The Claude D. Pepper
Older Americans
Independence Centers

2015-2016

Annual Directory
FOREWORD

The 2015-16 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 2015-16 Directory was prepared by the Claude D. Pepper Older Americans Independence Center Coordinating Unit at Wake Forest University.
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.
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Section I. Description of Center

The Boston OAIC is unique in its thematic focus on Function Promoting Therapies (FPTs) and its positioning across the entire spectrum of translational science from mechanism elucidation, preclinical proof-of-concept studies, biomarker validation, epidemiologic investigation to randomized trials of FPTs. The Boston OAIC integrates 19 NIH-funded studies of function promoting therapies, 3 Research Education Component projects, 3 pilot projects, and 3 developmental projects into an interdisciplinary program that is supported by a Leadership and Administrative Core, a Research Education Component (REC), a Pilot and Exploratory Studies Core (PESC), and 3 resource cores (Function Assessment Core, Preclinical Discovery Core, Biostatistical and Data Analysis Core). Our REC and PESC candidates include several rising stars in Geriatrics and Gerontology, including 3 Beeson and K grant awardees. The REC will recruit the most promising stars from a vast reservoir of talent at Harvard, Tufts and BU, and train them through a didactic education and mentored research program. Integration will be achieved by the PROMOTE Program that includes a research concierge service, research meetings, annual retreats, a website and a newsletter. The Boston OAIC is well integrated with the the Harvard Geriatrics and Gerontology research community and programs, including its T32 training grant, Harvard Clinical Translational Science Institute, the Roybal Center, The New England Geriatrics Research Clinical Education Center, and the Glenn Foundation Center for Biology of Aging.

Boston OAIC’s unique strengths include its focus on Function Promoting Therapies, emphasis on translation and commercialization, access to a large pool of talented young investigators, its extension across the entire spectrum of translational research, and its infrastructure for developing intellectual property and companies, and supporting several seminal randomized trials of FPTs.

<table>
<thead>
<tr>
<th>Programs and Components of the Boston OAIC</th>
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<tbody>
<tr>
<td>LEADERSHIP AND ADMINISTRATIVE CORE (Leader: Bhasin)</td>
</tr>
<tr>
<td>• Executive Committee</td>
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<tr>
<td>• Internal Advisory Board</td>
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<td>• External Advisory Board</td>
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<tr>
<td>• PROMOTE Program</td>
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<td>• LINK Program</td>
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<td>• Evaluation Unit</td>
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<tr>
<td>• Dissemination and Community Outreach</td>
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Section II. Research, Resources and Activities

A. Cores
   a. Function Assessment Core
   b. Preclinical Discovery and Small Animal Phenotyping Core
   c. Biostatistical Design and Analysis Core

B. Research

External Projects

<table>
<thead>
<tr>
<th>Boston OAIC Projects and Their Relation to Research Platforms of FPT Development</th>
<th>PI</th>
<th>Title</th>
<th>Specific Aims</th>
<th>Core Utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elucidation of Mechanisms/ Target Identification/ Biomarker Development</td>
<td></td>
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<tr>
<td>P1. Bhasin/ 5 R01 AG03715</td>
<td></td>
<td>Mechanisms of Androgen Action on Skeletal Muscle</td>
<td>Mechanisms that mediate androgen action on muscle progenitor cell differentiation</td>
<td>PDC</td>
</tr>
<tr>
<td>P2. Fielding/ USDA 58-1950-51000-062-01A</td>
<td></td>
<td>Effects of Nutrient Modulation on Skeletal Muscle in Aging Animals</td>
<td>A USDA-supported program to conduct molecular and intervention studies of effects of diet on age-related loss of muscle mass and function</td>
<td>PDC BDAC</td>
</tr>
<tr>
<td>P3. Rivas / 1KO1AG0472-47</td>
<td></td>
<td>Role of microRNAs in age-related muscle loss</td>
<td>To determine the role of microRNAs in mediating the loss of muscle mass with aging</td>
<td>PDC</td>
</tr>
<tr>
<td>P4. Wagers/ 5R01AG3350-3</td>
<td></td>
<td>Reversing age-related dysfunction of muscle stem cells</td>
<td>To characterize juvenile protective factors which can reverse age-related skeletal muscle dysfunction</td>
<td>PDC, BDAC</td>
</tr>
<tr>
<td>P5. Wagers/ 1R01AG0489-17</td>
<td></td>
<td>The role of GDF11 in development and aging</td>
<td>To determine the anti-geronic effects of GDF11 during development and aging</td>
<td>PDC</td>
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<tr>
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<tr>
<td>Intervention Trials of FPTs</td>
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<tr>
<td>P6. Lipsitz/ 2R01AG0250-37</td>
<td></td>
<td>Health Outcomes of Tai Chi In Subsidized Senior Housing</td>
<td>To determine the effects of Tai Chi on functional performance, health care utilization and costs in poor, elderly residents of low income housing facilities</td>
<td>FAC, BDAC</td>
</tr>
<tr>
<td>P7. Pahor, Fielding/ U01AG05049</td>
<td></td>
<td>The ENRGISE Study (Pahor overall PI; Fielding Tufts Site PI)</td>
<td>A pilot study to investigate effects of anti-inflammatory agents on serum cytokine levels and mobility.</td>
<td>FAC</td>
</tr>
<tr>
<td>P7. Wang/ 1R01 AT006367</td>
<td></td>
<td>Tai Chi &amp; Aerobic Exercise for Fibromyalgia</td>
<td>The effects of Tai Chi and aerobic exercise on physical function and wellbeing in patients with fibromyalgia</td>
<td>FAC; BDAC</td>
</tr>
<tr>
<td>P8. Bhasin/ 1RO1AG3754-7</td>
<td></td>
<td>Optimizing Protein Intake In Older Americans</td>
<td>Protein requirements for optimal anabolic response to FPTs in older adults with mobility limitation</td>
<td>FAC; BDAC</td>
</tr>
<tr>
<td>P9. Bhasin/ 1UO1</td>
<td></td>
<td>A Randomized Trial of a Fall Injury Prevention Strategy</td>
<td>To determine effectiveness of individually-tailored, risk factor-based fall injury prevention strategy</td>
<td>FAC</td>
</tr>
<tr>
<td>P1. Manson/ 1UO1-CA138962,S1</td>
<td></td>
<td>Vitamin D and OMEGA-3 TRIAL (VITAL)</td>
<td>The effects of vitamin D and omega-3 fatty acids on physical function and cardiovascular outcomes</td>
<td>FAC</td>
</tr>
<tr>
<td>P1. Fielding /PI of Tufts site</td>
<td></td>
<td>Nitrite Supplementation for Improving Physiological Function in Older Adults</td>
<td>To examine to examine the role of nitrite supplementation on vascular function and physical functioning in older at risk adults</td>
<td>FAC; BDAC</td>
</tr>
<tr>
<td>P1. Fielding/ USDA 58-1950-51000-</td>
<td></td>
<td>Nutrition, Exercise Physiology, and Sarcopenia</td>
<td>This USDA program studies effects of exercise and diet on age-related loss of muscle mass and function.</td>
<td>FAC, BDAC</td>
</tr>
</tbody>
</table>
### List of Development Projects: Innovation and Relevance to FPTs

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Investigators</th>
<th>Innovation/ Application to Other OAIC Projects</th>
<th>Cores</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP1. Minimal Clinically Important Difference of the Late-Life Function Instrument</td>
<td>PI: Jette (PROs, disability), Latham (Rehab, PT); Co-I: Beuchamp (Outcomes assessment)</td>
<td>To use anchor and distribution-based approaches to determine MCID of LLFI in older adults using data from the STRIDE study; these data will be useful in projects P6, P7, P9, P13</td>
<td>FAC</td>
</tr>
<tr>
<td>DP2. Functional Microscopy of Muscle Using 7T Magnetic Resonance Imaging and Spectroscopy</td>
<td>PI: Mukundan (Muscle Imaging, Spectroscopy); Jasuja (Muscle Biology; Biophysical Engineering)</td>
<td>Validate a novel method for quantitative assessment of myofibrillar space, muscle perfusion, O2 uptake, and fatigability using 7T MRI and Spectroscopy; of value to P1, P2, P3, P4</td>
<td>PDC</td>
</tr>
<tr>
<td>DP3. A Novel Randomization Strategy for Cluster-Randomized Trials</td>
<td>PI: Travison (Biostatistics); Allore (Biostatistics, Yale)</td>
<td>To develop a novel method for randomization in cluster randomized trials</td>
<td>BDAC</td>
</tr>
</tbody>
</table>

FAC, Function Assessment Core; PDC, Preclinical Discovery Core; BDAC, Biostatistical Design and Analytical Core

### C. Pilot and Exploratory Science Projects

PES1. MicroRNAs as predictors of anabolic response (Rivas)
PES2. Home-based Exercise to Improve Functional Status after Trans-catheter Aortic Valve Replacement (Kim)
PES3. Optimization of Transcranial Brain Stimulation to Improve Physical Function in Older Adults (Manor)
Section III. Research Education Component (REC) Projects: Provide names and funding subsequent to Pepper pilot funding.

1. Michael S. Lustgarten, PhD; The Effect of Prebiotic Supplementation on Lean Mass and Physical Function in Older Adults. Current Position: Scientist III, Exercise Physiology and Sarcopenia Laboratory, Jean Mayer USDA HNRCA, Tufts University. Mentor: Roger Fielding, PhD.

2. Caroline A. Kim, MD, MPH, SD candidate; Functional Status Trajectories After Transcatheter Aortic Valve Replacement. Current Position: T32 Postdoctoral Fellow and Geriatrician (The candidate will have assumed a faculty position as Instructor in Medicine early next year), Beth Israel Deaconess Medical Center and Harvard Medical School, Mentors: Edward Marcantonio, MD and Lewis Lipsitz, MD

3. Indranil Sinha, MD, Increased cyclooxygenase-2 activity mediates aging-associated decrease in skeletal muscle regeneration. Instructor in Surgery, Brigham and Women’s Hospital and Harvard Medical School. Mentors: Shalender Bhasin, MD, and Amy Wagers, PhD

Section IV. Publications: Provide only those that are a direct result of Pepper Center resources and list publications published in the 2015-2016 years only.


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

Thomas Gill, MD, Yale University, New Haven, CT 2009-present
Marco Pahor, MD, University of Florida, Gainesville, FL, 2013-present
Andrew Goldberg, MD, University of Maryland, Baltimore, MD, 2009-present
Please also send two additional and separate documents:

1. Recognition and Awards

<table>
<thead>
<tr>
<th>OAIC Investigator/ Role in OAIC</th>
<th>Honors</th>
</tr>
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<tbody>
<tr>
<td>Shalender Bhasin, Boston OAIC Director</td>
<td>Clinical Investigator Award of the Endocrine Society 2015; Research Mentor in Women’s Health Award of the Endocrine Society 2015</td>
</tr>
<tr>
<td>Roger Fielding, OAIC Associate Director, Director, FAC</td>
<td>Oluf Johnell Science Award for Excellence in Musculoskeletal Research, International Osteoporosis Foundation; Section editor, Calc Tissue Int; Associate Editor, J Gerontol Med Sci</td>
</tr>
<tr>
<td>Lewis Lipsitz, OAIC Associate Director, REC Director</td>
<td>Joseph T. Freeman Award, Gerontological Society of America, 2010; William Silen Lifetime Achievement in Mentoring Award, 2009-2010</td>
</tr>
<tr>
<td>Alan Jette, Director, Developmental Projects</td>
<td>Elected to Institute of Medicine, 2014; <em>John Maley Award, American Physical Therapy Association 2014</em>; McMillan Lectureship Award, APTA 2012; Charles M. Magistro Distinguished Service Award, Foundation for Physical Therapy 2014, Excellence in the Rehabilitation of Aging Persons Award, GSA 2011</td>
</tr>
<tr>
<td>Edward Marcantonio, Assoc. Director, REC</td>
<td>Outstanding Scientific Achievement in Clinical Investigation Award, American Geriatrics Society</td>
</tr>
<tr>
<td>Amy Wagers, Assoc Director, REC</td>
<td>Howard Hughes Early Career Investigatorship; Robertson Prize for translational stem cell research</td>
</tr>
<tr>
<td>Douglas Kiel, Co-Director, PESC</td>
<td>A. Clifford Barger Excellence in Mentoring Award in Geriatrics, HMS, 2013; Elected President, American Society of Bone Mineral Research</td>
</tr>
<tr>
<td>Jasuja, former PESC Awardee; now PDC Director</td>
<td>Patent on free testosterone calculator</td>
</tr>
<tr>
<td>Monty Montano, former PESC awardee, now PESC Director</td>
<td>Charter member, AIDS Clinical and Epidemiology Study Section; patent for biomarkers of anabolic response; Launched Biosyntax, LLC; Authored a book on Translational Medicine</td>
</tr>
<tr>
<td>Tuhina Neogi (RCDC Awardee, now an REC Faculty Mentor)</td>
<td>Osteoarthritis Research Society Young Investigator Award; Evans Junior Investigator Award; Panelist for developing treatment guidelines; appointed chair of FDA Advisory Committee</td>
</tr>
<tr>
<td>Chen Chen Wang (RCDC Awardee)</td>
<td>Appointed to Advisory Council of NCAAM; Appointed Chief of Department of Integrative Medicine</td>
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2. Minority Research:

