>Chaperone Proteins in a Primate Model of Age-Related Metabolic Disease</td>
<td>Kavanagh</td>
<td>NIA</td>
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<td>2009-2014</td>
<td>R37 AG018915</td>
<td>Exercise intolerance in elderly diastolic heart failure</td>
<td>Kitzman</td>
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<td>2009-2014</td>
<td>R01 AG033087</td>
<td>Intentional Weight Reduction and Physical and Cognitive Function - Look AHEAD ancillary study</td>
<td>Kritchevsky</td>
<td>NIA</td>
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<td>2009-2014</td>
<td>R01 AG032098</td>
<td>Genetic Determinants of Visceral Adiposity</td>
<td>Liu</td>
<td>NIA</td>
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<td>2009-2014</td>
<td>R01 HL101250</td>
<td>Epigenome-Wide Association Study of DNA Methylation and Artherosclerosis</td>
<td>Liu</td>
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<td>2009-2014</td>
<td>U01 MH086127</td>
<td>Prolonging Remission in Depressive Elderly (PRIDE)</td>
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<td>2009-2014</td>
<td>R01NR011186</td>
<td>Standardized Rehabilitation Therapy for ICU Patients with Acute Respiratory Failure TARGETT</td>
<td>Morris</td>
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<td>2009-2014</td>
<td>R01 HL093713</td>
<td>Effect of Fat Loss on Functional and Cardiovascular Benefits of Aerobic Exercise</td>
<td>Nicklas</td>
<td>NHLBI</td>
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<td>2009-2014</td>
<td>R01 AG020583</td>
<td>Loss of Fat Tissue and Functional Response to Exercise in Older, Obese Adults</td>
<td>Nicklas</td>
<td>NIA</td>
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<td>2009-2013</td>
<td>N01 HC95095</td>
<td>The CARDIA Computed Tomography Reading Center</td>
<td>Carr</td>
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<td>2009-2013</td>
<td>R21 AG033385</td>
<td>FBT-PET Study of Aging Skeletal Muscle</td>
<td>Delbono</td>
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<td>2009-2013</td>
<td>R01 AG033727</td>
<td>Estrogen, Angiotensin, and Diastolic Function</td>
<td>Groban</td>
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<td>2009-2013</td>
<td>R01 AG020572</td>
<td>Neural Signaling and Age-Related Cognitive Impairment</td>
<td>Nicolle</td>
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<td>2009-2013</td>
<td>R01 DK084172</td>
<td>The AMP-Activated Protein Kinase (AMPK) Antagonizes Inflammation Through SIRT1</td>
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<td>N01 HC95159</td>
<td>MESA SHARe</td>
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<td>R03 TW008091</td>
<td>Role of Calcium Channels in Aging Skeletal Muscle</td>
<td>Delbono</td>
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<td>N/A</td>
<td>A.D. Aware: Mentally Stimulating Activities for Treatment of Apathy in Early Stage Alzheimer's</td>
<td>Sink</td>
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<td>2009-2012</td>
<td>N/A</td>
<td>Comprehensive Program to Strengthen Physicians' Training</td>
<td>Williamson</td>
<td>Donald W. Reynolds Foundation</td>
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<td>R01 NS058700</td>
<td>Genetic Epidemiology of Cerebrovascular Disease and Cognition in Diabetes</td>
<td>Bowden</td>
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<td>R01 DK075681</td>
<td>FHS Genetic Epidemiology of Metabolic Diseases of Obesity</td>
<td>Carr</td>
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<td>K01AG030506</td>
<td>Vitamin D Status, Related Gene Polymorphisms and Physic</td>
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<td>R41/R42 AG030248</td>
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<td>R01 OH009251</td>
<td>Occupational Injuries Among Immigrant Poultry Workers: Development and Progression</td>
<td>Quandt</td>
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<td>JHS Magnetic Resonance Imaging (MRI) Reading Center, Substudy w/Jackson State University</td>
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<td>R01 HL085571</td>
<td>Predictors of Coronary Artery Calcification in an African American Cohort Subcontract w/University of Michigan, WFUHS Site PI</td>
<td>Carr</td>
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<td>R01 DA023573</td>
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<td>Deadwyler</td>
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<td>Single skeletal muscle fiber impairment with aging</td>
<td>Delbono</td>
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<td>R01 AR049003</td>
<td>Integrin Function in Cartilage</td>
<td>Loeser</td>
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<td>Phase III Study of Donepezil in the Irradiated Brain</td>
<td>Rapp</td>
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<td>2007-2012</td>
<td>R01 HL087103</td>
<td>Depression and Coronary Artery Atherosclerosis in Premenopausal Primates</td>
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<td>2007-2012</td>
<td>U01 AG010483</td>
<td>Multi-Center Trial to Evaluate Home-Based Assessment Methods</td>
<td>Sink</td>
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Wake Forest Pepper Center 2014-2015 Publications

2015 In Press


2015 Under Review


2015 Journal Publications


2014 Journal Publication List


15. Files, D. C., Xiao, K., Zhang, T., Liu, C., Qian, J., Zhao, W., Morris, P. E., Delbono, O., and Feng, X. The posterior cricoarytenoid muscle is spared from MuRF1-mediated muscle atrophy in mice with acute lung injury. PLoS.One.2014:(9)e87587-. PMC3909200.


Section V. External Advisory Board Members Names, Institutions and Years of service

Bret Goodpaster
Florida Hospital, Sanford|Burnham Medical Research Institute
2 year of service

Anne B. Newman
University of Pittsburgh
9 years of service

Stephanie Studenski
National Institute on Aging
2 year of service

Jay Magaziner
University of Maryland, Baltimore
2 year of service

Nir Barzilai
Albert Einstein College of Medicine
4 years of service

- Please note our board has been updated with the new cycle of our Pepper Center grant.
2014-15 Recognition and Awards

Stephen Kritchevsky, PhD
Editorial Board, Journal of Gerontology Medical Sciences, Editor-in-Chief
Editor, Journal of Gerontology Medical Sciences
American Society for Nutritional Sciences
Member of the Institute of Medicine Committee on the Review of the Health Effects in Vietnam Veterans of Exposure to Herbicides.
2014 WFSM Research Mentoring Award
Team Science Award, Claude D. Pepper Older Americans Independence Center, WFSM
Thomson Reuters Highly Cited Researcher, Thomas Reuters

Dalane W. Kitzman, MD
Chair, Cardiovascular Disease in Older Population Committee, AHA Council on Clinical Cardiology-Guest
Editor, Journal of American College of Cardiology
Editorial Board, Journal of Geriatric Cardiology, 2011 Guest Editor
Editorial Board, Journal of the American Geriatrics Society
Editorial Board, American Journal of Geriatric Cardiology
Kermit Glenn Phillips Endowed Chair in Cardiology 2014
Established investigator award from WFSM 2015

Michael Berry, PhD
Member of the Research Committee of the American Association of Cardiovascular and Pulmonary Rehabilitation (2000-present)
Southeast American College of Sports Medicine, Executive Board Member for Sponsorship and Exhibitors

Osvaldo Delbono, PhD
2014 Established Investigator in Basic Sciences Award
2014 WFSM Established Investigator in Clinical Sciences Award
Physiological Minireviews, Member, Editorial Board
Advisor on Neuromuscular Junction Alterations with Aging, National Institute on Aging
Member, NIH Cellular Mechanisms of Aging and Development Study Section
Editorial Board, Physiological Minireviews

Debra Diz, PhD
Editorial Boards for the following: Current Hypertension Reviews, Current Hypertension Reports
Associate Editor Frontiers in Integrative Physiology
Awards Committee Member Consortium for Southeastern Hypertension Control
Member, Council of Division Chairs the American Society for Pharmacology and Experimental Therapeutics
Abstract Reviewer for the following: American Heart Association, Council for High Blood Pressure Research, American Heart Association, National Sessions
Chair, Special Emphasis Panel on R25 Minority and Training Programs, NHLBI
NIH Reviewers Reserve
Special Emphasis Panels for R25 Minority and Training Programs, NHLBI
Committee for review of NHLBI R25 Cardiovascular Program
Program Project Reviews NHLBI
Fellowship Review Committees, F31. 32, 33. NIH
Small conference grant reviews, NHLBI
Loan Repayment applications, NIH
Member of Executive Board, Consortium for Southeastern Hypertension Control
Chair, External Advisory Committee, Minority Access for Research Careers (MARC), Winston-Salem State University
Member, External Advisory Board, Science, Technology & Engineering Programs, National Science Foundation Historically Black Colleges & Universities (HBCU-UP), Johnson C. Smith University

Kevin High, MD
Laureate Award, NC ACP Chapter
Reidar Wallin Teaching Award – WFU Molecular Medicine and Translational Science Graduate Program

Christina Hugenschmidt, PhD
Travel Award, Alzheimer’s Imaging Consortium Preconference (2015)
Travel Award, Alzheimer’s Association International Conference (2015)
Travel Award and Invitation to Attend, The Intersection of Metabolic and Cognitive Dysfunction Conference, National Institutes of Health (2015)

Edward Ip, PhD
Editorial Boards of the following: Psychometrika (published by the Psychometric Society) (Associate Editor), Journal of Educational & Behavioral Statistics (jointly published by the American Educational Research Association and the American Statistical Association) (Associate Editor)

Heidi Klepin, MD
Associate Editor, Journal of Geriatric Oncology, 2014-2016

Mary F. Lyles, MD
Best Doctors in America Award, Best Doctors, Inc.