Donato Rivas, Ph.D. received K08 award to study the Potential for microRNAs to serve as predictors of anabolic response to exercise. He was an RCDC candidate supported by a minority supplement.
Duke University Medical Center  
Claude D. Pepper Older Americans Independence Center

<table>
<thead>
<tr>
<th>Name</th>
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<th>Electronic Mail</th>
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</thead>
<tbody>
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<td>Deputy Director</td>
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</table>

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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**
Cathleen Colon-Emeric, MD, MHS, and Kenneth W. Lyles, M.D., Core Leaders
Tel: (919) 660-7517 (Colon-Emeric)  (919) 660-7520 (Lyles) FAX: (919) 684-8569
E-mail:  cathleen.colonemeric@dm.duke.edu; kenneth.lyles@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., and William Kraus, M.D., Core Leaders
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 focus 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;
Plan and develop funding strategies for cores and support of projects related to cores; 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 direct and coordinates activities to ensure continued integration of center activities. Collectively, the resources and activities surrounded 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.

A Data Integration Working Group serves as a mechanism through which center-wide research questions are developed and addressed, and the work of emerging Pepper Scholars is mentored and developed. 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). An example of this work can be found in the Peterson et al. publication (in press for 2015 and published in 2016) in which we describe a “A Novel Analytic Technique to Measure Associations Between Circulating Biomarkers and Physical Performance Across the Adult Life Span” – JG:MS). 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) (see Hirschey. Mol. Cell. Proteomics). Also new for this year we examined the impact of metabolites on body mass index and age (See Kraus WE, et al). This strengthened metabolomics influence within the OAIC has resulted from key investigations that provide innovative linkages between metabolic signatures, premature disease, heritability of premature disease, and functional decline (Hirschey MD. SIRT3 regulates progression and development of diseases of aging in Trends Endocrinol Metab). Our metabolic profiling capability is unique among Pepper Centers and is a valued collaborative resource to the overarching Pepper OAIC program nationally. Our biomarker work is not limited to metabolic investigations as our resource cores have wide ranging capabilities. One of our young scholars published work examining the impact of early life biomarkers as a marker of premature aging in young adults (See Belskey et. Al.; Proc Natl Acad Sci) which received substantial publicity and another scholar continues to provide evidence of the role of progenitor cell depletion in poor late life physical function (see Povsic etal JG:MS). Other scholars continued to build on our work in biomarkers of osteoarthritis (see pubs with Kraus V as senior author). A review of our publications below highlights the breadth of our supported investigations.

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*.

**Ongoing 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**

**Ongoing Pilot Projects led by Pepper Scholars are:**

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

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

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

**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-ongoing)

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

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

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 –2015-2016

PUBLICATIONS 2015


Huffman KM, Pieper CF, Hall KS, St Clair EW, Kraus WE. Self-efficacy for exercise, more than disease-related factors, is associated with objectively assessed exercise time and sedentary behaviour in rheumatoid arthritis. Scand J Rheumatol. 2015;44(2):106-110. PMID: 25222824; PMCID: PMC4356639.


Hybels CF, Pieper CF, Payne ME & Steffens DC. Late-life depression modifies the association between cerebral white matter hyperintensities and functional decline among older adults. American Journal of Geriatric Psychiatry 2016;24:42-49. DOI: 10.1016/j.jagp.2015.03.001. First published online 12 March 2015. PMCID: PMC4567962


Kannan S, Kurupati RK, Doyle SA, Freeman GJ, Schmader KE, Ertl HC. BTLA expression declines on B cells of the aged and is associated with low responsiveness to the trivalent influenza vaccine. Oncotarget. 2015 Aug 14;6(23):19445-55. PMID:26277622


Hirschey MD, Zhao Y. Metabolic regulation by lysine malonylation, succinylation, and glutarylation. Mol. Cell. Proteomics. 2015;14(9):2308-2315. PMID: 25717114; PMCID: PMC4563717


**PUBLICATION 2016**


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
2015

Harvey Jay Cohen, M.D., Professor of Medicine, Division of Medicine, Duke University Medical Center
Honors:
Member, of a LLC, 2017 International Association of Geriatrics and Gerontology Congress
2013 – 2017
President, American Federation of Aging Research (AFAR)

Cathleen Colon-Emeric, M.D., Associate Professor of Medicine, Division of Geriatrics
Duke University Medical Center
Honors:
Nominated for the Duke School of Medicine Clinical Mentoring Award.
Accepted to the Duke Academic Leadership Innovation and Collaborative Engagement (ALICE) Program

Dr Louis DeFrate, Sc.D., Assistant Professor in the School of Medicine, Division of Orthopaedic
Duke University Medical Center
Honors:
ACL Study Group Traveling Scientist (2016-2018)
Kappa Delta Young Investigator Award (2016)
American Academy of Orthopaedic Surgeons and Orthopaedic Research Society

Katherine S. Hall, Ph.D., Assistant Professor of Medicine, Division of Geriatrics, Duke University and Durham VA Medical Centers
Honors:
Program Committee Member, International Association of Gerontology & Geriatrics (IAGG) World Congress
Elected Secretary-Treasurer, IAGG Council of Student Organizations
Elected Communications Chair, Society of Behavioral Medicine, Military and Veterans Health Special Interest Group
Member, American College of Sports Medicine Strategic Health Initiative for Older Adults

Virginia Kraus, M.D., Ph.D., Professor of Medicine, Division of Rheumatology and Immunology
Honors:
President of the Osteoarthritis Research Society International (OARSI)
Kappa Delta award from AAOS
Kappa Delta award from ORS

William Kraus M.D., Professor of Medicine, Division of Cardiology
Duke University Medical Center
Honors:
Elected Vice President, American College of Sports Medicine.
Miriam C. Morey, Ph.D. Professor of Medicine, Division of Geriatrics Duke University and Durham VA Medical Center

Honors:
Member, American College of Sports Medicine Strategic Health Initiative for Older Adults,
   Exercise is Medicine Subcommittee for Older adults
Nominated, Paul B. Magnuson Award

Kenneth E. Schmader, M.D., Professor of Medicine, Duke University Medical Center VA Medical Center

Honors:
Respiratory Syncytial Working Group, Advisory Committee on Immunization Practices,
   Centers for Disease Control

Heather E Whitson, M.D., Assistant Professor of Medicine, Division of Geriatrics Duke University Medical Center

Honors:
Outstanding Committee Service Award, AGS Research Committee
Program Chair, American Geriatrics Society
   approved by Board as Vice Chair, Research Committee, AGS
Served on the Institute of Medicine Committee on Public Health Approaches to Eye Health and Vision Impairment
Distinguished Nominee, Duke School of Medicine Research Mentoring Award
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. 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.

HOSPICE and PALLIATIVE CARE
Kimberly Johnson, MD – Ongoing

1) What are hospices in the Carolinas doing to increase access to hospice care for older African Americans in their service area. (2011-ongoing)

Experts and national organizations recommend that hospices work to increase service to African Americans, a group historically underrepresented in hospice. The objective of this study was to describe strategies among hospices in North and South Carolina to increase service to African Americans and identify hospice characteristics associated with these efforts. We used a cross-sectional survey which examined the frequency of community education/outreach, directed marketing, efforts to recruit African American staff, cultural sensitivity training, and goals to increase service to African Americans.

Of 118 eligible hospices, 79 (67%) completed the survey. Over 80% were at least somewhat concerned about the low proportion of African Americans they served, and 78.5% had set goals to increase service to African Americans. Most were engaged in community education/outreach, with 92.4% reporting outreach to churches, 76.0% to social services organizations, 40.5% to businesses, 35.4% to civic groups, and over half to health care providers; 48.0% reported directed marketing via newspaper and 40.5% via radio. The vast majority reported efforts to recruit African American staff, most often registered nurses (63.75%). Nearly 90% offered cultural sensitivity training to staff. The frequency of strategies to increase service to African Americans did not vary by hospice characteristics, such as profit status, size, or vertical integration, but was greater among hospices that had set goals to increase service to African Americans. These findings suggest that many hospices are engaged in efforts to increase service to African Americans. Future research should determine which strategies are most effective.
2) **Increasing access to hospice care for older African Americans: a National study**
*Kimberly Johnson, M.D., (2013-Ongoing)*

African Americans use hospice at lower rates than Whites. The overall goal of this work is to identify best practices among hospice providers in reaching African Americans. The study includes 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 overall goal is to identify best practices among hospice providers in reaching older African Americans.

To-date, we have enrolled 204 hospices across the United States. The vast majority of hospices were not-for-profit (79.4%), freestanding (70.1%), and located in the South (52.9%). Nearly 70% offered cultural competency training and 52% participated in community education and outreach to increase service to African Americans, most commonly involving churches, social service agencies, and healthcare providers. Participating hospices reported that the most successful strategies included partnerships with churches and community physicians with large numbers of African Americans. The least successful strategies to reach African Americans included the use of printed material or other advertising. We are involved in ongoing analyses which will lead to specific recommendations for hospice providers to increase service to African Americans in their communities.

3) **Racial Differences in Outcomes of Older Adults Receiving Inpatient Palliative Care Consultation (Pepper Pilot 2014-2016)**
*(ongoing)*

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 overall goal of this study is to examine differences in characteristics of African Americans and Whites receiving inpatient palliative care consultation, including reason for consultation, discharge disposition, and advance care planning.

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).

We also examined differences between the 2 racial groups in code status before and after inpatient palliative care consultation (IPCC). African Americans were more likely to be full code before (45.2% vs. 30.9%, p=0.01) and after (25.0% vs. 12.1%, p=0.002) IPCC. Among those who were full code before IPCC, 44.7% of African Americans and 60% of Whites changed their code status. After controlling for age, gender, diagnosis, and location, Blacks had a higher odds of being full code before (AOR 1.98 [1.21, 3.23]) and after (AOR 2.65 [1.45, 4.85]) IPCC. These findings suggest that efforts to increase access to inpatient palliative care consultation for seriously ill African Americans may reduce use of some life-prolonging therapies and improve the quality of end-of-life care.


4) Understanding Caregivers’ Views about Policies for Resolving Disagreements about the Use of Life-Sustaining Treatments

Lawmakers, hospitals, and professional societies have developed policies for resolving intractable conflicts when families request treatments for seriously-ill patients that clinicians believe are futile or otherwise inappropriate. These “futility policies” attempt to balance patient autonomy in medical decision-making, as expressed by their families acting as surrogate decision-makers, with physicians’ rights to not prescribe treatments that they believe are nonbeneficial or harmful. Although the goal of these policies is to ensure that all patients are treated equitably, a number of factors suggest that African Americans are more likely than Whites to find themselves in conflicts which trigger the use of futility policies, the outcome of which most often upholds clinicians’ assessments of futile care. First, African Americans are
more likely than Whites to want life-sustaining therapies in cases that clinicians believe are unlikely to lead to recovery, increasing the risk for conflict over treatment decisions. Second, African Americans’ views are more often guided by cultural values which emphasize the sanctity of life (in whatever form) and spiritual beliefs about the redemptive value of suffering. These beliefs often conflict with physicians’ judgments about what is an acceptable quality of life and their strategies to relieve suffering. Third, most hospital committee members who render decisions in futility cases are culturally different from African Americans and unlikely to share their perspectives. Despite these concerns, to our knowledge, those charged with developing futility policies have not systematically considered the perspectives of African Americans who may be disproportionately affected by such policies.

Therefore, the overall goal of this research is to compare the perspectives of African Americans and Whites on current futility policies and potential changes to these policies that would ensure fair consideration of their perspectives. Using focus groups and semi-structured interviews, the specific aims of this work are:

**Aim 1**: Compare beliefs and attitudes among African American and White caregivers of seriously ill patients regarding conflict management when caregivers request treatments that clinicians believe are futile or inappropriate.

**Aim 2**: Compare views of African-American and White caregivers of seriously ill patients regarding provisions which should be included in a “fair” process for resolving disagreements between caregivers and clinicians about the use of life-sustaining therapies.

**Aim 3**: Develop recommendations for conflict management policies which address the concerns and perspectives African Americans of African Americans and Whites.

This work will lead to recommendations which consider the perspectives of racially diverse groups of older adults in resolving conflicts between caregivers of seriously ill patients and physicians over the use of life-sustaining therapies.

**Duke Pepper Center Minority Supplement Awardee 2012-2014, Pepper REC Scholar 2016-2018**

*Rasheeda K. Hall, MD, MHS, MBA*

Dr. Rasheeda Hall is an Instructor 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 completed and proposed research is summarized below.

1. **Chronic kidney disease and recurrent falls in nursing home residents: a retrospective cohort study (completed).** This study examined whether chronic kidney disease (CKD) is associated with recurrent falls in older adults in nursing homes (NHs). We used data abstracted over a six month period from 510 NH residents with a history of falls. Thirty-five percent of the NH residents had CKD. In adjusted analyses, the incidence of recurrent falls was similar in those with and without CKD [fall rate ratio (FRR) 1.00, 95% confidence interval (CI) 0.97-1.02]. Orthostatic hypotension (FRR 1.52, 95% CI 1.12-2.05), history of falls during the prior six month period (FRR 1.25, 95% CI 1.05-1.49), cane or walker use (FRR 1.64, 95% CI 1.16-2.33), and ambulatory dysfunction (FRR 1.47, 95% CI 1.23-1.75) were independently associated with increased fall rate. CKD was not an important predictor of falls in this cohort of nursing home residents with prior falls. Instead, traditional fall risk factors were much more strongly associated with recurrent falls.

2. **Utilization of acute care among patients with ESRD discharged home from skilled nursing facilities (completed).** Older adults with ESRD often receive care in skilled nursing facilities (SNFs) after an acute hospitalization; however, little is known about acute care use after SNF discharge to home. This study used Medicare claims for North and South Carolina to identify patients with ESRD who were discharged home from a SNF between January 1, 2010 and August 31, 2011. Nursing Home Compare data were used to ascertain SNF characteristics. The primary outcome was time from SNF discharge to first acute care use (hospitalization or emergency department visit) within 30 days. Cox proportional hazards models were used to identify patient and facility characteristics associated with the outcome. Among 1223 patients with ESRD discharged home from a SNF after an acute hospitalization, 531 (43%) had at least one rehospitalization or emergency department visit within 30 days. The median time to first acute care use was 37 days. Characteristics associated with a shorter time to acute care use were black race (hazard ratio [HR], 1.25; 95% confidence interval [95% CI], 1.04 to 1.51), dual Medicare-Medicaid coverage (HR, 1.24; 95% CI, 1.03 to 1.50), higher Charlson comorbidity score (HR, 1.07; 95% CI, 1.01 to 1.12), number of hospitalizations during the 90 days before SNF admission (HR, 1.12; 95% CI, 1.03 to 1.22), and index hospital discharge diagnoses of cellulitis, abscess, and/or skin ulcer (HR, 2.59; 95% CI, 1.36 to 4.45). Home health use after SNF discharge was associated with a lower rate of acute care use (HR, 0.72; 95% CI, 0.59 to 0.87). There were no statistically significant associations between SNF characteristics and time to first acute care use. Almost one in every two older adults with ESRD discharged home after a post-acute SNF stay used acute care services within 30 days of discharge. Strategies to reduce acute care utilization in these patients are needed.

2. **CANDIDATE’S PROPOSED RESEARCH PLAN for 2016-ongoing**

**Resilience in Older Dialysis Patients.** Adults over age 65 are the most rapidly growing population initiating dialysis; however, 2/3 experience functional decline within six months. Before interventions to promote resilience after dialysis initiation can be developed, we need a
better understanding of how to measure it. Resilience can be described as recovery after each dialysis session (day-to-day resilience), and as maintenance of functional status after development of end-stage renal disease (long-term resilience, figure). Long-term resilience is influenced by the chronic inflammatory state of end stage renal disease that is manifest by protein-energy wasting and frailty. Day-to-day resilience is influenced by the acute intermittent stress of hemodialysis, when the cardiovascular system is exposed to rapid hemodynamic shifts, and the dialysis membrane’s foreign material promoting inflammation. Interventions such as multifactorial geriatric assessment may improve both day-to-day and long-term measures of resilience.

**Aim 1. Identify feasible, reliable, sensitive measures of day-to-day resilience for older dialysis patients.**

1a. Determine the range and within-subject variability in physical activity (PA) using step activity monitors and a self-reported fatigue score over 14 days and in relation to timing of dialysis.

1b. Determine the correlation between within-subject trajectories of fatigue score and PA and between a self-reported, validated measure of recovery time and an objective measure of recovery time from PA data.

**Aim 2. Identify feasible, reliable, sensitive measures of long-term resilience for older dialysis patients.**

2a. Describe the change in function [short physical performance battery (SPPB), handgrip, and activities of daily living (ADLs)] over the first six months of dialysis (administered on a mid-week dialysis day at baseline, 3 months, and 6 months) and between dialysis and non-dialysis days (administered twice over a 48 hour period).

2b. Determine the correlation between within-subject performance in the Functional Independence Measure (FIM), physical performance measures (SPPB, handgrip) and ADLs.

**Significance:** Completion of these aims will identify optimal measures of resilience in an older dialysis population and provide Dr. Hall with feasibility and measurement pilot data supporting an intervention development grant application.

**Approach.** A sample of 30 subjects ≥65 years who initiated hemodialysis within the past 30 days will be recruited. Exclusions include non-ambulatory status, dependence in all ADLs, advanced dementia, non-English speaking, and hospice enrollees. Subject screening, recruitment and consent will occur at dialysis units within 15 miles of Duke; in this area, there are 250 prevalent hemodialysis patients aged ≥65 years and 15 new patients/month. Clinical characteristics (comorbidities, intradialytic weight gain, hemodialysis access, hemoglobin, dialysis adequacy, and albumin) will be obtained from medical records. Subjects will undergo home PA monitoring with accelerometers for 14 days. During this time, study personnel will call subjects each weekday to ask subjects to report their fatigue score at that moment on a numeric rating scale (0-10). A validated measure of recovery time will be obtained at baseline. Functional measures will be tested in the dialysis unit before dialysis on a mid-week dialysis at baseline, 3, and 6 months (SPPB, handgrip strength, Lawton
ADLs, and Katz ADLs). During the same week, these measures will be repeated on a non-dialysis day in each subject’s home. Simultaneously, a physical therapist will conduct a home assessment involving the Functional Independence Measure (FIM).

**Aim 1 analysis** will calculate the proportion of subjects who complete the study protocol, the distribution of self-reported recovery time and within-subject changes in fatigue score and PA counts. Bivariate associations will test whether mean fatigue scores and PA counts are similar on dialysis and non-dialysis days. Associations of clinical characteristics with longitudinal changes in fatigue score and PA counts will be assessed using a mixed model with repeated measures logistic regression. Within-subject trajectories of fatigue score and PA counts will assess correlation between the two measures. Kaplan-Meier survival analysis will estimate time to recovery after dialysis using within-person changes in fatigue score and PA counts. The cut-points that will define time to recovery will be determined from the distribution of fatigue scores and PA counts. Mixed models to estimate the average within-person correlation between self-reported recovery time and recovery time derived from survival analyses. A sample size of 30 will provide power to detect correlations with moderate to large effect sizes (r>.3) with a confidence interval of 0.1, but is not large enough for modeling with covariate adjustment.

**Aim 2 analysis** will examine the distribution of individual and group means of physical performance and ADLs over time. Mixed models with repeated measures design will evaluate within-subject and between-subject variability at each time-point (baseline, 3 months, and 6 months) and include a home-clinic factor to measure slopes for each functional measure. This model will also identify the change score in each dyad. The correlation coefficient will be used to evaluate the relationships between each functional measure and FIM and the relationships between SPPB and handgrip (objective measures) and ADL scores (subjective measures) using the mixed model approach. **Interaction with Duke OAIC Cores:** Both aims will be supported by the Dr. K. Hall in the Physical Measures Core and Dr. Pieper of the Analysis Core, who have developed data management and analysis protocols for dealing with the complex accelerometer data generated by this project. In addition, Dr. V. Kraus of the Molecular Measures Core will work with this scholar to explore the relationship of IL-6, CRP, s-VCAM, miRNA, and LPS to functional measures of resilience as a mentored basic science integration experience. Two papers resulting from this work are published, 1 is currently in press, and 3 are in preparation (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

**Cathleen Colón-Emeric, MD, MHS**
Minority Trainee:
*Michael Cary, RN, PhD,* is doing big data research on the impact of clusters of co-morbidities on functional recovery after hip fracture, and developing machine learning algorithms for implementation in the electronic medical record that can identify high risk patients who require additional interventions.
Publications Pertaining to Minority Research:

2015

2016
The Johns Hopkins University
Claude D. Pepper Older Americans Independence Center
2016 OAIC Annual Directory

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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.

The JHU OAIC has six cores that work synergistically to accomplish these goals. The Leadership and Administrative Core provide scientific leadership, organization and infrastructure to lead and oversee the frailty-focused activities of the JHU OAIC. The Research Career Development Core (RCDC) provides research training, infrastructure, salary support and protected time to junior faculty who will become leaders and mentors in scholarship on frailty. The Pilot and Exploratory Studies Cores (PESC) supports cutting-edge pilot and exploratory studies that advance the development of effective prevention and /or therapies for frailty. Resource Core 1: Biostatistics Core provides data analytic and management expertise, and the development of new methodologies, for research on frailty. Resource Core 2: Biological Mechanisms Core provides state of the art expertise, infrastructure, and technology necessary to move forward biological and etiological research related to frailty. Resource Core 3: Clinical Translation and Recruitment Core provides clinical research training, oversight, and support in developing and implementing clinical research studies among frail older adults.

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.

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Section II. RESEARCH, RESOURCES AND ACTIVITIES

II.A. RESOURCE CORE-1 (RC-1): BIOSTATISTICS CORE
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The Johns Hopkins Older Americans Independence Center (OAIC) has empowered by many-fold the creation of significant research, training and practice paradigms for addressing frailty in older adults. The functions supplied by the Resource Core 1 (RC-1) Biostatistics Core have been central in this. They include: our central role in the mentorship and training of junior colleagues in the statistics of frailty and aging; our development and dissemination of emerging resources and technologies for data
management and analysis; our provision of database and statistical expertise and support to scholarship on frailty and aging, needed methodological innovation, and collaborative intellectual leadership for the creation and translation of research on frailty. Outcomes of this Core, in collaboration in this OAIC and beyond, include advancement of knowledge on the ascertainment, biological and etiological underpinnings, health consequences, and treatment of frailty, research surfacing significant methodological challenges to the study of frailty, and the creation of intellectual capital and infrastructure for further advances. These have laid crucial groundwork for intervening on frailty. For close to 14 years our Biostatistics Core has dedicated a critical mass of leadership from gerontologically informed biostatisticians toward the amelioration of frailty in older adults through our OAIC, and its leadership has dedicated the same to research on aging for more than 20 years. Our leadership and our external advisory committee consider it crucial that this Core continue to contribute to the OAIC’s overarching aims through the intellectual innovation, collaboration and support it provides. We propose to supply these contributions through specific aims to:

1. Mentor junior scholars supported by our Research Career Development Core (RCDC) and broader OAIC, with the goals of optimizing their: access to data analytic expertise and support; usage of modern database and analytic resources; training in quantitative methods needed to effect high quality research and effectiveness of collaboration with statistical colleagues. In all, we aim for mentored faculty to gain: recognition of the analytic challenges posed by the complexity of data on frailty, resources to accomplish valid and insightful research, and the ability to translate research into clinical practice.

2. Provide resources in data infrastructure and emerging computing technologies essential to discovery on frailty, and not possible absent an OAIC or its equivalent. We would continue to create modern, integrated, user-focused databases for the collection, documentation, and dissemination of high-quality clinical and biological data; and assist access to data onsite and that are publicly available, and to powerful analytic and computing hardware and software residing within this Core, OAIC, and our institution.