Charles E. McCall, MD
Member, NIH NCRR special review panel for K30 grants
Member, NIH NCRR special review study group for Clinical Translation Sciences Awards.
Honoree: Invited review on the Epigenetics of Systemic Inflammation.

Michael Miller, PhD
Member, NHLBI GUIDing Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) DSMB (2012-present)
Member, NIDDK Restoring Insulin Secretion (RISE) DSMB (2012-2013)
Member, Hypoglycemia in Diabetics DSMB (U Penn, 2010-present)
Member, NIDDK D2D Protocol External Evaluation Committee (2012)
Member, NIA AD Clinical Trials Special Emphasis Panel, (2013)
Member, NHLBI Appointed GUIDing Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) DSMB (2012-present)
Member, NIDDK Appointed Restoring Insulin Secretion (RISE) DSMB (2012-2014)
Member, NIA Appointed Tai Chi: Moving for Better Balance DSMB (2014-present)

Anthony Molina, PhD
Molecular Biology of Aging, Trainee, Ellison Medical Foundation
Barbara Nicklas, PhD
Standing member NIA Aging Systems and Geriatrics study section
2014 WFSM Established Investigator in Clinical Sciences Award

Snezana Petrovic, MD
American Journal of Physiology, Renal Physiology, member Editorial Board
Member of Geriatric Nephrology Advisory Group, American Society of Nephrology

Carol A. Shively, PhD

Jeff D. Williamson, MD, MHS
Best Doctors in America Award, Best Doctors, Inc.
Reviewer – NIH NINDS Special Emphasis Panels ZNS1 SRB G(68) and G(70)
Wake Forest Team Science Award (2014)
Best Doctors in America Award (2014)
NIH NINDS Special Emphasis Panels ZNS1 SRB (2014)
Member, AHA/ACC Guidelines Committee for Treatment of Hypertension (American Geriatrics Society Representative) (2014-15)
MINORITY RESEARCH AT THE WAKE FOREST UNIVERSITY SCHOOL OF MEDICINE PEPPER CENTER
2014

General Brief Description of Minority Activities:

The Maya Angelou Research Center on Minority Health (MA-RCMH) has been established by the WFUSM to address issues related to racial and ethnic health disparities. Its overarching goal is to enhance wellness, improve quality of life, and reduce the burden of disease in underrepresented minorities through a comprehensive program in four core areas: health education, career/leadership development, research, and dissemination/application of new research findings for more effective and efficient health care approaches.

A key feature of the MA-RCMH is its model campus/community partnership involving WFUSM, the Reynolda Campus of Wake Forest University, Winston-Salem State University (a historically Black college/university) and the Forsyth County community at-large. This partnership brings the vast experiences, knowledge base and resources of each partner to bear on health problems of underrepresented minorities.

Minority Supplements:

Kevin High’s R24AG044325 received a diversity supplement to fund Candice McNeil in HIV/Aging research. Dr. McNeil was also accepted to the Butler-Williams program at NIA this summer along with Candace Parker-Autry (OB/GYN). That program has, as a major goal, diversity in science workforce and health disparities research.

Barbara Nicklas currently has a Research Supplement to Promote Diversity in Health-Related Research Program (PA-05-015) award to support the postdoctoral training of Dr. Tina Ellis Brinkley. This would be an administrative supplement to grant #1R01 AG027529; “Exercise Training and Inflammatory Risk Factors for Disability”.

Research and Career Development Proposed for the OAIC Investigator Ha T. Nguyen has a minority supplement funded through the Pepper OAIC. The Principal Investigator is Dr. Stephen Kritchevsky, PhD, and Co-investigator is Dr. Ha T. Nguyen.

Minority Trainee(s):

Dr. Jeff Williamson, Head, Section on Gerontology and Geriatric Medicine of Geriatrics currently mentors Jamehl Demons, MD, Assistant Professor, Gerontology and Geriatrics and the Maya Angelou Center.

Dr. Barbara Nicklas, Associate Professor in the Department of Geriatrics currently mentors Tina Ellis Brinkley, Assistant Professor, Gerontology and Geriatrics.

Dr. Barbara Nicklas, Associate Professor in the Department of Geriatrics currently mentors Anthony Molina, Assistant Professor, Gerontology and Geriatrics.

Dr. Capri Foy, Assistant Professor in the Division of Public Health Sciences, currently mentors Ms. Lashaunda Holmes, as part of a Diversity Supplement to the R21 study “Prosocial Behavior and Exercise among Older Adults”. Ms. Holmes is a recent graduate of Winston-Salem State University.

Dr. Debra Diz, Director, Hypertension & Vascular Research Center (HVRC), Professor of General Surgery, mentors Dr. Mesia Steed a post-doctoral fellow in the HVRC. Dr. Diz also directs two training programs for increasing diversity in our graduate programs: R25 HL092618 Short-term summer research training for
increased diversity and R25 GM064245 Post-baccalaureate Research Education Program Scholars (PREP) at WFUSM.

Dr. Tina Brinkley, Assistant Professor, Section on Gerontology and Geriatric Medicine mentored Rachael Kennedy, and she was recently accepted into Howard University Medical School.

Dr. Brinkley also participates in the R25 HL092618 Short-term summer research training for increased diversity and R25 GM064245 Post-baccalaureate Research Education Program Scholars (PREP) as career mentor, participates in the PREP journal club as a faculty evaluator, and has given presentations on her research to these groups in 2011 and 2012.

Dr. Osvaldo Delbono, Professor in the Department of Internal Medicine, Section on Gerontology and Geriatric Medicine currently mentors Alexander Birbrair, graduate student in the Neuroscience Program.

Dr. Lynne Wagenknecht, is a mentor to Kristen Hairston, MD, Assistant Professor, Medicine/Endocrinology, on an institutional K-12 award, on the topic of dietary interventions to reduce visceral adiposity in African American women.

Dr. Anthony Marsh, Associate Professor of Heath and Exercise Science, mentored Jayson Hull, an AA student from Winston Salem State University, on a Summer Research Fellowship funded by the Translation Science Center at Wake Forest University. The research project examined the influence of two sets of testing instructions on the performance of the 400 m walk test.

Dr. Thomas Register, Professor, Pathology mentored Nigel Bethel, an AA student from Elizabeth City State University, on a Summer Research Fellowship funded by the Excellence in Cardiovascular Sciences Summer Research Program at Wake Forest University. The research project examined body composition of non-human primates in a new study of the effects of diet on health and behavior.

Dr. Paul Laurenti is primary mentor for Sean Simpson, PhD. He is an Assistant Professor, Biostatistical Sciences and K01 awardee.

Minority-Related Research Project(s):

Snezana Petrovic Collaboration with Drs. Barry Freedman, Tom DuBose, and Susan Sumner and Susan McRitchie from RTI on a metabolomics project related to African American Diabetes Heart Study.

Dr. Thomas Register, Professor, Pathology. Dr. Register collaboratively with Dr. Barry Freedman in the assessment of African Americans in the African American Diabetes Heart Study which is designed to evaluate and understand cardiovascular disease risk in African Americans with Diabetes.

Dr. Jamehl Demons, Assistant Professor, Department of Medicine, Section on Gerontology and Geriatric Medicine. Dr Demons is Principal Investigator of the Wake Forest Field Center for the AIM_HIGH trial (NHLBI ), a randomized trial evaluation long-acting niacin for secondary CVD prevention.

Dr. Peter Morris, Associate Professor, Pulmonary, Critical Care, Allergy, and Immunologic Medicine. Dr. Morris is collecting gender, race, and ethnicity data on the 126 of 326 subjects enrolled within the R01NR011186-01 Standardized Rehabilitation for ICU Patients with Acute Respiratory Failure. This study will provide the information for US hospitals to prioritize and budget for the rehabilitation needs of patients with ARF by demonstrating that Standardized Rehabilitation Therapy, initiated in the ICU, reduces hospital stays with immediate and sustained improvement in function and quality of life for patients with ARF.
Publications Pertaining to Minority Research:


Focus of OAIC at Yale

The mission of the Yale Older Americans Independence Center (OAIC) is to provide intellectual leadership and innovation for aging research that is directed at enhancing the independence of older persons. The unifying theme of the Yale OAIC is the investigation of multifactorial geriatric health conditions, encompassing single conditions resulting from multiple contributing factors or affecting multiple outcome domains and multiple conditions occurring simultaneously. The conceptual underpinning is that geriatric health conditions are determined by the co-occurrence of multiple predisposing and precipitating factors. These conditions and factors, in turn, affect a range of health outcomes. The predisposing factors may be at the genetic, molecular, physiologic, impairment, disease, or socio-demographic level, while the precipitating factors may be behavioral, environmental, social, medical, or psychological. As a related focus, the Yale OAIC also aims to advance the science of clinical decision making in the face of tradeoffs and multiple competing outcomes. This includes developing strategies to elicit older persons’ health outcome priorities.
The aims of the Yale OAIC are to:
   1) foster the career development of future academic leaders, from multiple disciplines, in aging research;
   2) train investigators, biostatisticians and other methodologists in the skills necessary to design, conduct, analyze, and disseminate findings from studies of multifactorial geriatric health conditions;
   3) develop and disseminate design and analytic techniques for conducting studies of multifactorial geriatric health conditions;
   4) develop strategies for recruiting and retaining a broad spectrum of older persons, including minorities, into studies of multifactorial geriatric health conditions;
   5) investigate the causative mechanisms of, and develop and test effective treatments for, geriatric health conditions from a multifactorial research perspective;
   6) develop strategies to enhance clinical decision making in the setting of multiple health conditions;
   7) encourage and facilitate interdisciplinary research (basic, translational and clinical) that connects to our focus on multifactorial geriatric health conditions;
   8) develop and implement strategies that will facilitate the translation of OAIC research into practice and policy.