3. Stimulate and advance research on frailty at our institution, by:
   a. Providing analytic and data management support for research on frailty sponsored as high-priority by this OAIC, including RCDC and Pilot and Exploratory Studies Core (PESC) projects, external projects (EPs) and development projects (DPs) of other Cores. Specifically we would create sound study designs; assist the secure collection and housing of data; and design and implement valid statistical analyses to address studies’ scientific aims. We would further collaborate with RC-2 to ensure the development of valid, reproducible findings from the many molecular markers that Core makes available and with RC-3 to avail expertise and resources on the design, analysis and implementation of translational studies to OAIC-affiliated researchers.
   b. Developing new methodologies for data analysis needed to translate basic research into clinical practice. Methods created through this Core’s DPs have significantly advanced capability for validating frailty phenotypes and endophenotypes, laid groundwork for the study of frailty through genome and next-generation sequencing, and developed a framework for evaluating the dynamical properties of physiological systems and their implications for frailty. Building on these, we now propose work to further elucidate a potential multisystem etiology underlying frailty, design mechanistic studies to evaluate the dynamics of such an etiology, and translate resulting findings into intervention designs.

4. Partner with our fellow OAIC Cores, the scholarly community on aging at Johns Hopkins, and fellow OAICs to promote scholarship on frailty and aging, its translation into effective prevention and intervention strategies, and heighten its visibility. We would continue to provide
active leadership in our Leadership Council (LC) within our Leadership and Advisory Core (LAC) in identifying cutting-edge directions for the science of frailty; collaborate with all OAIC Cores and colleagues within and outside our institution, to advance knowledge on frailty and subsequent directions for translation between basic and clinical research; maintain a website optimizing public access to the advances of this OAIC, and attract new scientists to research on frailty.

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

To accomplish (A), we provide analytic and data management support for high priority research on frailty by assisting researchers in the design, development, and implementation of data systems; data acquisition and cleaning; refinement of study hypotheses; study design; design and implementation of data analyses; and preparation of manuscripts, presentations, and applications for research funding. To accomplish (B), we develop and test new methodologies for data analysis needed to translate basic research into clinical practice.

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.

In this reporting period, we additionally have provided scientific leadership in four emerging topics that are key to the advancement of frailty research:

1) The first is our continuing RC1 Development Project 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 systematically 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. 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. These findings were published in the American Journal of Epidemiology. Efforts are underway to validate the results in the Cardiovascular Health Study.

2) The second 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. 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. These findings were published in the Journals of Gerontology: Medical Sciences in November 2015.

3) A third project is the development of a statistical methodology program in causal inference related to frailty. This project emerged from engagement with JHU School of Public Health faculty who participated in a pair of Committee for National Statistics / NIA sponsored conferences on innovative study designs for causal inference. To develop this topic, Dr. Bandeen-Roche formed a working group that also includes Dr. Xue (RC1 director), Dr. Gross (RCDC awardee) and faculty in Biostatistics, Mental Health, and Geriatric Medicine. The goal is the development novel statistical methods built around an important scientific question in aging, namely elucidating the etiology of frailty and role of multisystem dysregulation. This project is well under development and we envision the submission of a grant application in the coming months.

4) A fourth project is led by Dr. Reyhan Westbrook and uses Interleukin 10tm1Cgn (IL10tm) mice as a model of chronic inflammation and declining health span to test the hypothesis that older IL10tm frail mice would have alterations similar to frail, older humans in measured parameters of glucose metabolism, oxygen consumption (VO2), respiratory quotient (RQ), spontaneous locomotor activity, body composition and plasma adipokine levels. In order to test this hypothesis, Dr. Westbrook and his team performed insulin tolerance tests, glucose tolerance tests, body composition analysis, indirect calorimetry with activity monitoring, and plasma adiponectin and leptin measurements in cohorts of 3, 10, and 20 month old IL10tm female mice and compared them to age and gender matched C57Bl/6 mice. Dr. Xue and student analyst Parichoy Pal Choudhury assisted Dr. Westbrook with the analysis of data on oxygen consumption and body composition measures. Interestingly, old IL10tm mice had significantly decreased VO2 when normalized by lean mass, but not when normalized by fat mass or the lean/fat mass ratio. In addition, NMR based body composition analysis and dissection weights show that fat mass is decreased with age in IL10tm mice compared to controls. Dr. Westbrook won 1st prize in the Post-Doctoral Fellow & Junior Faculty category for his poster at the 7th Annual Research on Aging Showcase at the Johns Hopkins Bloomberg School of Public Health in April 2014, and presented a poster at the 2015 Annual Pepper Center meeting in April 2015. The results of this project are reported in a manuscript which is under final review by collaborators and will be ready for submission shortly. In the meantime,
Parichoy is leading a paper on the methods that were developed to test local and global differences in oxygen consumption trajectories between the experimental groups.

The RC1 continues to play important national and international scientific leadership roles. Dr. Bandeen-Roche led a symposium on “Disparities in Physical Functioning and Frailty among Older Americans: Findings from the NHATS,” at the 2015 Annual Meeting of the Gerontological Society of American in Orlando, FL on November 21, 2015. At the National Pepper Centers Annual Meeting held in April 2016, Dr. Bandeen-Roche led the session on “ICTR workgroup on aging – research and educational CTSA/OAIC collaborations to move translation forward.”

During this reporting period (May 2015 to present), the RC1 Biostatistics Core assisted 21 researchers in 15 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 9 publications to date in this reporting period. In addition, we’ve provided statistical consultation to two other U01s led by other Pepper center PIs. The RC1 has most recently provided mentorship to Drs. Brown (RCDC), Gross (RCDC), Mathur (Pilot), McAdams Demarco (RCDC, Pilot) and Piggott (external project) regarding K-award development. Additionally, RC1 has played an essential role in the development, implementation and management of the online frailty assessment calculator that launched in January 2016. We currently have over 40 registered users from the United States, Europe, Asia, Australia, and the Caribbean.

Dr. Bandeen-Roche was recognized with the 2016 Marvin Zelen Leadership Award in Statistical Science by the Harvard T.H. Chan School of Public Health.

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

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In Year 13 of our award, the Resource Core 2 (RC-2) OAIC Biological Mechanisms Core 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. In the past decade, advances in molecular biology, in “omics” and in computational technologies have provided a logical basis for searching and identifying specific biomarkers associated with human phenotypes and diseases. These approaches can not only provide markers for human disease that are useful for nosology in heterogeneous clinical phenotypes but, more importantly, provide deep insight into pathophysiology and disease mechanisms that will form the bases for therapy. Consequently, the rationale for RC-2 is to provide the expertise, technology access and infrastructure, mentoring, and training necessary to facilitate the highest quality etiologic research in frailty.
Specific Aims:

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.** This aim brings the relevant technologies to the investigator either by core-supported analysis (genetic, genomic, epigenetic), access to a specialized JHU laboratory (telomere length, mitochondrial function, proteomic) or through an outside vendor (genetic, epigenetic, metabolomic) for biological measurements. However, choice of technology, access to expertise, study design, bioinformatics and integrative omics data analyses are supported within this core.

2) **To provide access to relevant biological samples from human subjects and animal models using either fresh or stored samples, and whole animals as needed to study frailty.** The core will assist in identifying the relevant samples and provide access, along with assistance and training in sample procurement and processing, as needed by each supported investigator.

3) **To facilitate the translation of RC-2 frailty research findings into intervention- or prevention-focused clinical studies in collaboration with the leadership of all other cores.** This aim focuses on molecular and computational methods for translational projects that are similar to aim 1 (discovery) but will usually differ in matters of scale and access to biological materials.

4) **To provide training, mentorship and guidance to the most promising junior investigators who can contribute to frailty research using molecular studies.** RC-2 faculty 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.

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.

During this reporting period (Year 13), RC-2 continues to evolve into a comprehensive molecular core that builds on the evolving science, infrastructure, and expertise across the Johns Hopkins Medical Institutions. Multiple senior leaders from across the JHMI have been engaged to supply the necessary expertise and infrastructure and to a) facilitate analytical strategies needed to analyze genetics and epigenetics data being generated, b) incorporate measurements of oxidative stress, mitochondrial function, inflammatory cytokines, senescent TCell 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 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.
Important new findings include the following:


Key outcomes or other progress by 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 is in press with Aging Cell 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, who published a manuscript and is submitting a second this year as she completes her PhD (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. Ongoing work in this areas has led to the publication of two papers in the frail mouse model in 2015, including one on mitophagy abnormalities and one on the interface between angiotensin system, aging, and inflammation. Bioinformatics necessary to integrate and interpret biological data: Additional measurement expertise for biomechanical measurement related to aging and inflammation has also been added in the past year with new collaborations developed with the Department of Bioengineering under the leadership of Denis Wirtz, PhD. This has resulted in the publication of one manuscript and the development of a second one related to a novel way to measure cellular aging. This may have broad clinical implications and will continue to be an ongoing developmental effort.

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 investigators Burks, 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. This includes mouse tissues to Enid Neptune from Pulmonary medicine, Linda Resar from Hematology, Denis Wirtz from Bioengineering, and to a newly funded stem cell investigator, Aleksandra Leszczynska with a recent Pilot award.

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 Vitamin D study U01 led by Dr. Appel, “Vitamin D Supplements to Prevent Falls in Older Adults: A Dose-Response Trial,” and the losartan study detailed in the PESC section, where we provide inflammatory measurement expertise, and a U01 led by Dr. Walston focused on inflammatory phenotype and intervention development in collaboration with Dr. Bandeen-Roche and others in RC1. Finally, the RC2 has helped to facilitate the development of a novel wound care technology that targets diabetic and chronic non-healing wounds in older adults. Building on an ARB based approach, investigator Abadir and Walston have leveraged and NIA R21 and Maryland technology development grant to 4 separate patents and to the development of a commercialization strategy that has resulted in the licensing of the technologies to a startup Biotech company in Baltimore. The first publication is in revision to Science Translational Medicine.

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. Tyesha 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, Resar, Franco, Gross, Piggott, Brown, Hogue, Chung, Neptune, and Fedarko as they develop manuscripts related to frailty, aging, inflammation, mitochondrial biology, and the renin angiotensin system.

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, including a keynote address on the biology of frailty in 2015 and a frail mouse symposium in 2016.

RC2 Development projects, 2014-2016:

- **Year 11-12 RC-2 Development Project: “Integrative omics analyses of the IL10Tm/Tm frail mouse”** PI: Dan Arking, PhD; co-investigator: Dr. Reyhan Westbrook, OAIC Diversity Supplement Awardee. The IL10Tm/Tm mouse, like frail humans, develops age-related skeletal muscle weakness, endocrine abnormalities, inflammatory pathway activation, mitochondrial abnormalities, and early mortality. These findings support the further use of this mouse to dissect molecular pathways that may impact frailty. During the first year of this award, Dr. Westbrook collaborated extensively with Dr. Rafael De Cabo of the NIA in order to more extensively characterize the metabolic phenotype of this mouse model. Findings include marked decrease in metabolic rate later in life, as well as marked decrease in fat pads and adipokines. Manuscript is developed and nearly ready for submission.

  - From this same project, metabolomic profiling has been completed and analysis is underway. Significant differences in tryptophan metabolism, in TCA cycle components, and in lipid metabolites between chronically inflamed and control mice have been identified. Working with Dr. Walston and members of the Biology of Healthy Aging Research team, Dr. Westbrook has established collaborative efforts for improved targeted detection methodology with Dr. Ruin Moaddel at the NIA and with Dr. Anne Le of Johns Hopkins Department of Pathology. Each of these investigators is working closely with him and with the OAIC RC2 to optimize a targeted detection approach for crucial pathways related to energy expenditure, mitochondrial energy production, and tryptophan metabolism. This work is crucial to the developmental efforts of the OAIC in that it provides an important new tool in detecting frailty and chronic inflammation related metabolic alterations that highlight underlying organismal vulnerabilities related to frailty and inflammation. This work has resulted in the awarding of the 2016 AFAR Translational Research Post-Doctoral Fellowship Award to Dr. Westbrook. This award enables him to continue on this line of investigation, and will allow him to translate his mouse related findings into human subjects with an eye towards improving diagnostics for frailty and chronic inflammation consequences in older adults.