The disciplines and interdisciplinary collaborations represented in the Yale Pepper Center include:

- Analytical Sciences
- Behavioral Sciences
- Biostatistics
- Biotechnology
- Cardiology
- Cellular and Molecular Physiology
- Clinical and Translational Science
- Comparative Medicine
- Diabetes and Endocrinology Research Center
- Economics
- Endocrinology
- Epidemiology
- Gastroenterology
- General Internal Medicine
- Genetics
- Geriatrics
- Gerontology
- Health Policy
- Hematology
- Human Translational Immunology
- Imaging Core
- Immunobiology
- Infectious Disease
- Internal Medicine
- Medical Informatics
- Molecular, Cellular and Developmental Biology
- Mouse Research Pathology Core
- Neurobiology
- Neurology
- Neuropsychology
- Neurosurgery
- Nursing
- Obstetrics and Gynecology
- Occupational Therapy
- Ophthalmology
- Outcomes Research and Evaluation, Center for
- Orthopaedics and Rehabilitation Pathology
- Pharmacology
- Physical Therapy
- Physiology and Metabolic Cluster
- Primary Care
- Psychiatry
- Public Health
- Pulmonary/Critical Care
- Rheumatology
- Sleep Medicine
- Sociology
- Statistical Genomics and Proteomics
- Surgery
- Urogynecology
- Vascular Biology and Transplantation
A1. LEADERSHIP AND ADMINISTRATIVE CORE

Thomas M. Gill, MD, Leader
Terri R. Fried, MD, Co-Leader
Joanne M. McGloin, MDiv, MS, MBA, Center Administrator
Denise Acampora, MPH, Center Co-Administrator
Peter A. Charpentier, MPH, Associate Leader

The overarching objective of the Leadership and Administrative Core (LAC) is to advance the field of multifactorial geriatric health condition research. The LAC, under the PI, is ultimately responsible for strategic planning, organization, administrative operations and evaluation of the OAIC research and training program. A special effort is devoted to ensure the cohesion of the Center and maintenance of an interdisciplinary and translational research focus on the common research theme, which is "the investigation of multifactorial geriatric health conditions". The key LAC tasks are achieved by the Core Leader, Co-Leader, Administrator and three committees: the Executive Committee, the Internal Advisory Committee, and the External Advisory Committee.

The activities and responsibilities of the LAC are to:
1) oversee the coordination, integration, and administration of all aspects of the Yale OAIC, including the utilization of core resources, with other research and training programs at Yale, and foster collaborations that will accomplish the OAIC goals;
2) ensure the conduct of academically productive, innovative, high impact, and clinically safe research by Pepper Scholars, Resource Cores, Pilot/Exploratory Studies (PESs), and External Projects;
3) ensure the independent review and oversight of OAIC research and the training of Pepper Scholars;
4) foster the career development of junior faculty from multiple disciplines into independent investigators and academic leaders in aging research;
5) recruit and encourage outstanding junior and senior faculty to focus their research on aging, particularly multifactorial geriatric health conditions, with an emphasis on translation between basic and clinical research;
6) identify and facilitate productive collaborations with other institutions and OAICs;
7) monitor university, government and fiscal matters, ensure the preparation of necessary progress reports and administrative documents relating to the award, and collaborate with the NIA project office and Coordinating Center on OAIC activities.

Taken together, the LAC provides support for planning, organizational, evaluation, and administrative activities relating to the other Cores and to the OAIC as a whole. The LAC is responsible for monitoring, stimulating, sustaining, evaluating, and reporting progress toward the overall goals of the OAIC.
A2. PILOT/EXPLORATORY STUDIES CORE (PESC)

Albert Shaw, MD, PhD, Core Leader
Mary E. Tinetti, MD, Co-Leader
Denise Acampora, MPH, Co-Leader

The primary goal of the Pilot/Exploratory Studies Core (PESC) is to facilitate the development of innovative and rigorous research studies that will enhance our understanding of the pathogenesis, etiology, diagnosis, prevention, and management of multifactorial geriatric health conditions, leading ultimately to the development of efficacious and cost-effective interventions to increase or maintain the independence of older Americans.

To achieve the goals stated above, the specific aims are to:
1) solicit and select the most meritorious research proposals for PESC funding;
2) provide investigators of Pilot / Exploratory Studies (PESs) with access to resources from the other OAIC Cores;
3) identify potential opportunities for co-sponsorship of PESs;
4) identify potential opportunities for collaboration among PESC investigators;
5) monitor the progress of PESs;
6) provide assistance so that the PESs can be successfully developed into independently funded grant applications;
7) ensure the safety and protection of human subjects and vertebrate animals enrolled in PESs.

Priority for PESC funding will be given to junior investigators as well as to accomplished mid-career and senior investigators who wish to redirect or expand their research to the study of multifactorial geriatric health conditions. In addition to traditional one- or two-year PESs, a new Expedited Pilot Program (EXPI) funds small grants capped at a maximum of $5000 and awarded within 4 weeks of application. Priority for these grants will be given to junior investigators and are intended for research activities in which a rapid infusion of a relatively small amount of funds will facilitate a successful extramural grant application. These two PESC grant mechanisms will provide crucial support and access to the research infrastructure provided by the OAIC Operations and Biostatistics Cores, facilitating future external grant support that will advance our understanding of multifactorial geriatric health conditions.
A3. RESEARCH CAREER DEVELOPMENT CORE (RCDC)

Terri Fried, MD, Core Leader
Albert Shaw, MD, PhD, Co-Leader
Denise Acampora, MPH, Co-Leader

The overall goal of the Research Career Development Core (RCDC) is to identify highly promising early-stage investigators (junior faculty) and to provide support promoting their development as independent investigators and leaders in aging research. The RCDC seeks to provide these investigators, designated as “Pepper Scholars”, with the knowledge and skills to conduct biological, translational, and clinical studies of multifactorial geriatric health conditions and to obtain subsequent funding from a broad range of sources. The outcomes and career advancement goals for Pepper Scholars include: 1) publication of research results in high-impact journals; 2) success in obtaining independent funding, both to support further career development and to support specific projects; 3) development of leadership skills necessary to manage research teams and to become successful mentors themselves.

To achieve the goals stated above, the specific aims are to:

1) identify highly promising junior faculty with a strong interest in aging research as Pepper Scholars, with priority given to faculty whose research focuses on multifactorial geriatric health conditions;
2) promote the development of these Pepper Scholars as independent investigators through the provision of salary, project, infrastructure/technical, and other career development support;
3) provide Pepper Scholars with priority access to the Resource Cores’ expertise and services for the design, conduct, and analysis of studies addressing multifactorial geriatric health conditions;
4) provide mentorship in aging to Pepper Scholars selected from disciplines outside of geriatrics;
5) provide oversight of research and career development progress for Pepper Scholars and to provide support for subsequent grant development;
6) identify a group of junior faculty affiliates who receive more limited support in order to promote their development as potential future Pepper Scholars and to support additional career development and research applications;
7) provide opportunities for participation in local and national research and career development workshops and seminars with a focus on aging research and in relevant networking and advocacy initiatives.

The RCDC works with the Leaders of the other Cores to identify the necessary resources (e.g. research assistants, biostatisticians, etc.) for studies being conducted by RCDC awardees, to facilitate and ensure that the awardees’ studies adhere to the OAIC’s multifactorial focus, and to monitor the progress of these studies. During the course of the studies, the RCDC, together with the LAC and Resource Cores, assists junior investigators to develop their research into independently funded grant applications.
A4. BIOSTATISTICS CORE

Heather G. Allore, Ph.D., M.S., Core Leader
Peter H. Van Ness, Ph.D., MPH, Core Co-Leader

The overarching goals of the Biostatistics Core (BC) are to provide design and analytical services to investigators conducting studies of multifactorial geriatric health conditions; to develop and disseminate new design and analytical techniques for conducting studies with older persons; and to train a cadre of clinical investigators, biostatisticians, and epidemiologists in skills necessary to design, conduct, and analyze gerontologic studies. The BC provides state-of-the-art research design and biostatistical expertise for the Yale OAIC with the following specific aims.

1) To collaborate with Pepper Scholars, Pilot and Exploratory Studies Core investigators, Operations Core colleagues, and investigators of External Projects, to achieve the mission of the Yale OAIC in promoting the understanding and treatment of multifactorial geriatric health conditions.

2) To develop new and sound methods that address the challenges of designing and analyzing studies in basic, translational, and clinical geriatric/aging research, with special emphasis on introducing helpful statistical methods from other disciplines.