- **Year 13 RC-2 Development Project: “Altered skeletal muscle metabolic pathways in the pathogenesis of sarcopenia.”** PI: Pingbo Zhang; Mentors: Richard Semba, Luigi Ferrucci. Sarcopenia plays a central role in frailty. Our ongoing studies demonstrate that muscle quality, defined as the amount of strength generated by a unit of muscle mass, is a better definition for sarcopenia than muscle mass or muscle strength alone. Muscle quality shows a linear decline with older age. The biological pathways that lead to the age-related decline in muscle quality are not well understood. Animal studies show that there are circulating factors, most of which are uncharacterized, that rejuvenate aging skeletal muscle. Using a targeted metabolomics approach, our preliminary studies have identified three novel metabolic pathways involving circulating polyamines, methionine, and tryptophan in association with muscle quality in older adults. It is not known whether these same metabolites are altered in skeletal muscle itself or whether the plasma and skeletal muscle tissues levels of metabolites are correlated. We hypothesize (1) low putrescine (a polyamine), high methionine, and high tryptophan in both
skeletal muscle and plasma are associated with low muscle quality, and (2) there is a significant correlation of polyamines, methionine, and tryptophan levels between skeletal muscle and plasma. The specific aims are to characterize the relationship of skeletal muscle and plasma (1) polyamines, (2) methionine, and (3) tryptophan with muscle quality in adults and to examine the correlation of polyamines, methionine, and tryptophan between plasma and skeletal muscle. To address these hypotheses, we will measure skeletal muscle and plasma metabolites in cross-sectional, pilot study of 80 adults who have quadriceps muscle biopsy, plasma, and concurrent muscle quality measurements in the Baltimore Longitudinal Study of Aging. Metabolites will be measured using liquid chromatography-tandem mass spectrometry. These metabolites are potentially modifiable risk factors. Further insight of their relationships with the age-related decline in muscle quality may drive new investigations that target specific metabolic pathways involved in sarcopenia. Pilot data from this study will be used to support a future NIH grant application on sarcopenia and frailty. Progress Updates: Plasma metabolites have been measured in 80 BLSA participants using LC-MS/MS. Metabolites were extracted and concentrations were measured. In the next few months, skeletal muscle samples from the same 80 BLSA participants will be homogenized using a bead-based homogenizer in combination with a simple extraction protocol. Skeletal muscle metabolites will be measured using the same methods as for plasma.

Externally Supported projects:

- 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 K23 AG0305005 and new related R01AG046441: Age Related Changes in Angiotensin Receptors and its Role in Chronic Inflammation. This project receives ongoing support.
- Andy Feinberg, MD. NIH/NIA R01AG042187: 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

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In order to more effectively meet JHU OAIC’s goal of translating frailty-related etiological discoveries into clinical studies that help maintain independence in older adults, and to overcome the substantial barriers to success in clinical investigation for junior investigators, the leadership of this OAIC made a
The Resource Core 3 (RC-3) Clinical Translation and Recruitment Core provides to supported OAIC investigators: 1) comprehensive training and mentorship in clinical research that spans from study design through implementation through outcome interpretation, 2) clinical research space and assistance with all aspects of forms and protocol development, data collection, and recruitment of human subjects, 3) an active registry of more than 1000 older adults who have consented to be contacted for aging and frailty related studies, and 4) synergy with other cores in order to optimize all aspects of frailty-related study design, data collection, and biological measurement and junior faculty training. This synergy is greatly augmented core leader, Dr. Robert Wise, who has considerable expertise in the development, implementation, and conduct of 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 the Losartan pilot study (Dr. Lee), the recruitment and coordinating needs of the ATP skeletal muscle kinetics pilot (Dr. Weiss), and the coordinating and measurement needs of our RCDC and Pilot scholars, as needed. The core also 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 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 of 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) 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.

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 aging and frailty. The utilization of this registry will be prioritized to OAIC supported investigators.
Healthy Aging Studies Unit: The central hub of RC-3 is the Healthy Aging Studies Unit (HASU; formerly called the Clinical Translational Unit). In 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. The HASU was founded on the Bayview Medical Campus, adjacent to the Division of Geriatric Medicine and Gerontology clinical sites and adjacent to the Biology of Healthy Aging laboratories. It supports recruitment and clinical translation for RCDC and PESC supported investigators Abadir, Weiss, and Schoenborn, and external projects led by Feinberg, Leng, Chung, and Walston. It includes the frailty registry (described below) and also supports Dr. Walston’s study of the “Physiologic and Molecular Basis of the Syndrome of Frailty” (IRB# NA_00052046; also known as MAPPS). Dr. Leng’s influenza focused R01 receives support to recruit and study over 150 individuals, and Dr. Walston is recruiting over 600 older adults in a surveillance study of pneumococcal colonization in response to vaccination sponsored by the CDC (PI: Harrison).

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. There are currently over 1200 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: Peter Abadir, MD, Jeremy Walston, 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.

OAIC Pilot Study: Nancy Schoenborn, MD: “Understanding patient preferences for prognosis communication among older adults across the spectrum of frailty.” Please see full description provided in the Pilot Core report. RC-3 provides recruitment assistance.

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 has provided 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 Dr. Walston’s MAPPS study and the OAIC RC-3 has provided 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.

CDC/MD Department of Mental Health and Hygiene / Johns Hopkins Bloomberg School of Public Health: L. Harrison (PI). “Surveillance study of pneumococcal colonization in response to vaccination.” RC-3 provides recruitment, scheduling, and assessment/measurement.

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

U01: J Walston: “Variability of inflammatory markers in older adults.” Funding is pending for this study. If funding is forthcoming, recruitment for this study would commence in the summer/fall at JHU. RC3 personal would be responsible for the implementation and recruitment of this study.

R23: J Walston: “Lactoferrin Pilot.” Funding is pending for this study. If funding is forthcoming, recruitment for this study would commence in the summer/fall at JHU. RC3 personal would be responsible for the implementation and recruitment of this study.

Data and Safety Monitory Board (DSMB): An OAIC DSMB was established to provide independent safety review for all OAIC interventional human subjects studies. All five members of the DSMB are external to the OAIC, with two members from the University of Maryland, 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 first convened in February 2014 to carefully review and discuss its operating charter. The DSMB then met in May 2014 and has since met every 6 months, with the most recent meeting taking place in January 2016. 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. Reports and minutes from each meeting have been submitted to the NIA Program Officer. The next meeting will take place in July 2016.
II.D.  RESEARCH CAREER DEVELOPMENT CORE (RCDC)
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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. Per NIA director, this RCDC will be restructured as a Research Education Component for the coming year.

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.

RCDC awardees, 2015-2016:

1) Charles Brown, MD. “The association between baseline frailty and postoperative delirium or functional decline after cardiac surgery, and a potential intervention to improve outcomes.” Mentors: Charles Hogue, Jeremy Walston. This study aims 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 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 outcome. Progress Updates: Dr. Brown has successfully enrolled 80 patients (goal was n=72). Further enrollment is also ongoing. He is evaluating data for data cleaning, missing-ness, and will next begin analyzing the data for manuscripts.
   - Awarded an Johns Hopkins inHealth grant to evaluate mobility after cardiac surgery
   - Awarded an International Anesthesia Research Society Grant
   - Awarded a Johns Hopkins Clinician Scientist Award.

2) Alden Gross, PhD, MHS. Research Career Development Core (RCDC). “Intersection of Domain-specific Cognitive Performance and Frailty: An Integrative Data Analysis.” Mentors: 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. Progress Updates: A manuscript was recently published in Journals of Gerontology: Medical Science. Dr. Gross was awarded an NIA K01 award, starting in April 2016.
- Gross AL (PI). NIH/NA K01 AG050699. Intersection of Physiologic Frailty and Cognitive Performance in Older Adults: An Integrative Data Analysis

3) 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: Drs. Jon Resar, Gary Gerstenblith, and Bruce Leff. This study proposes to: 1) evaluate the prognostic impact of frailty on outcomes following TAVR, through a retrospective analysis of this patient group to evaluate whether pre-procedure frailty is independently associated with adverse outcomes among elderly patients undergoing TAVR for AS; 2) evaluate the impact of TAVR on frailty through a prospective observational study of elderly patients with AS undergoing TAVR at JHMI with serial assessment of frailty before and at one month and six months after TAVR; and 3) investigate inflammation as a pathophysiologic link between aortic stenosis and frailty by evaluating pre- and post-TAVR levels of inflammatory markers that are implicated as a possible link between the pathophysiology of AS and frailty. Progress Updates: Dr. Hasan has an approved IRB protocol for his proposed studies: IRB00054646. There have been no adverse events to date. Dr. Hasan met and reviewed statistical plans with Biostatistics Core Leader, Dr. Bandeen-Roche. Preliminary statistical analysis for retrospective study is underway. Recruitment for prospective study has begun and is ongoing. As part of the prospective study, Dr. Hasan has begun a collaborative efforts with Drs. Karin Neufeld and Atsushi Kamiya of the Department of Psychiatry to study delirium and its impact in the same patient population. Dr. Hasan is also planning a substudy to evaluate provider and patient perceptions of frailty within the prospective study; this should begin in June. Dr. Hasan presented at the JHU OAIC Pepper Scholars Meeting on “Frailty in Elderly Patients Undergoing Transcatheter Aortic Valve Replacement (TAVR) for Symptomatic Severe Aortic Valve Stenosis” on February 3, 2016.

Significant results:

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

Key outcomes or other progress:

The JHU OAIC RCDC has helped to establish the careers of many of its RCDC-supported faculty through the successful support of K01/K23 funding. Drs. Peter Abadir, George Wang, Frank Lin, Rita Kalyani, Mara McAdams-DeMarco, and Yuri Agrawal have each been awarded NIH career development awards in the past several years. Most recently, RCDC awardee Dr. Alden Gross received a K01 award (after receiving a merit score of 10), for his project “Intersection of Physiologic Frailty and Cognitive Performance in Older Adults: An Integrative Data Analysis” that began in April 2016. Additionally, Drs. Abadir and Leng, both former RCDC supported scholars, received their first R01 awards with OAIC support in the past years. 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.

II.E. PILOT / EXPLORATORY STUDIES CORE

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The overall goal of the OAIC 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 and continuing into Year 12, the current reporting period. 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.

The PESC studies in Year 13 have been both methodologically and substantively innovative. The PES-1 concerns a potential novel treatment for frailty and frailty related conditions. PES-2 has utilized state-of-the art technology (magnetic resonance spectroscopy), applied it to frailty research, specifically to core areas of frailty-related biological focus of this OAIC. Newly funded PES 3-6 explore a range of important frailty studies, including stem cell reparability in mice, clinical utility among thyroidectomy patients and ESRD patients, and a qualitative study on patient perspectives on frailty.

Pilot Studies, 2014-2016:

1) Peter Abadir, MD; Jeremy Walston, MD: “A Study of Muscle Strength Maintenance in Older Adults” (Funded July 2013). 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. Progress Updates: As of February 2016, 20 participants have compliantly completed the study; 4 participants are currently active in the study and active recruitment is ongoing, with a target of 24 per-protocol completers. This study was reviewed and approved for continuation by the DSMB of the JHU OAIC in January 2016. The DSMB will review the study again in July 2016.

2) Robert G. Weiss, MD: “Energy Production in Frailty: Skeletal Muscle ATP Kinetics in Frail, Older Adults” (Funded July 2013). 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 31P 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. Progress updates: Enrollment and assessment is underway with support from OAIC RC-3 staff. As of February 2016, Dr. Weiss and staff have enrolled and performed the plantar flexion 31P MRS/MRI stress test in approximately 19 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 7 frail have been studied.