3) To train the next generation of geriatric statisticians, epidemiologists, and junior investigators in Gerontologic Biostatistics research methods specific to studies of multifactorial geriatric health conditions, e.g., accounting for multicomponent interventions addressing multiple health outcomes, analyzing longitudinal data in ways that differentiate pathological and non-pathological changes in health over time, and handling missing data due to death.
A5. OPERATIONS CORE

Vincednt J. Quagliarello, MD Core Leader
Peter A. Charpentier, MPH, Core Co-Leader
Joanne M. McGloin, MDiv, MS, MBA, Co-Leader

The overall goal of the Yale OAIC Operations Core (OC) is to provide operational methods, staff, resources, and expertise necessary to ensure the efficient and successful completion of the full range of research projects (e.g., observational, interventional, basic/translational) focused on multifactorial geriatric health conditions. As a result, the OC will enhance the scientific productivity of OAIC research and facilitate its overall objectives. The Operations Core for the OAIC provides the seamless integration of Field personnel tasks with Data Management/Informatics operations. This streamlined organization optimizes resources, increases efficiency and implementation of clinical and translational research, and facilitates integration of data collection and data management efforts.

Collaborating with all Yale OAIC Cores, the specific aims to achieve the Operations Core goal are to:

1) provide personnel for recruitment and retention of diverse research participants, and comprehensive data management systems, to support OAIC External Projects;
2) provide consulting support for operational aspects of proposal preparation;
3) provide training of investigators and study staff regarding operational tasks;
4) develop, test, and implement new OC methods;
5) collaborate with RCDC, PESC, and Biostatistics Cores to facilitate coordinated strategies to develop, implement, and monitor the conduct of Yale OAIC-related studies;
6) provide support for the design and conduct of a novel OC Development Projects.

a. Developing the Mechanism(s) for Action for DRIVER and PREHAB - Biostatistics Core
   Peter N Peduzzi, PhD, Professor of Public Health (Biostatistics)

b. Methodology Development for Longitudinal Studies of Precipitating Events - Biostatistics Core
   Joel A Dubin, PhD, Associate Professor of Statistics and Actuarial Science, University of Waterloo, Canada

c. Geriatrics Research Instrument Library (GRIL) - Data Management and Informatics Core
   Cynthia A Brandt, MD, MPH, Professor of Emergency Medicine and Anesthesiology (Medical Informatics)

d. Promoting Research Participation among Black and Hispanic Older Adults - Field Core
   Holly G Prigerson, PhD, Professor of Sociology in Medicine and of Geriatrics, Weill Cornell Medical College

e. Analysis Methods for Spatial Factors on Geriatric Health - Biostatistics Core
   Theodore Holford PhD, Susan Dwight Bliss Professor of Public Health (Biostatistics) and of Statistics

f. Ordinal Regression Models for Aging Research – Biostatistics Core
   Peter Van Ness, Ph.D., MPH, Senior Research Scientist, Medicine (Geriatrics) and Lecturer in Epidemiology (Chronic Diseases)

g. Phenotype and Genotype Diversity in Age-Related Macular Degeneration – Biostatistics Core
   Josephine Hoh, PhD, Associate Professor of Epidemiology and of Ophthalmology and Visual Science

h. Eliciting Older Persons’ Preferences among Competing Outcomes – Field Core
   Terri Fried, MD, Professor of Medicine (Geriatrics)

i. Study Designs and Analytic Methods for Pilot Projects with Small Sample Sizes- Biostatistics Core
   Heather Allore PhD, MS, Associate Professor of Medicine (Geriatrics) and of Public Health (Biostatistics)

j. The Pepper Informatics, Revision 2 Implementation Project – Data Management and Informatics and Field Cores
   Peter Charpentier, MPH, Director of Data Management and Informatics, Yale Program on Aging
k. *Uncovering the Multifactorial Nature of AMD Pathogenesis with Systems Biology* - Biostatistics Core
   Hongyu Zhao, PhD, Ira V. Hiscock Professor of Public Health (Biostatistics) and of Genetics and of Statistics

l. *Cognitive Impairment in the ICU: Bayesian Joint Models of the Time-Dependent Confounding between Multiple Medications and Manifestations of Delirium* - Biostatistics Core
   Terrence Murphy, PhD, Assistant Professor of Medicine (Geriatrics)

m. *Adverse Event Monitoring and Reporting among Older Adults Participating in Multifactorial Intervention Trials* - Operations Core
   Manisha Juthani-Mehta, MD, Associate Professor of Medicine (Infectious Diseases)

n. *A real-world quasi-experimental investigation of haloperidol effectiveness in treating delirious older medical patients under intensive care* – Biostatistics Core
   Ling Han, MD, PhD, Senior Research Scientist, Internal Medicine (Geriatrics)

a. Sidney T Bogardus Jr, MD (strategies to improve goal setting for older persons)
b. Joel A Dubin, PhD (new methodologies for studying geriatric health conditions)
c. William T Gallo, PhD (geriatric health conditions from the perspective of a health economist)
d. Cary P Gross, MD (barriers to participation of older cancer patients in clinical trials)
e. Margaret A Pisani, MD, MPH (older patients in the intensive care unit setting)
f. Karyn Frick, PhD (environmental enrichment as mnemonic enhancer for aging male and female mice)
g. Joseph Agostini, MD (benefits and harms of total medication use)
h. Albert Shaw, MD, PhD (alterations in toll-like receptor signaling in older adults)
i. JoAnn Foody, MD (tradeoffs between clinical outcomes in older persons with multiple morbidities)
j. Daniel Goldstein, MD (mechanisms of impaired immunity in aging)
k. Julie Ann Sosa, MD (effects of surgery on older patients with primary hyperparathyroidism)
l. Carlos Fragoso, MD (pulmonary function and sleep)
m. Lisa Barry, PhD (effect of depression on disability burden over time)
n. Sarwat Chaudhry, MD (heart failure as a multifactorial geriatric syndrome)
o. Manisha Juthani-Mehta, MD (UTI in nursing home patients)
p. Arthur Simen, MD, PhD (multifactorial risk for late life depression)
q. Leora Horwitz, PhD (heart failure readmissions in high and low performing hospitals)
r. Stephanie Halene, MD (modeling myelodysplasia in aging adults)
s. Sandy Chang, MD, MHS (trajectories of cognitive function and their impact on hospitalizations, functional disability, and death in older adults with COPD)
t. Robert Pietrzak, PhD, MPH (post disaster psychological adaptation in older persons)
u. Praveen Mannam, MD (MKK3 as a mediator of sepsis and lung injury in the elderly)

v. Elizabeth Erekson, MD, MPH (frailty and functional status of older women seeking treatment for urinary incontinence)

w. Joan Monin, PhD (the health effects of older persons’ relationships and caregiving)

x. Kasia Lipska, MD (hospitalizations for diabetes complications)

y. Raimund Herzog, MD (energy substrates and molecules associated with health and disease).

z. Terrence Murphy, PhD (cognitive impairment in the ICU)

aa. Melissa Knauert, MD, PhD (sleep and delirium in the ICU)

bb. Daniel Weinberger, PhD (pneumococcal vaccine impact in geriatric populations)
B3. Other Research Activities

a. Other Completed OAIC Studies

IS
“Home-based Hip Fracture Intervention Project”
Mary E. Tinetti, M.D. (Principal Investigator)
1992-1997

IDS-1
“Trial of a PREHABilitation Strategy for At-Risk Elders“
Thomas M. Gill, M.D. (Principal Investigator)
1997-2003

IDS-2
“Driver-Related Rehabilitative Intervention for the Elderly”
Richard Marottoli, M.D., M.P.H. (Principal Investigator)
1997-2004

IDS-3
“Mechanisms of Insulin Resistance in Aging”
Gerald I. Shulman, M.D., Ph.D. (Principal Investigator)
Loretta DiPietro, Ph.D.
1997-2002

b. Completed Supplemental Awards

“GenTrack Data Systems”
Peter Charpentier, MPH

“Cardiac Stress Testing to Screen Prior to Exercise Training”
Thomas M. Gill, MD

“Pepper Informatics”
Peter Charpentier, MPH

“Development of Experimental Designs and Analytic Methods for Multifactorial Interventions”
Heather Allore, PhD, MS

“Developing a National Mouse Mammary Tumor Tissue Array Resource”
Caroline Zeiss, PhD, BVSc

“Gerontological Research, Algorithms, and Statistical Programs (GRASP)”
Heather Allore, PhD, MS
C. Pilot Studies

**Year 01 (1992-1993)**
Psychosocial Intervention in Elderly Stroke Patients: Screening and Assessment  
Thomas Glass, PhD  
Professor of Epidemiology – Johns Hopkins University

Identifying Precipitating Factors for Delirium in Hospitalized Elderly Patients  
Sharon Inouye, MD, MPH  
Professor of Medicine – Harvard University

Congestive Heart Failure in the Elderly: Role of Left Ventricular Function on Prognosis and Management  
Harlan Krumholz, MD, MSc  
Harold H. Hines Professor of Medicine and Epidemiology and Public Health, Yale University

**Year 02 (1993-1994)**
Psychosocial Intervention in Elderly Stroke Patients: Intervention  
Thomas Glass, PhD  
Professor of Epidemiology – Johns Hopkins University

Prevention of Delirium in Hospitalized Elderly Patients  
Sharon Inouye, MD, MPH  
Professor of Medicine, Harvard University

Study of Older Driver Assessment Instrument  
Richard Marottoli, MD, MPH  
Professor of Medicine, Yale University