3) Aleksandra Leszczynska, PhD: “Effect of Age and Frailty on the Reparative Capacity of the Stem Cell Secretome” (Funded November 2015 - May 2016). Frailty and advanced age are associated with a diminished capacity to respond to a superimposed stress of disease or injury. One reason for this vulnerability may be an associated decline in the performance of stem cells. In addition to differentiating to vascular and muscle cells, bone marrow mesenchymal stem cells (MSCs) also - and more importantly - release paracrine factors which have anti-inflammatory and anti-apoptotic properties and which “turn on” or “turn up” intrinsic repair mechanisms. Dr. Leszczynska and colleagues seek to understand how frailty and age affect the paracrine function of MSCs at baseline and under stress. They will investigate how frailty- and age-related changes in MSCs affect their paracrine secretome, and how frailty- and age-related changes in MSC paracrine function influence their cardio-protective effects. They will also examine whether and if so how age- and frailty-related differences in MSC paracrine function are amplified by stress. Finally, they will study whether frailty- and age-related changes in MSC paracrine function can be modified by exposure to factors from young, non-frail MSCs, or from stressed cardiomyoblasts. Progress Updates: Data has been gathered to submit a manuscript, possibly to the journal, Aging Cell, in the coming months. A poster on this work, entitled “Changes in the Exosomal Component of Young vs. Old MSC Secretome may Underlie Differences in their Regenerative Potential,” was presented at the 2016 Pepper Centers Annual meeting on April 18, 2016.
4) **Aarti Mathur, MD:** "Frailty status as a predictor of alterations in speech, swallowing, and quality of life after thyroidectomy in the elderly population" (Funded November 2015). In the United States there are between 118,000 to 166,000 thyroidectomies performed annually, of which 25% are performed in people over the age of 65. There is a paucity of data regarding the impact of thyroidectomy on voice, swallowing, and quality of life in the elderly population, although this population may be at greater risk than younger patients. Additionally, voice and swallowing function also change with age due to atrophy of the cartilaginous and muscular support of the larynx. Our central hypothesis is that there is a high incidence of voice and swallowing dysfunction after thyroidectomy in the elderly population and that frailty status may help predict which patients are more prone to these changes. Identifying patients at risk to develop these problems is critical for the development of therapeutic interventions. The main goal of this proposal is to perform a pilot study to explore the association of frailty status as a predictor of post-thyroidectomy alterations in voice and swallowing function in elderly patients. This will serve as critical preliminary data for an NIH mentored career development award. Additionally, this pilot can support the collection of other thyroid specific markers that may augment the predictive power of frailty and can be studied more fully in the final study. **Progress Updates:** the study has received IRB approval, and recruitment is underway.

5) **Mara McAdams DeMarco, PhD:** "Prehabilitation for Older Adults with End Stage Renal Disease on the Kidney Transplant Waitlist" (Funded November 2015). “Prehabilitation” is a novel approach to increase functional capacity and physiologic reserve. We will enroll 60 older adults with ESRD (including 50% frail and 50% nonfrail patients) who are likely to receive KT within 3-6 months (both live and deceased donor recipients). A prehabilitation program of moderate aerobic exercise and resistance exercises will occur at Johns Hopkins Hospital in conjunction with the Department of Physical Medicine and Rehabilitation and will be ongoing for 3 months at a minimum (duration of prehabilitation will be the time between enrollment and KT). The main goal of aim 1 will be to identify an optimal prehabilitation regime that can be systematically administered to all older adults who will receive a KT. We will assess feasibility through: recruitment, enrollment, retention, and adherence rates. We will also look at outcomes of the prehabilitation including changes in walk speed and quality of life at the time of KT. Additionally, we will test whether prehabilitation has a positive impact on short- and long-term outcomes in frail and non-frail older KT recipients. Participants in the pilot study will be compared to recent matched controls from our ongoing cohort study of frailty in KT recipients. We will leverage this ongoing R01 funded study as a practical mechanism to identify appropriate controls to represent outcomes under the standard of care. We will test for a change in frailty status after KT for those enrolled in the pilot study and our controls. We will test whether participants in a prehabilitation program have improvements in frailty status after KT as well as better short-term (length of stay, early hospital readmission, and DGF) and long-term (acute rejection, graft loss and mortality) outcomes than controls. We will also test for differences in important and clinically meaningful subgroups: by frailty status at evaluation for KT. **Progress Updates:** The study has received IRB approval (JHSPH IRB 00006786) as of March 23, 2016, and recruitment is underway. We are calling participants to start scheduling the prehabilitation next week. Also, we have completed the physician Delphi study on frailty and prehabilitation. The study contained 2 rounds of 47 and 43 clinicians, respectively (both response rates >90%). We developed a consensus about frailty in the second round and prehabilitation in the first round. We will be presenting our findings on the consensus on frailty at the COAH Showcase on Aging on 4/22 and have submitted an abstract on this topic to the Gerontological Society of America Annual meeting.
6) Nancy Schoenborn, MD: "Understanding patient preferences for prognosis communication among older adults across the spectrum of frailty" (Funded to start March 2016). There is growing literature supporting the clinical application of frailty. How frailty and its prognostic implications should be communicated with patients in the clinical setting has not been explored. This is a critical knowledge gap that needs to be addressed in order to more widely apply frailty in clinical practice to improve the care of older adults. Older adults who are frail or pre-frail may not have a specific terminal illness and their increased risk for mortality and functional decline may be over the time frame of a few years. Therefore, frail older adults may have different expectations and preferences around prognosis communication than previously studied populations. This proposal aims to better understand the perspectives and preferences of older adults across the frailty spectrum, regarding whether and how they would like to receive communication about frailty-informed prognosis information in clinical settings. Because little is known about this area, we propose focus groups with 30-40 adults to understand the range of patient perspectives. We plan to recruit the participants from an existing registry of older adults maintained by the Older Americans Independent Center (OAIC) where the participants’ frailty status has already been assessed. If we find that the participants have more to say and the focus group was not providing enough individual attention to allow each participant to fully express their opinions, we will replace one focus group with individual interviews to ensure that we fully capture the patients’ perspectives. We will investigate the range of older adult perspectives regarding 1) whether patients want to know the associated mortality risk and functional dependency risk as predicted by frailty status; 2) for those patients who want to know the above information, how they would prefer to receive the prognosis communication. We will also explore the factors that modify and influence these perspectives and preferences. Progress updates: The study has IRB approval and recruitment efforts began in March 2016.

Significant results:

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


Key outcomes or other progress:

Previously funded PESC Studies:

Honggang Cui, PhD: “The Specific Delivery of Pharmaceuticals into Mitochondria” (Funded July 2013-June 2015). 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. Progress Updates: A poster, “A Dual Peptide Conjugation Strategy for Improved Cellular Uptake and Mitochondria Targeting,” was presented at the 2015 Annual Pepper Centers Meeting. This work has been published in the journal, Bioconjugate Chemistry.


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

Qian-Li Xue, PhD: “Effects of Inflammation, Hormonal Alteration and mTOR Signaling in Modulating Age-related Declines in Muscle Strength.” Dr. Xue and colleagues are conducted a pilot trial with 24 female low capacity runner (LCR) rats. LCR rats were 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 high capacity runners (HCR). The investigators included a rapamycin+metformin arm to test the hypothesis that metformin may counteract the “diabetogenic” effects of rapamycin. In addition Dr. Xue and colleagues measured serum levels of inflammatory biomarkers and anabolic hormones and fasting glucose repeatedly over time, and collected muscle biopsies to measure histologic parameters of Soleus and EDL muscles including fiber type count and protein content.

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. This study was published in the Aging:

- Xue QL, Yang H, Li HF, Abadir PM, Burks TN, Koch LG, Britton SL, Carlson J, Chen L, Walston JD, Leng SX. Rapamycin increases grip strength and attenuates age-related decline in
Mary Armanios: “Telomere length and Clinical Outcomes in the Women’s Health Aging Study.” This study aimed 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. There has previously been no trial of this size 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 with high data quality. She is currently completing an interim analysis with support from the OAIC Biostatistics Core.

Aliaksei Pustavoitau, MD, “A Prospective Cohort Study Evaluating the Use of p16INK4a Transcriptional Factor Level as a Marker of Molecular Age and Predictor of Perioperative Outcomes.” Dr. Pustavoitau is an anesthesiologist with a long standing interest in determining risk factors for adverse outcomes in older adults undergoing surgery. This study investigated associations between p16 levels in CD3+ LDPB of elderly patients undergoing coronary artery bypass surgery and frailty and chronological age, as well as the association between p16 levels and length of ICU and hospital stay, morbidity and mortality. This study was published in Experimental Gerontology:


II.F. LEADERSHIP AND ADMINISTRATIVE CORE
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The Leadership/Administrative Core (LAC) spearheads the vision for the Johns Hopkins Older Americans Independence Center (JHU OAIC), sets goals through which to implement it, and assures energy and quality in accomplishing goals. It leads in identifying the next generation of research on frailty that should be created, supports research planning and recruitment of investigators, and sets and monitors progress benchmarks. It is the OAIC base for recruiting and nurturing a critical mass of investigators dedicated to the creation of innovative, high impact research essential to the prevention and treatment of frailty in older adults. It administrates the OAIC and its Cores for soundness of operations and accomplishes required reporting. It promotes a stimulating intellectual environment around scholarship on frailty so as to attract outstanding researchers and knit them into an interdisciplinary community. It creates visibility for the accomplishments of the OAIC locally and globally. It is led by OAIC Principal and Co-Principal Investigators with diverse disciplinary expertise.
and institutional reach, closely engages the leaders of all other OAIC Cores, and is robustly advised by a Leadership Council which it engages monthly, an Internal Advisory Committee engaged quarterly, and an External Advisory Board which reviews it annually. The LAC provides essential leadership in planning, integrating, sustaining, implementing and monitoring OAIC operations. Its goals are to ensure the conduct of these OAIC functions within the broader goals of the support of research aiming to develop new strategies to enhance independence in older Americans and the creation of a new generation of research leaders in the field. To these ends, the specific aims of the LAC are to:

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.

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.

In summary, the JHU OAIC LAC provides vision, leadership and management in the development and maintenance of a tightly focused and interdisciplinary program of scholarship on frailty in older adults. It works to assure that this OAIC contributes significantly to frailty-related advances, shifts paradigms for concepts and methods to enhance independence for older persons, and achieves high and broad-reaching impact by:

- Ensuring a coherent research agenda for the OAIC and the highest quality of resultant science;
- Propelling discoveries into prevention / intervention strategies to prolong independence for older adults;
- Soundly administering OAIC resources and implementing processes to promote productivity, quality, and synergistic interactions between the cores;
- Recruiting outstanding junior and senior scholars to a focus on frailty;
- Organizing the Cores in the provision of infrastructure, expertise, mentorship, and training needed to produce the next generation of scholars interested in ameliorating frailty-related adverse outcomes and optimize their career development;
- Promoting the visibility of frailty-related scholarship and investigators across JHU, the country, and world.
Please see the following results and outcomes:

**Scientific Leadership:** Our OAIC has worked closely with investigators from across the Johns Hopkins Medical Institutions to foster the highest quality science related to aging and frailty as evidenced by numerous publications, including recent **high visibility, high impact symposia and publications**. The Leadership Council of our OAIC has helped to develop key areas of focus for potential intervention development in the renin-angiotensin system, in inflammation and the immune system, mitochondrial biology, sarcopenia, hearing and vestibular function, and in overall risk assessment using the frailty phenotype. 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 OAIC has continued to foster programs that enable important scientific developments around frailty research. The JHU OAIC collaboration-building project, known as the **Pepper Scholars Program**, has continued to hold ongoing monthly research-in-progress sessions that allow for OAIC-supported investigator interaction and discourse, along with progress updates and access to mentors and methodological experts. **These monthly investigator forums** have convened supported faculty together with the OAIC leadership and members of the broader community on aging to discuss research in progress together. These been incredibly helpful in optimizing the quality of investigators’ findings, creating a network and community among those involved with our OAIC, and helping to focus and propel the science of frailty.

The OAIC PI and co-PI also have continued to convene the **Frailty and Multisystem Dysregulation Working Group**, one of the core research working groups based in the JHU Center on Aging and Health. This group meets twice monthly to engage in scientific discussion, project and grant planning, manuscript development, and funding strategies. This group convenes both supported and affiliated faculty who form the most dedicated core of researchers on frailty at our institution to envision, advance, and develop research on important questions on the amelioration of frailty and its consequences and the translation of effective strategies into clinical practice. It has 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 has continued its efforts on **Roadmap Development for the Field of Frailty Research**. In February 2015, JHU OAIC leaders and investigators held a retreat where an initial roadmap was developed with four main priority areas: clinical practice; multisystem dysregulation; basic biology; and measurement. Over the past year, we have used the ongoing frailty working group meetings to further develop and define the roadmap. We have also created sub-working groups in each of these priority areas, which meet regularly to discuss and move forward specific objectives. For example, the measurement priority group held a series of meetings during the fall and winter of 2015-2016 to comprehensively review theories of frailty, clinical perspectives on frailty, and distinctions between primary and secondary frailty. The group is currently preparing a manuscript on a measurement paradigm for frailty assessment.
In an attempt to standardize the practice of frailty assessment and the computing algorithm, the JHU OAIC recently launched an updated online Frailty Assessment Calculator. Using the standardized measures of the frailty phenotype, the instrument was designed to maintain syndrome construct validity while maximizing feasibility and usability in both research and clinical settings. It can be accessed here: http://www.johnshopkinssolutions.com/solution/frailty/.