Predicting Differential Patterns of Response to Challenge  
Teresa Seeman, PhD  
Professor of Medicine and Epidemiology – UCLA

**Year 03 (1994-1995)**
Dissemination of Fall Reduction Information  
Dorothy Baker, PhD, RN-C  
Research Scientist (Geriatrics), Yale University

Depression in Elderly Medical Homecare Patients  
Martha Bruce, PhD, MPH  
Professor of Sociology in Psychiatry – Weill Cornell Medical College

Cumulative Call Back Rate in Mammography  
Joann Elmore, MD, MPH  
Professor of Medicine – U. of Washington

The Sociodemographic Factors Associated with Medical Expenditures Prior to Death  
Colleen Grogan, PhD  
Professor of Social Service Administration – U. of Chicago
Functional MRI Studies of Motor Recovery from Stroke
Dana Leifer, MD
Associate Professor of Neurology - Weill Cornell Medical College

Cognitive Function, Self Efficacy Beliefs and Behavioral Function in the Elderly
Emily Richardson, PhD
Assistant Research Professor Psychology - U. of Colorado

Response to Challenge as a Mechanism of Successful Aging
Teresa Seeman, PhD
Professor of Medicine and Epidemiology – UCLA
and
Loretta DiPietro, PhD
Professor and Chair of Exercise Science, George Washington University

**Year 04 (1995-1996)**
Measuring Satisfaction with Medical Services for Elderly Veterans with Comorbid Medical and Psychiatric Illnesses
Benjamin Druss, MD, MPH
Professor of Health Policy and Management – Emory University

Factors Associated with Short-term Mortality and Site of Death of Older Homecare Patients.
Terri Fried, MD
Professor of Medicine (Geriatrics), Yale University

Predictors of Recovery of ADL Function among Disabled Older Persons Living in the Community
Thomas Gill, MD
Professor of Medicine (Geriatrics) and of Investigative Medicine and of Epidemiology and Public Health, Yale University

Analysis of Age-Related Changes in Human Osteoblasts
Mark Horowitz, PhD
Professor Orthopaedics and Rehabilitation, Yale University

Stressors as Risk Factors for Late Onset Major Depression
Carolyn Mazure, MD
Professor of Psychiatry and of Psychology, Yale University

Studies on the Relationship Between Lactational Vasometer Episodes and Those of Menopause
Steven Palter, MD
Medical and Scientific Director, Gold Coast IVF

Effect of Estrogen Administration on Fluid Regulation Responses to Hypertonicity in Post Menopausal Woman
Nina Stachenfeld, PhD
Associate Professor of Epidemiology, Yale University

Impact of Treatment and Adherence and Adequacy of Follow-up Health Care on Outcome of Congestive Heart Failure
Viola Vaccarino, MD, PhD
Professor of Medicine and Chair of Epidemiology – Emory University
Year 05 (1996-1997)
Goal-Setting in the Care of Patients with Dementia: The Differing Perspectives of Patient, Family, Case Manager, and Physician
Sidney Bogardus, Jr., MD
Associate Clinical Professor of Medicine (Digestive Diseases), Yale University

Acute Effects of Exercise on Glucose Disposal, Growth Hormone and IGF-I in Healthy Older People
Loretta DiPietro, PhD
Professor and Chair of Exercise Science, George Washington University

Iodide Channels in Thyroid Gland
Peying Fong, PhD
Associate Professor of Anatomy and Physiology - College of Veterinary Medicine, Kansas State University

The Role of IL-6 in Osteoporosis
Karl Insogna, MD
Professor of Medicine (Endocrinology), Yale University

Identifying Risk Factors Influencing Glycemic Control in Outpatient Elderly Patients
Sandra Moody-Ayers, MD
Associate Clinical Professor of Medicine (Geriatrics), U. of California – San Francisco

Measuring the Meanings Underlying Global Self-Rated Health
Carol van Doorn, PhD
Private Practise, Therapist

Depression and Marriage in Older Couples
Mark Whisman, PhD
Professor of Psychology and Neurosciences, U. of Colorado

Pigment Epithelium-Derived Factor (PEDF) and Survival of Identified Ganglion Subtypes in the Aging Primate Retina
Kenneth Wikler, PhD
Executive Director, Bell Falla & Associates

Mechanisms of Epileptogenesis in the Aged Brain
Anne Williamson, PhD
Associate Adjunct Professor of Neurosurgery, Yale University

Year 06 (1997-1998)
Evoked Potentials Evidence for Premature Aging in Alcoholic Subjects
Nashaat Boutros, MD
Professor and Chair, Department of Psychiatry, University of Kansas – Kansas City School of Medicine

Do Changes in Heterochromatin Affect Drosophila Life Span?
Stewart Frankel, PhD
Associate Professor of Biology, University of Hartford
Alcohol Consumption among Cognitively Impaired Adults: Prevalence, Patterns of Use and Association with Functional Dependence
M. Carrington Reid, PhD, MD
Associate Professor of Medicine - Weill Cornell Medical College

Visual Attention Training for Older Drivers
Emily Richardson, PhD
Assistant Research Professor Psychology - U. of Colorado

**Year 07 (1998-1999)**

A Diagnostic Criteria for Traumatic Grief in Late Life
Holly Prigerson, PhD
Professor of Sociology in Medicine and of Geriatrics, Weill Cornell Medical College

Werner Gene: Cellular Processes Leading to Premature Aging and Reduced Life Span
Anna Marie Szekely, MD
Associate Research Scientist Genetics and Neurology, Yale University

**Year 08 (1999-2000)**

Feasibility of Using Conjoint Analysis to Access Preferences in Treatment of Knee Osteoarthritis in Adults
Liana Fraenkel, MD, MPH
Professor of Medicine (Rheumatology), Yale University

Skeletal Effects of Age Related Changes in Calcium Metabolism in Men
Barbara Gulanski, MD, MPH
Associate Professor of Medicine (Endocrinology), Yale University

Effects of Aging and Stress on Hippocampal Plasticity and Memory
Jeansok J. Kim, PhD
Professor of Psychology and Neurobiology and Behavior - University of Washington

Identification of Protein Kinase Mediators of Drug Desensitization
Henrik G. Dohlman, PhD
Professor of Biochemistry and Biophysics and of Pharmacology - University of North Carolina - Chapel Hill

Premature Aging a Genetic Disorder, Williams Syndrome
Barbara Pober, MD, MPH
Professor of Medical Sciences, Quinnipiac University School of Medicine

**Years 09 and 10 (2000-2002)**

The Influence of Self-Stereotypes on AMI Recovery (2 years)
Becca Levy, Ph.D.
Associate Professor of Epidemiology and Public Health and of Psychology, Yale University

Investigation into Underlying Mechanisms of Racial Differences in Susceptibility to Osteoporosis
Urszula Masiukiewicz, M.D.
Assistant Clinical Professor of Medicine (Endocrinology), Yale University
Therapy for Traumatic Grief in Widowed Seniors  
Holly Prigerson, Ph.D.  
Professor of Sociology in Medicine and of Geriatrics, Weill Cornell Medical College

Modifiable Risk Factors for Nursing Home Acquired Pneumonia (2 years)  
Vincent Quagliarello, M.D  
Professor of Medicine (Infectious Disease), Yale University

Cognitive Behavioral Therapy for Older Adults with Chronic Back Pain  
M. Carrington Reid, Ph.D., MD  
Associate Professor of Medicine – Weill Cornell Medical College

**Year 11 (2002-2003)**  
Involuntary Job Loss as a Precipitating Event for Functional Decline and Depressive Symptoms among Predisposed Workers  
William T Gallo, PhD  
Associate Professor of Epidemiology and Biostatistics, School of Public Health, City University of New York

Alterations in Oxidative Stress Response with Human Aging  
Nikki J Holbrook, PhD  
Retired, Adjunct Professor of Medicine and Pathology, Yale University

Modifiable Risks for Nursing Home Acquired Pneumonia  
Vincent J. Quagliarello, MD  
Professor of Medicine (Infectious Disease), Yale University

**Year 12 (2003-2004)**  
Novel Cognitive Enhancer for the Aged: Protein Kinase C Inhibition  
Amy Arnsten, M.D.  
Professor of Neurobiology and Psychology, Yale University

Improving Shared Decision Making in Older Adults with Knee Osteoarthritis: A Pilot Trial  
Liana Fraenkel, M.D.  
Professor of Medicine (Rheumatology), Yale University

**Year 13 (2004-2005)**  
Age-Related Differences in Sleep-Disordered Breathing in Patients with Acute Ischemic Stroke  
Dawn Bravata, MD  
Associate Professor of Medicine, Indiana University

Mechanisms of Rod-Dependent Cone Survival in Aging Retina  
Caroline Zeiss, PhD, BVSc  
Professor of Comparative Medicine, Associate Professor of Ophthalmology and Visual Science, Yale University

**Years 14 and 15 (2005-2007)**  
Aging and Memory CD8+ T Cell Survival  
Insoo Kang, MD  
Associate Professor of Medicine (Rheumatology), Yale University
Year 16 and 17 (2008-2009)
Heart Failure as a Multifactorial Geriatric Syndrome
Sarwat Chaudhry, MD
Associate Professor of Medicine (General), Yale University

A Multifactorial Model of Emphysema: The Effects of Smoking and Age on TLR-Regulated Pathways
Patty Lee, MD
Associate Professor of Medicine (Pulmonary), Yale University

Interaction of Multiple Genetic and Dietary Factors in AMD Pathogenesis
Caroline Zeiss, PhD, BVSc
Professor of Comparative Medicine, Associate Professor of Ophthalmology and Visual Science, Yale University

Year 18 (2010-2011)
Identification of endogenous and exogenous anti-aging compounds.
Ruslan Medzhitov, MD, PhD
David W. Wallace Professor of Immunobiology, Yale University

DNA methylation of HOXA11: An epigenetic link between aging, obesity and pelvic organ prolapsed.
Kathleen Connell, MD
Associate Professor of Obstetrics and Gynecology (Urology), University of Colorado

Year 19 (2011-2012)
The effect of ambiguity on treatment preferences in the elderly.
Ifat Levy, PhD
Associate Professor of Comparative Medicine and of Neurobiology, Yale University

Regulation of aging by host cell factor C1 and O-GlcNAc signaling.
Xiaoyong Yang, PhD
Associate Professor of Comparative Medicine and of Physiology, Yale University

Year 20 (2012-2013)
MicroRNAs as biomarkers of aging.
Frank Slack, PhD
Professor of Pathology and Medicine, Harvard University

Year 21 (2013-2014)
Multifactorial Nature of Age-related Hearing Loss in a Mouse Model of Mitochondrial Pathology
Gerald S Shadel, PhD
Professor of Pathology and of Genetics, Yale University

The Role of Multiple Peripheral Metabolites on Cognitive Performance in Older Persons
Raimund Herzog, MD, MHS
Assistant Professor of Medicine (Endocrinology), Yale University
Dyspnea in Older Persons: A Multifactorial Geriatric Health Condition
Carlos Vaz Fragoso, M.D.,
Associate Professor of Medicine, (Geriatrics), Yale University

**Year 22 (2014-2015)**

Role of the Telomere Binding Protein CTC1 in the Maintenance of Stem Cell Function
Sandy Chang, PhD, MD
Associate Professor of Laboratory Medicine and of Pathology, Yale University

The Role of Intramuscular Adipocytes in Dysfunction of Aged Muscle
Matthew Rodenheffer, PhD
Assistant Professor of Comparative Medicine and of Molecular, Cellular, and Developmental Biology

Rapid Pilot award to support “Circadian Rhythms and Immune Responses in Aging”.
Ruth Montgomery, PhD
Associate Professor of Medicine, (Rheumatology, Yale University)
### Section III. Career Development Subsequent to Pepper Support