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

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

The OAIC 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 February 24, 2016 to review the second year of the renewal and provide big-picture guidance going forward. The meeting included an overview of the center’s aims and accomplishments since the last EAB meeting in August 2014, with discussion of the prior feedback provided by the EAB and an overview of the OAIC core structure and supported scholarship. The group also discussed strategic planning efforts in the preceding year, including a review of the Frailty Research Retreat, and held a strategic discussion on the OAIC’s opportunities, challenges, and renewal planning, including: international leadership in the field of frailty; 10-year vision for the center, and the integration of frailty into clinical decision-making. The thoughtful and motivating feedback and discussion from this meeting has helped to propel our scientific efforts during the remainder of the reporting period. The next EAB meeting will take place in the fall of 2016.

The OAIC 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. Reports and minutes from each meeting have been submitted to the NIA Program Officer. The next meeting will take place in July 2016.

In partnership with the Division of Geriatric Medicine and the Center on Aging and Health, the OAIC sponsors a monthly Scientific Seminars Series of invited scientific presentations, including presentations by: Dr. Neal Fedarko, OAIC Pilot Core Leader in November 2015; Dr. Karen Bandeen-Roche, OAIC Co-PI, in December 2015; and Dr. Leocadio Rodriguez Manas, MD, PhD, Head of the
Department of Geriatrics at Hospital Universitario de Getafe (Madrid) and Professor of Geriatric Medicine (School of Medicine, Universidad Europea de Madrid) in May 2016.

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. In December 2015, our faculty participated in a joint speed-networking event for the aging trainees from UMB, Johns Hopkins, and NIA. Most recently, faculty, fellows and students from JHU, UMaryland, and NIA jointly participated in the annual Research on Aging Showcase on April 22, 2016. Trainees presented posters and our faculty from these institutions served as judges.

**Significant results:**

Our group continues to play important national and international scientific leadership roles. The OAIC has held several high profile symposia during this reporting period. Dr. Bandeen-Roche led a symposium on “Disparities in Physical Functioning and Frailty among Older Americans: Findings from the NHATS,” at the 2015 Annual Meeting of the Gerontological Society of American in Orlando, FL on November 21, 2015. Dr. Walston led a symposium entitled “A Mouse Model of Chronic Inflammation, Sarcopenia and Phenotypic Frailty,” at the 2016 International Conference on Frailty and Sarcopenia Research in Philadelphia PA on April 28, 2016.

We organized strong participation from our OAIC at the National Pepper Centers Annual Meeting held in April 2016. Our PI, Dr. Jeremy Walston, co-PI, Dr. Karen Bandeen-Roche, and Biostatistics Core Director, Dr. Qian-Li Xue, attended, along with supported investigators Drs. Abadir (former RCDC), Brown (RCDC), Gross (RCDC), Leszczynska (Pilot), and Mathur (Pilot). Drs. Walston and Bandeen-Roche participated as Senior Faculty personnel, Drs. Brown, Gross, and Leszczynska presented at the poster session, and Dr. Bandeen-Roche led the session on “ICTR workgroup on aging – research and educational CTSA/OAIC collaborations to move translation forward.” Additionally, Dr. Walston moderated the panel discussion on “Early Human Trials in Translation” and Dr. Abadir served as one of the facilitators for the junior faculty clinical round table discussion.

**Key outcomes or other progress:**

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 and Pilot 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. Most recently, RCDC awardee Dr. Alden Gross received a K01 award (after receiving a merit score of 10), “Intersection of Physiologic Frailty and Cognitive Performance in Older Adults: An Integrative Data Analysis,” that began in April 2016. Drs. Abadir and Leng, both former RCDC supported scholars, received their first R01 awards with OAIC support in the past years. 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. RC-2 supported his work through measurements of inflammatory cytokines. Dr. Walston is a member of Dr. Piggott’s mentorship team, and Dr. Bandeen-Roche is a member of his Mentorship Advisory Committee. 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 Westbrook (P30AG021334-11S1)**

*Mentor: Jeremy Walston, MD*  
*Funded July 2013-2015.*

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 has applied 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). 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 has taken 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 facilitated 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 has also benefitted 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 has gained important translational insights in this process as well, and learned 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 aims to develop a critical mass of under-represented minority investigators within this OAIC

**Research Plan Overview:** Dr. Westbrook focused on two major projects during his post-doctoral fellowship at Johns Hopkins as described below. The first project built on his considerable metabolic expertise and aimed 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 helped to lead the RC-2 development
project on the integration of ‘omic’ analyses in the frail mouse. This enabled Dr. Westbrook to learn important new skills in molecular biology and in complex analytical modeling as described below.

The IL10Tm/Tm mouse, like frail humans, develops age-related skeletal muscle weakness, endocrine abnormalities, inflammatory pathway activation, mitochondrial abnormalities, and early mortality. These findings support the further use of this mouse to dissect molecular pathways that may impact frailty. During the first year of this award, Dr. Westbrook collaborated extensively with Dr. Rafael De Cabo of the NIA in order to more extensively characterize the metabolic phenotype of this mouse model. Findings include marked decrease in metabolic rate later in life, as well as marked decrease in fat pads and adipokines. Manuscript is developed and nearly ready for submission.

From this same project, metabolomic profiling has been completed and analysis is underway. Significant differences in tryptophan metabolism, in TCA cycle components, and in lipid metabolites between chronically inflamed and control mice have been identified. Working with Dr. Walston and members of the Biology of Healthy Aging Research team, Dr. Westbrook has established collaborative efforts for improved targeted detection methodology with Dr. Ruin Moaddel at the NIA and with Dr. Anne Le of Johns Hopkins Department of Pathology. Each of these investigators is working closely with him and with the OAIC RC2 to optimize a targeted detection approach for crucial pathways related to energy expenditure, mitochondrial energy production, and tryptophan metabolism. This work is crucial to the developmental efforts of the OAIC in that it provides an important new tool in detecting frailty and chronic inflammation related metabolic alterations that highlight underlying organismal vulnerabilities related to frailty and inflammation. This work has resulted in the awarding of the **2016 AFAR Translational Research Post-Doctoral Fellowship Award to Dr. Westbrook**. This award enables him to continue on this line of investigation, and will allow him to take his mouse related findings into human subjects with an eye towards improving diagnostics for frailty and chronic inflammation consequences in older adults. Dr. Westbrook was recently selected for a **Provost’s Postdoctoral Fellowship**, where he will continue his work characterizing the frailty phenotype using metabolomics methods.

**Current list of presentations includes:**

- **Poster Presenter at The Bayview Research Symposium Baltimore, Maryland (November 2013)**
- **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.**
  The Metabolic Characterization of Interleukin-10tm1Cgn Mouse Reyhan Westbrook, Rafa de Cabo, Jackie M. Langdon, Cindy N. Roy, Jeremy Walston
- **Poster Presenter at the Claude D. Pepper Older Americans Independence Centers Annual Meeting Bethesda, Maryland (April 2014)**
  The Metabolic Characterization of the Interleukin-10tm1Cgn Mouse R. Westbrook, R. de Cabo, J.M. Langdon, C.N. Roy, J. Walston
- **Poster Presenter at The Bayview Research Symposium Baltimore, Maryland (October 2014)**
  The Metabolic Characterization of the Interleukin-10tm1Cgn Mouse R. Westbrook, R. de Cabo, J.M. Langdon, C.N. Roy, J. Walston
- **Presentation at the Pepper Scholars Program Research in Progress: Reyhan Westbrook, PhD, “The Metabolic Characterization of the Interleukin-10tm1Cgn Mouse.” November 5, 2014.**
- **Poster Presenter at the Gerontological Society of America annual meeting Washington D.C. (November 2014)**
  The Metabolic Characterization of the Interleukin-10tm1Cgn Mouse R. Westbrook, R. de Cabo, J.M. Langdon, C.N. Roy, J. Walston
• Poster presenter at Johns Hopkins Department of Medicine Research Retreat Baltimore Maryland (March 2015) Metabolic Alterations in the Frail Mouse Model R. Westbrook, R. de Cabo, J.M. Langdon, C.N. Roy, J. Walston

• Oral presenter at the Division of Geriatric Medicine and Gerontology Grand Rounds (March 26, 2015) "Metabolic Alterations in the Frail Mouse Model."

• Oral presenter: Reyhan Westbrook, PhD: The Metabolic Characterization of the Interleukin-10tm1Cgn Mouse, as part of the symposium “A Mouse Model of Chronic Inflammation, Sarcopenia and Phenotypic Frailty” (Chair: Dr. Walston) at the International Conference on Frailty and Sarcopenia Research, Philadelphia, PA, April 28, 2016.


**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)**
- Charles Brown. Awarded an Johns Hopkins inHealth grant to evaluate mobility after cardiac surgery, 2016
- Charles Brown. Awarded a Johns Hopkins Clinician Scientist Award, 2016

**Carlson, Michelle (RCDC)**

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

Gross, Alden (RCDC)

Kalyani, Rita (RCDC/Pilot)

Leng, Sean (RCDC/Pilot)
- Sean X Leng. R01, NIAID: Influence Vaccine Failure in Adults Over Age 75: Role of Chronic CMV Infection. Funded January 2014.

Lin, Frank R. (RCDC)

Makary, Martin (RCDC)

McAdams-Demarco, Mara (RCDC)
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.

Punjabi, Naresh (External Project)

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. 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)

Publications, 2015-2016


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

<table>
<thead>
<tr>
<th>EAB Member</th>
<th>Affiliation</th>
<th>Years of Service</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joan E. Bailey-Wilson, Ph.D.</td>
<td>Head, Statistical Genetics Section; Co-Branch Chief, Inherited Disease Research Branch; National Human Genome Research Institute; National Institutes of Health</td>
<td>8</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>3</td>
</tr>
<tr>
<td>Howard Bergman, M.D.</td>
<td>Chair, Department of Family Medicine, Professor of Family Medicine, Medicine and Oncology, Dr. Joseph Kaufmann Professor of Geriatric Medicine, McGill University</td>
<td>3</td>
</tr>
<tr>
<td>Harvey J. Cohen, M.D.</td>
<td>Division Chief of Geriatrics, Director of the Center for the Study of Aging and Human Development, Duke University Medical Center</td>
<td>13</td>
</tr>
<tr>
<td>Luigi Ferrucci, M.D., Ph.D.</td>
<td>NIA Scientific Director, Senior Investigator and Chief, Longitudinal Studies Section</td>
<td>13</td>
</tr>
</tbody>
</table>
1. Recognition and Awards (non-grant honors and awards):

   - Dr. Karen Bandeen-Roche received the 2016 Marvin Zelen Leadership Award in Statistical Science by the Harvard T.H. Chan 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
2016 OAIC Annual Directory

Section I. Description of Center
The Mount Sinai OAIC’s goal is to stimulate, develop, and fund research directed at improving quality of life and independence of older adults with serious illness and their caregivers. In the first five years, our OAIC became a national resource for research training in geriatric palliative care, as well as a key contributor in the movement to improve quality of care for our nation’s sickest patients. The OAIC’s specific aims are:

1. To expand a comprehensive transdisciplinary research program focused on: a) improving quality of life, independence, and function and b) developing and testing models of improving care for older adults living with serious 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 expand a research infrastructure that will a) support new and ongoing research in the care of seriously ill older adults 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-PRE (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.
Nathan Goldstein, MD; R. Sean Morrison, MD; Juan Wisnivesky, MD, PhD (Research Education Component [REC] Core Co-leaders)

The purpose of the Mount Sinai Claude D Pepper OAIC’s Research Education Component (REC) will be to provide junior faculty with an interest in improving the care of older adults with serious illness the educational activities and training experiences, and to promote the development of future research leaders. The specific objectives of the REC are to:

1. Recruit talented faculty from different disciplines who are committed to academic careers improving the care of older adults with serious illness
2. Provide advanced training in research methodologies needed to conduct high quality, ethical, and multidisciplinary palliative care research for seriously ill older adults
3. Provide multidisciplinary mentorship and individually tailored career development plans
4. Support trainees to conduct and disseminate research studies to assess questions related to the health and independence of older adults or related palliative care issues
5. Facilitate attainment of academic and life skills to sustain long-term success as independent investigators and future leaders in geriatric and palliative care medicine
6. Prepare and assist trainees in obtaining external funding to continue an academic research career.