<table>
<thead>
<tr>
<th>Pilot P.I. Name and Current Status</th>
<th>Pepper Pilot and/or RCDC Support: Title, Dates</th>
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</thead>
<tbody>
<tr>
<td>Sharon Inouye, MD, MPH</td>
<td>“Prevention of Delirium in Hospitalized Elderly Patients” - 1992-93</td>
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<td></td>
<td>“Identifying Precipitating Factors for Delirium in Hospitalized Elderly Patients” - 1993-94</td>
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<tr>
<td>Milton and Shirley F. Levy Family</td>
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<tr>
<td>Chair and Professor of Medicine at Harvard Medical School</td>
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<tr>
<td>Director, The Aging Brain Center, Institute for Aging Research, Hebrew Senior Life, Boston, MA</td>
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<tr>
<td>Thomas A. Glass, Ph.D.</td>
<td>“Psychosocial Intervention in Elderly Stroke Patients: Screening and Assessment” – 1992-93</td>
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<tr>
<td>Professor of Epidemiology, John</td>
<td>“Psychosocial Intervention in Elderly Stroke Patients: Intervention” – 1993-94</td>
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<tr>
<td>Hopkins University, Bloomberg</td>
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<tr>
<td>School of Public Health</td>
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<td>Senior Associate Member, Johns</td>
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<tr>
<td>Hopkins Center on Aging and Health</td>
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<tr>
<td>Harlan M. Krumholz, M.Sc., MD</td>
<td>“Congestive Heart Failure in the Elderly: Role of Left Ventricular Function on Prognosis and Management” - 1992-93</td>
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<tr>
<td>Harold H. Hines, Jr. Professor of</td>
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<tr>
<td>Medicine (Cardiology) and of</td>
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<td>Investigative Medicine and of</td>
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<td>Public Health, Yale University</td>
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<td>Professor in the Institute of</td>
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<td>Social and Policy Studies, Yale</td>
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<td>University</td>
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<tr>
<td>Director, Yale-New Haven Hospital</td>
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<tr>
<td>Center for Outcomes Research and</td>
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<td>Evaluation</td>
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<td>Director, Yale Robert Wood</td>
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<td>Johnson Clinical Scholars Program</td>
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<td>Member, Institute of Medicine</td>
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<tr>
<td>Richard Marottoli, MD, MPH</td>
<td>Professor of Medicine – Geriatrics, Yale University</td>
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<td></td>
<td>Director, Yale New Haven Hospital Dorothy Adler Geriatric Assessment Center</td>
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<tr>
<td>Joann Elmore, MD, MPH</td>
<td>Professor of Medicine, University of Washington</td>
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<tr>
<td>Teresa E. Seeman, PhD</td>
<td>Professor of Medicine (Geriatrics) and of Epidemiology, David Geffen School of Medicine, UCLA</td>
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<td></td>
<td>Core Leader, UCLA OAIC Research Operations Core</td>
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<tr>
<td>Dorothy Baker, PhD, RN-C</td>
<td>Research Scientist (Geriatrics), Yale University</td>
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<td>Name</td>
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<tr>
<td>Martha L. Bruce, Ph.D., MPH</td>
<td>Professor of Sociology in Psychiatry, Weill Cornell Medical College and the Clinical Epidemiology Program at the Cornell Graduate School of Medical Sciences</td>
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<td></td>
<td>Associate Vice Chair for Research, Dept of Psychiatry, Weill Cornell Medical College</td>
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<tr>
<td>Dana Leifer, MD</td>
<td>Associate Professor of Neurology, Weill Cornell Medical College</td>
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<tr>
<td>Benjamin Druss, MD, MPH</td>
<td>Professor of Health Policy and Management, Emory University</td>
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<td></td>
<td>Rosalynn Carter Chair in Mental Health, Rollins School of Public Health, Emory University</td>
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<tr>
<td>Colleen Grogan, Ph.D.</td>
<td>Professor of Social Service Administration, University of Chicago</td>
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<tr>
<td>Terri Fried, MD</td>
<td>Professor of Medicine (Geriatrics), Yale University</td>
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<td></td>
<td>Co-Director Yale Program on Aging</td>
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<td>Co-Director Yale Pepper Center</td>
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<td>Core Leader, Research Career Development Core, Yale Pepper Center</td>
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<td>Thomas M. Gill, MD</td>
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<tr>
<td>Humana Foundation Professor of Medicine</td>
<td>Professor of Epidemiology (Chronic Diseases)</td>
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<td>Professor of Investigative Medicine</td>
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<td>Director, Yale Training Program in Geriatric Clinical Epidemiology</td>
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<td>Director, Yale Program on Aging</td>
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<td>Director, Yale Pepper Center</td>
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<td>Director, Yale Center for Disability and Disabling Disorders;</td>
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<td>Mark Horowitz, Ph.D.</td>
<td>Professor Orthopaedics and Rehabilitation, Yale University</td>
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<tr>
<td></td>
<td>Vice Chair for Research, Yale Core Center for Musculoskeletal Disorders and Director of the Cell Core</td>
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<tr>
<td>Carolyn Mazure, Ph.D.</td>
<td>Norma Weinberg Spungen and Joan Lebson Bildner Professor of Psychiatry and of Psychology, Yale University</td>
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<tr>
<td></td>
<td>Director, Women's Health Research at Yale</td>
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<tr>
<td>Steven Palter, MD</td>
<td>Medical and Scientific Director, Gold Coast IVF, Syosset, NY</td>
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<tr>
<td>Nina Stachenfeld, Ph.D.</td>
<td>Senior Research Scientist in Obstetrics, Gynecology and Reproductive</td>
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<tr>
<td>Science, Yale University</td>
<td>Associate Professor of Epidemiology (Environmental Health), Yale University</td>
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<tr>
<td>Viola Vaccarino, MD, Ph.D.</td>
<td>Professor of Medicine (Cardiology), Emory School of Medicine</td>
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<td></td>
<td>Professor and Chair, Department of Epidemiology, Rollins School of Public Health, Emory University</td>
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<td></td>
<td>Director, Emory Program in Cardiovascular Outcomes Research and Epidemiology</td>
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<tr>
<td>Sidney Bogardus, Jr., MD</td>
<td>Associate Clinical Professor of Medicine (Digestive Diseases), Yale University</td>
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<tr>
<td>Loretta DiPietro, Ph.D., MPH</td>
<td>Professor and Chair of the Department of Exercise Science, George Washington University</td>
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<td></td>
<td>Director, Physical Activity in Public Health – MPH Program, George Washington University</td>
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<td>Peying Fong, Ph.D.</td>
<td>Associate Professor of Anatomy and Physiology, College of Veterinary Medicine, Kansas State University</td>
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<td>Karl Insogna, MD</td>
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<tr>
<td>Professor of Medicine (Endocrinology), Yale University</td>
<td>Director, Yale Bone Center</td>
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<td>Sandra Moody-Ayers, MD</td>
<td>Associate Clinical Professor of Medicine (Geriatrics) University of California, San Francisco</td>
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<td>Carol van Doorn, Ph.D.</td>
<td>Private Practice, Therapist, Fredrick, MD.</td>
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<td>Professor of Psychology and Neurosciences, University of Colorado, Boulder</td>
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<tr>
<td>M. Carrington Reid, Ph.D., MD,</td>
<td>Irving Sherwood Wright Associate Professor of Medicine (Geriatrics), Weill Cornell Medical College</td>
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<tr>
<td>Emily D. Richardson, Ph.D.</td>
<td>Assistant Research Professor, Psychology, University of Colorado at Boulder</td>
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<td>Holly G. Prigerson, Ph.D., MS</td>
<td>Professor of Sociology in Medicine and of Geriatrics, Weill Cornell Medical College</td>
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<td>Anna Marie Szekely, M.D.</td>
<td>Associate Research Scientist in Genetics and in Neurology, Yale University</td>
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<td>Liana Fraenkel, MD, MPH</td>
<td>Professor of Medicine (Rheumatology), Yale University</td>
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<td>Barbara I. Gulanski, MD, MPH</td>
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<td>Jeansok J. Kim, Ph.D.</td>
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<td>Professor of Medical Sciences, Quinnipiac University, School of Medicine</td>
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<tr>
<td>Associate Professor, Epidemiology and Biostatistics, CUNY School of Public Health at Hunter College</td>
<td>Functional Decline and Depressive Symptoms among Predisposed Workers” 2002-2005</td>
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<td>Nikki J Holbrook, PhD</td>
<td>Retired Adjunct Professor of Medicine and Pathology, Yale University</td>
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<td>Cary Gross, MD</td>
<td>Professor of Medicine (General) and of Epidemiology (Chronic Diseases) and in the Institute of Social and Policy Studies, Yale University</td>
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<td>Margaret Pisani, MD, MPH</td>
<td>Associate Professor of Medicine (Pulmonary), Yale University</td>
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<tr>
<td>Joel Dubin, PhD</td>
<td>Associate Professor of Statistics and of Actuarial Science, University of Waterloo, Canada</td>
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<tr>
<td>Karyn Frick, PhD</td>
<td>Professor of Psychology, University of Wisconsin, Milwaukee</td>
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<td>Amy Arnsten, PhD</td>
<td>Professor of Neurobiology and of Psychology, Yale University</td>
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<tr>
<td>Cynthia Brandt, MD, MPH</td>
<td>Professor of Emergency Medicine and of Anesthesiology (Medical Informatics), Yale University</td>
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<td>Dawn Bravata, MD</td>
<td>Associate Professor of Medicine, School of Medicine, Indiana University</td>
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<tr>
<td>Joseph Agostini, MD</td>
<td>National Medical Director, Medicare, Aetna, Inc. Hartford, CT</td>
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<tr>
<td>Albert Shaw, MD, PhD</td>
<td>Associate Professor of Medicine (Infectious Diseases), Yale University</td>
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<tr>
<td>JoAnn Foody, MD</td>
<td>Associate Professor of Medicine, Harvard Medical School</td>
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<tr>
<td>Josephine Hoh, PhD</td>
<td>Professor of Medicine (Cardiology) and of Immunobiology, Yale University</td>
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<td>Josephine Hoh, PhD</td>
<td>Associate Professor of Epidemiology (Environmental Health) and of Ophthalmology and Visual Science, Yale University</td>
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<td>Insoo Kang, MD</td>
<td>Associate Professor of Medicine (Rheumatology), Yale University</td>
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<td>Julie Ann Sosa, MD, MA, FACS</td>
<td>Professor of Surgery (Endocrine) and of Medicine, Duke University</td>
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<tr>
<td>Lisa Cataldi-Barry, PhD, MPH</td>
<td>Assistant Professor of Psychiatry, University of Connecticut, Center on Aging</td>
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<td>Carlos Vaz Fragoso, MD</td>
<td>Associate Professor of Medicine (Geriatrics), Yale University</td>
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<td>Sarwat Chaudhry, MD</td>
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<td>Manisha Juthani-Mehta, MD</td>
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<tr>
<td>Arthur Simen, MD, PhD</td>
<td>Associate Professor of Medicine (Infectious Diseases), Yale University Program Director, Infectious Diseases Fellowship Program</td>
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<tr>
<td>Director, Pfizer Inc., Research and Development, Cambridge, Massachusetts</td>
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<td>Assistant Professor (Adjunct) of Psychiatry, Yale University</td>
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<td>Patty Lee, MD</td>
<td>Associate Professor of Medicine (Pulmonary), Yale University</td>
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<td>Leora Horwitz, MD, MHS</td>
<td>Associate Professor (Adjunct) of Medicine (General), Yale University</td>
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<td>Associate Professor, Department of Population Health, NYU School of Medicine</td>
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<td>Ruslan Medzhitov, PhD</td>
<td>David W Wallace Professor of Immunobiology, Yale University Member, National Academy of Sciences Member, Institute of Medicine</td>
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<tr>
<td>Stephanie Halene, MD</td>
<td>Assistant Professor of Medicine (Hematology), Yale University</td>
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<td>Kathleen Connell, MD</td>
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<tr>
<td>Associate Professor of Obstetrics and Gynecology (Urogynecology), University of Colorado</td>
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<td>Xiaoyong Yang, PhD</td>
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<td>Sandy S. Chang, MD, MHS</td>
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<td>Robert Pietrzak, PhD, MPH</td>
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<td>Frank Slack, PhD</td>
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<tr>
<td>Praveen Mannam, MBBS, MS</td>
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<tr>
<td>Name</td>
<td>Title</td>
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<tr>
<td>Elisabeth Erekson, MD, MPH</td>
<td>Assistant Professor of Obstetrics and Gynecology</td>
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<tr>
<td>Gerald S Shadel, PhD</td>
<td>Professor of Pathology and of Genetics, Yale University</td>
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<tr>
<td>Raimund Herzog, MD, MHS</td>
<td>Assistant Professor of Medicine, Section of Endocrinology, Yale University</td>
</tr>
<tr>
<td>Joan Monin, PhD</td>
<td>Assistant Professor of Epidemiology (Chronic Diseases), Yale University</td>
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<tr>
<td>Kasia Lipska, MD, MHS</td>
<td>Assistant Professor of Medicine (Endocrinology), Yale University</td>
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<tr>
<td>Terrence Murphy, PhD</td>
<td>Assistant Professor of Medicine (Geriatrics), Yale University</td>
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<tr>
<td>Melissa Knauert, MD, PhD</td>
<td>Instructor in Medicine (Pulmonary), Yale University</td>
</tr>
<tr>
<td>Daniel Weinberger, PhD</td>
<td>Assistant Professor of Epidemiology (Microbial Diseases), Yale University</td>
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<tr>
<td>Sandy Chang, PhD, MD</td>
<td>“Role of the Telomere Binding Protein CTC1 in the Maintenance of Stem Cell Function” – 2014-2015</td>
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<td>Associate Professor of Laboratory Medicine and of Pathology, Yale University</td>
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<tr>
<td>Matthew Rodenheffer, PhD</td>
<td>“The Role of Intramuscular Adipocytes in Dysfunction of Aged Muscle” – 2014-2015</td>
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<tr>
<td>Assistant Professor of Comparative Medicine and of Molecular, Cellular, and Developmental Biology</td>
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<tr>
<td>Ruth Montgomery, PhD</td>
<td>“Circadian Rhythms and Immune Responses in Aging” – 2015 (Rapid Pilot)</td>
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<tr>
<td>Associate Professor of Medicine (Rheumatology), Yale University</td>
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2014


2015


## Section V. Yale Pepper Center External Advisory Board

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>Years of Service</th>
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<tbody>
<tr>
<td>Ana Maria Cuervo, M.D., Ph.D.</td>
<td>Albert Einstein School of Medicine</td>
<td>2 years</td>
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<tr>
<td>Kevin P. High, M.D.</td>
<td>Wake Forest Baptist Medical Center</td>
<td>2 years</td>
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<tr>
<td>Edward R. Marcantonio, M.D.</td>
<td>Harvard Medical School</td>
<td>2 years</td>
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RECENT SCIENTIFIC RECOGNITION AND AWARDS

YALE UNIVERSITY
OAIC FACULTY

Thomas M. Gill, MD

Merit Award, National Institutes of Health, 2005-2015
Visiting Professor, University College of London, 2013
Visiting Professor, Hebrew Rehabilitation Center, Boston, 2013
Visiting Professor, Houston Methodist Hospital/ Baylor College of Medicine Geriatric, 2014
Member, Fellowship Committee, Gerontological Society of America, 2012–
Chair, Advisory Committee, Beeson Career Development Award Program, 2013–

Terri Fried, MD

Visiting Professor, University of Massachusetts Medical Center, 2013

Heather Allore, PhD

Women’s Midcareer Leadership Competitive Application, American Association of Medical Colleges, 2014

Bianca Buurman, RN PhD

Merck/American Geriatrics Society New Investigator Award, 2014

Andrew B. Cohen, DPhil, MD

Selected Participant, Hartford Change AGEnts Policy Institute, The John A Hartford Foundation, 2014
Presidential Poster Award for Ethics, American Geriatrics Society, 2015
Selected Participant, National Institute on Aging Butler-Williams Scholars Program, 2015

Leo M. Cooney, Jr., MD

Connecticut Magazine, Top Doctors, 2013
Best Doctors in America, 2013
David J Leffell Prize for Clinical Excellence, Yale School of Medicine, 2014

Kumar Dharmarajan, MD, MBA

Hartford Scholar in Geriatric Medicine, American Federation for Aging Research, 2012-2013
Paul B. Beeson Career Development Award in Aging Research, American Federation for Aging Research, 2014-2019
John Dodson, MD

Merck/American Geriatrics Society New Investigator Award, 2014

Lauren Ferrante, MD

Selected Participant, National Institute on Aging Butler-Williams Scholars Program, 2014
Recipient, (GEMSSTAR) Grants for Early Medical/Surgical Subspecialists’ Transition to Aging Research, 2015-2017

Stephanie Halene, PhD

Biomedical Trust Fund Award, Yale School of Public Health, 2014

Ling Han, MD, PhD

Official Delegate to Chinese Congress and Exposition on Gerontology and Health Industry, Suzhou, China, The Gerontological Society of America, 2014

Manisha Juthani-Mehta, MD

Fellow, Infectious Disease Society of America, 2013

Melissa Krauert, MD, PhD

Yale Center for Clinical Investigation (YCCI) Clinical and Community-Based Research Scholar Awards, 2015-2017

Becca Levy, PhD

Ewald W. Busse Research Award for Excellence in Social and Behavioral Sciences, International Association of Gerontology and Geriatrics, 2013
Senior Scholar Award for Research Related to Disadvantaged Older Adults, Gerontological Society of America and Senior Services of America, 2014

Kasia Lipska, MD, MHS

Junior Faculty Scholar, Yale Center for Clinical Investigation, 2013
T. Franklin Williams/GEMSSTAR Scholar, 2013
Paul B. Beeson Career Development Award in Aging Research, American Federation for Aging Research, 2014-2019
Una Makris, MD
Merck/American Geriatrics Society New Investigator Award, 2015

Praveen Mannam, MBBS, MS
Recipient, (GEMSSTAR) Grants for Early Medical/Surgical Subspecialists’ Transition to Aging Research, 2012-2014

Richard Marottoli, MD, MPH
Best Doctors in America, 2013
Chair, Medical Advisory Board, Connecticut Department of Motor Vehicles, 2015

Ruslan Medzhitov, PhD
Else Kröner-Fresenius-Foundation Inaugural International Prize in Immunology, 2013
Inaugural Lurie Prize in the Biomedical Sciences from the Foundation for the National Institutes of Health, 2013
Co-recipient, Vilcek Prize for Biomedical Science, 2013
Member, Institute of Medicine, 2013

Terrence Murphy, PhD
Accredited Professional Statistician™ by the American Statistical Association, 2012
Merck/American Geriatrics Society, New Investigator Award, 2014

Brian O’Hartaigh
Health Service Research Award, Gerontological Society of America, 2013

Alexander Panda, MD, MPH
Beeson Career Development Awards in Aging Research 2012-2017

Vincent Quagliarello, MD
New York Magazine, Best Doctors, 2007 - 2013
Connecticut Magazine Best Doctors, 2013
Best Doctors in America, 2007-2013
Visiting Professor, Mt. Sinai School of Medicine, New York, NY, 2013
Mary E Tinetti, MD
Best Doctors in America, 2010-2014
Connecticut Magazine Best Doctors, 2013

Carlos Vaz Fragoso, MD
Recipient, 10th annual Ralph L. Horwitz Department Lectureship, 2013

Lisa Walke, MD
Women Professional Development Scholar, American Association of Medical College, 2013
Harvard Macy Institute Scholar, 2013
New York Magazine, Best Doctors, 2014
Fellow, American Geriatrics Society, 2014
Practice Change Leader for Aging and Health, 2015

Daniel Weinberger, PhD
Bill and Melinda Gates Foundation, Global Health Award, 2014
Yale Center for Clinical Investigation (YCCI) Scholar Award, 2015-2017

Xiaoyong Yang, PhD
New Scholar Award, Ellison Medical Foundation, 2011-2015
Research Scholar Award, American Cancer Society, 2015
Minority trainees:

1. Heidi J. Zapata, MD, PhD: Effects of Age and HIV Infection on C-type lectin receptor function
2. Lauren Ferrante, M.D.: Critical Illness, Disability, and Vulnerability in Older Persons

Minority Research

1. Understanding Advance Care Planning as a Dyadic Process
   Terri R. Fried, Principal Investigator

Background/Rationale:
The concept and process of advance care planning (ACP) is undergoing an evolution, from the completion of documents by an individual specifying treatment preferences in the case of decisional incapacity, to an act of communication. Communication between patients and surrogates regarding patients’ values and preferences is particularly important because surrogates are frequently involved in treatment decision making for acutely ill patients. Despite the importance of patient-surrogate communication, little is known about this dyadic aspect of ACP. The few existing observational studies examining communication rely on either patient or surrogate report alone, without concomitantly examining the perspectives of both. Prior work of the Principal Investigator has studied dyads’ engagement in ACP as a process of health behavior change. This work has demonstrated that older persons and surrogates are frequently in different stages of behavior change regarding communication about end-of-life issues. As a consequence, sizeable proportions of pairs disagree about whether they are in the Action/Maintenance stage, meaning they disagree about whether engagement in ACP has occurred. In addition, there are also substantial proportions who agree that engagement in ACP has not occurred. However, the barriers to and facilitators of agreement about engagement in ACP have not been examined. Whether agreement about engagement in ACP leads to a shared understanding of the patient’s treatment goals, one of the key outcomes of ACP engagement, is also unknown.

Objectives:
The objectives of this study are to: (a) examine quantitatively the association between older person-surrogate agreement regarding the components of ACP behavior change and agreement regarding older persons’ treatment goals; (b) elucidate qualitatively the barriers to and facilitators of older person-surrogate dyads reaching agreement that they have achieved the Action/Maintenance stage of (have engaged in) ACP.

Methods:
Participants will be 304 veterans age 55 and older and the person they identify as their surrogate decision maker. Dyads will undergo a quantitative telephone interview designed to identify their Stage of Change for four key ACP behaviors as well as Decisional Conflict and Values/Beliefs regarding ACP and to characterize older person-surrogate agreement regarding the older
person’s treatment goals, so that the relationships among these variables can be modeled. Women and minorities will be oversampled to facilitate the analysis of race/ethnicity and gender as mediating variables. A subset of approximately 50 dyads will undergo a follow-up joint telephone open-ended interview. Content analysis of the transcripts will be conducted to develop a taxonomy of barriers to and facilitators of dyads’ reaching agreement that they have engaged in ACP. In the preliminary first phase of the study, 25 dyads participated in both joint telephone and in-person interviews in order to establish the feasibility and safety of performing open-ended interviews by telephone.

Findings/Results:

Enrollment is nearly complete. Of the 261 veterans, 35% are non-White (predominantly African-American) and 45% female. In preliminary analysis, overall, approximately 40% were in the A/M stage for completion of a living will or health care proxy, 44% in the A/M stage for communication about quality versus quantity of life, and 68% in the A/M stage for communication about life-sustaining treatment. While stage of change did not differ according to gender, non-White veterans were significantly less like than White veterans to be in the A/M stage for ACP behaviors (P < .05).

Figure: Percentage of veterans in A/M stage for ACP behaviors according to race

2. Ethnic differences in respiratory impairment.

OBJECTIVE: Spirometric Z scores by lambda-mu-sigma (LMS) rigorously account for age-related changes in lung function. Recently, the Global Lung Function Initiative (GLI) expanded LMS spirometric Z scores to multiple ethnicities. Hence, in aging populations, the GLI provides an opportunity to rigorously evaluate ethnic differences in respiratory impairment, including airflow limitation and restrictive pattern.

METHODS: Using data from the Third National Health and Nutrition Examination Survey, including participants aged 40-80, we evaluated ethnic differences in Global Lung Function Initiative (GLI)-defined respiratory impairment, including prevalence and associations with mortality and respiratory symptoms.
RESULTS: Among 3506 white Americans, 1860 African Americans and 1749 Mexican Americans, the prevalence of airflow limitation was 15.1% (13.9% to 16.4%), 12.4% (10.7% to 14.0%) and 8.2% (6.7% to 9.8%), and restrictive pattern was 5.6% (4.6% to 6.5%), 8.0% (6.9% to 9.0%) and 5.7% (4.5% to 6.9%), respectively. Airflow limitation was associated with mortality in white Americans, African Americans and Mexican Americans-adjusted HR (aHR) 1.66 (1.23 to 2.25), 1.60 (1.09 to 2.36) and 1.80 (1.17 to 2.76), respectively, but associated with respiratory symptoms only in white Americans-adjusted OR (aOR) 2.15 (1.70 to 2.73). Restrictive pattern was associated with mortality but only in white Americans and African Americans-aHR 2.56 (1.84 to 3.55) and 3.23 (2.06 to 5.05), and associated with respiratory symptoms but only in white Americans and Mexican Americans-aOR 2.16 (1.51 to 3.07) and 2.12 (1.45 to 3.08), respectively.

CONCLUSIONS: In an aging population, we found ethnic differences in GLI-defined respiratory impairment. In particular, African Americans had high rates of respiratory impairment that were associated with mortality but not respiratory symptoms.