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:

1. 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.
2. 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.
3. 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.
4. Foster collaborative research among investigators from different disciplines, specialties, and institutions.

Melissa Aldridge, PhD (Population Research and Effectiveness (PRE) Core) - . The Population Research and Effectiveness (PRE) Core 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. This core has been highly productive in providing consultations and support for numerous OAIC investigators confronted with methodological and analytic issues that occur in the study of older adults with serious illness. Our Core’s consultants have a broad range of knowledge regarding research methods to serve as potential consults to
OAIC investigators. Resources and expertise are provided in a variety of ways and throughout all phases of the research process - from design to interpretation and presentation of findings.

1. To provide sophisticated, cutting edge methodological, statistical, and programming support to OAIC investigators.
2. To apply advanced research and statistical methodology (e.g., propensity scores, instrumental variable estimation, competing risk analysis) used in other fields but not commonly applied to aging-related research.
3. To collaborate closely with the RCDC and RCDSC to ensure that junior faculty obtain research methods training to advance their current knowledge and expertise.
4. To create and manage a large, population-based dataset to be used by OAIC investigators for research regarding individuals with serious illness (DP-1) and advance the methods to analyze these data (DP-2).

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:

1. 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);
2. 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;
3. 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;
4. To provide data management, in coordination with RC-RDA, for studies supported by the other OAIC cores;
5. 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

Improving Adjustment For Selection Bias in Studies of Continuous Treatments (PI: Melissa Garrido, PhD) (DP-1)

Description: This research methods based developmental project seeks to identify improved methods to account for selection bias in observational and quasi-experimental research which is a research priority in the field of geriatric palliative care. Propensity scores are one common and practical way to account for confounding due to selection bias, however, most propensity score guidance focuses on dichotomous treatments despite the fact that many treatments for older adults, such as drug dosage, have continuous values. Artificially dichotomizing continuous treatments can obscure important nonlinear relationships between treatment and outcome, and matching on multiple levels of a continuous treatment is impractical. Weighting may reduce selection bias, however, “best practices” for weighting samples by propensity scores for treatments with continuous values are not well-developed. To address this gap, this project will utilize a Monte Carlo simulation in which a propensity score is estimated parametrically and non-
parametrically. The PI will use inverse probability weights (IPW) based on the estimated propensity scores to adjust for selection bias and estimate treatment effects in scenarios with a continuous treatment. The specific aims are: 1) Evaluate the covariate balance, bias and efficiency of treatment effect estimates obtained after weighting the sample with IPWs from parametric and non-parametric propensity scores; and 2) Determine the minimum sample size necessary to obtain stable treatment effect estimates from a sample weighted by parametric and non-parametric propensity scores. In addition to providing useful data on the relative performance of propensity score weights constructed parametrically and non-parametrically, this study will inform an R21 application (NIA PA: 13-335) to understand the relative performance of propensity score weighting techniques in studies of categorical treatments using both simulated and empirical geriatric palliative care data. Studies of categorical treatments require multiple propensity scores and thus understanding the relative performance of weights based on a single propensity score will be key to understanding their ability to reduce selection bias in models with multiple propensity scores. The RC-PRE will provide expert statistical consultations for this study.

Chris Woodrell, MD: Dr. Woodrell received a Bachelor of Arts in biochemistry from Swarthmore College in 2001 and subsequently worked as a research technician in basic science laboratories working to examine malignant gene expression and cellular mechanisms of wound healing. He received his MD from the Icahn School of Medicine at Mount Sinai in 2011 where he subsequently completed his Internal Medicine residency and fellowship training in Hospice and Palliative Medicine. Dr. Woodrell is currently a research fellow who will be joining the faculty of the Department of Geriatrics and Palliative Medicine at Mount Sinai in July of 2016 as a Clinician Investigator. Dr. Woodrell’s research interest is to improve the delivery of palliative care to older adults with Hepatocellular Carcinoma (HCC). His research will identify predictors of inpatient palliative care consult among older patients with HCC by combining two pre-existing datasets of patients at Mount Sinai Hospital to determine which HCC patients receive palliative care and the relationship of demographic and disease characteristics to referral. He will then go on to create a cohort of hospitalized HCC patients referred to palliative care matched with a group of those who did not in order to measure the difference in readmission, Emergency Department visits, and Intensive Care Unit admission. Like Dr. Horton, Dr. Woodrell is at a critical juncture in his career development. He needs funds to protect his time so he can continue his research endeavors and become competitive to apply for his own funding.

C. Pilots
Project 1. Development of a cohort of Medicare patients with advanced dementia

Principal investigator: Carolyn Zhu, PhD – Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai Co-investigators: Christopher Murtaugh, PhD -- Visiting Nurse Services of New York (VNSNY) Center for Home Care Policy and Research; Stanley Moore (Consultant, Programming/Data Management)

Background and Specific Aims: Dementia is a progressive terminal illness with many complications in the advanced stages. At these advanced stages, many patients continue to be treated with aggressive and costly therapies without clear health benefits, exerting substantial strain on the healthcare systems. Our understanding of costs of advanced dementia is mostly based on findings from observational studies of nursing home or hospitalized patients, and often defined by a decedent sample. Estimates from observational studies on the effects of treatments on patient outcomes also may be biased due to potential endogeneity that arises from the non-random assignment of patients to different treatments. While Medicare claims have been used to identify patients with dementia, claims data lack information on disease severity. This pilot study
will explore the feasibility of combining data from several sources (e.g., Medicare claims, assessment data) to identify patients with advanced dementia, and explore the variation in treatment patterns to identify instrumental variables methods to obtain unbiased estimates of treatment on patient outcomes. The specific aims are: 1) To determine the feasibility of identifying patients with advanced dementia by combining Medicare claims data and measures of cognitive and functional impairment and behavioral difficulties available in the Outcome and Assessment Information Set (OASIS); 2) To examine whether patients identified with advanced dementia are associated with worse health outcomes (e.g., higher mortality, institutionalization, hospitalizations, hospice use); 3) To explore variation in treatment patterns (e.g., parenteral therapy) to identify instrumental variables that are predictive of treatment to correct for non-random assignment of patients to treatment groups.

The study uses Medicare administrative, claims and home health patient assessment (i.e. Outcome and Assessment Information Set, or OASIS) data from a previous study of heart failure led by Dr. Murtaugh (VNSNY). The sample will be derived from existing data that include all patients with Medicare fee-for-service hospitalizations discharged to home health care in a one year period (July 2009 through June 2010).

Progress/Status: We have made significant progress toward completing Aims 1 and 2. Specifically, we have successfully obtained the Data Use Agreement Reuse request for the VNSNY Medicare dataset. Working closely with the VNSNY research team led by Dr. Chris Murtaugh and data management consultant, Stanley Moore, we have created a sample of 857,073 Medicare beneficiaries with at least one home health care episode from 7/2009 to 06/2010 who have had at least one OASIS evaluation in 2009 (July-December). The prevalence of Alzheimer’s disease, as defined by the CCW chronic condition warehouse from Medicare claims, was 15.5% (n=133,100), and 32.4% with Alzheimer’s disease and related dementias (n=278,076).

We used data on symptom and functional status assessment in the OASIS as proxies to clinical staging variables in the Functional Assessment Staging procedure (FAST) and the Global Deterioration Scale (GDS). In individuals with AD, we identified 23,991 patients (18.0%) with Moderately Severe Cognitive Decline (FAST stage 5), and 11,082 with Severe or Very Severe Cognitive Decline (FAST stage 6 and above).

To date, we have completed the descriptive (bivariate) analyses comparing beneficiary characteristics and outcomes by dementia severity. We have estimated initial logistic regression models to examine the relationship between advanced dementia and outcomes. Results in Table below show that after controlling for individual demographics, comorbidities, prior healthcare utilization, and disabilities, more advanced dementia, as measured by the FAST scores, is associated with higher likelihood of death, hospice use, and home health utilization, but relationship between advanced dementia and hospital admissions, use of skilled nursing care, and ED use are less clear. We are currently refining these models.

<p>| Table. Logistic regression results of effect of advanced dementia on health outcomes |
|-----------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                                   | Death | Hospitalization | SNF | ED | HHA | Hospice |
| Reference group (FAST stage&lt;5)    | --    | --              | --  | -- | --  | --        |
| Moderately Severe Cognitive Decline | 1.087*** | 1.021 | 1.066** | 1.012 | 1.087*** | 1.098*** |</p>
<table>
<thead>
<tr>
<th>(FAST stage 5)</th>
<th>(0.027)</th>
<th>(0.022)</th>
<th>(0.025)</th>
<th>(0.021)</th>
<th>(0.025)</th>
<th>(0.029)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe or very severe Cognitive Decline (FAST stage &gt;=6)</td>
<td>1.166*** (0.038)</td>
<td>0.982 (0.028)</td>
<td>0.988 (0.030)</td>
<td>0.969 (0.026)</td>
<td>1.320*** (0.039)</td>
<td>1.188*** (0.042)</td>
</tr>
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</table>

Models controlled for age, gender, race/ethnicity, comorbidities, and prior 6 month health services use

Future directions: Over the next few months, we expect to complete the remaining analytic tasks. We plan to submit an abstract in February for the Alzheimer’s Association International Conference based on our findings to date. By mid-2016, we expect to have prepared a manuscript to submit for publication based on the completed analyses for Aims 1 and 2.

Project 2. A Descriptive Analysis of Hospice Care for Patients with Advanced Heart Failure: The Role of Implantable Cardiac Devices in Hospice Use and Other Outcomes

Principal investigator: Miriam Ryvicker, PhD – Visiting Nurse Services of New York (VNSNY) Center for Home Care Policy and Research Co-Investigators: 1) Christopher Murtaugh, PhD (Co-Investigator, VNSNY Center for Home Care Policy and Research); 2) Laura Gelfman, MD (Co-Investigator, Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai); 3) Yolanda Barrón-Vayá, MS (Statistician, VNSNY); 4) Stanley Moore (Consultant, Programming/Data Management)

Background and specific aims: Advanced Heart Failure (AHF) affects nearly 5 million people in the U.S. It is characterized by symptom burden, diminished quality of life (QOL), and high costs. Hospice care has the potential to improve clinical outcomes and QOL for patients with AHF by improving symptom control and clarifying goals of care and treatment preferences. At the same time, treatment modalities such as implantable cardiac devices have the potential to improve heart functioning and thus extend life while reducing symptom burden. However, data on the types of individuals who elect to receive implantable devices and their effect on hospice use and other outcomes is lacking, given that randomized trials are not feasible due partly to ethical concerns about withholding treatment. The specific aims of this study are to: (1) Describe the population of home care patients with AHF who do and do not receive implantable cardiac devices. Sub-aim: Predict who receives an implantable cardiac device with explanatory factors, including patient demographic factors (e.g., age, race/ethnicity), provider-level practice patterns and other measures potentially serving as instrumental variables; (2) Examine the relationship between implantation of a device, hospice use and outcomes such as hospital readmission, nursing home admission, and mortality controlling for baseline patient characteristics. Sub-aim: Examine potential interaction effects between device implantation and hospice use on other outcomes.

The study uses Medicare administrative, claims and home health patient assessment (i.e., Outcome and Assessment Information Set, or OASIS) data from a previous study of home care patients with AHF conducted by Co-Investigator Dr. Gelfman in collaboration with Dr. Murtaugh. The universe of potential study patients includes Medicare beneficiaries who were hospitalized for heart failure and then discharged to home health care between 7/01/2009 and 6/30/2010. Hospice and other health care use as well as mortality are being assessed for comparable groups of patients with and without implantable devices over a period of at least 6 months.
Methods: Project management tasks: We obtained permission from CMS to add Dr. Ryvicker and Ms. Barrón-Vayá to the Data Use Agreement held by Dr. Gelfman for her study of hospice care for AHF patients. We worked closely with programmer/data management consultant Stanley Moore in order to define sample selection criteria, identify patients who received a left ventricular assist device (LVAD), define study variables and configure the analytic dataset with appropriate data documentation. We developed an analytic plan detailing the anticipated approach for addressing each study aim, including a combination of descriptive analysis, logistic regression, propensity score matching, and hazard modeling. Additionally, we initiated a collaboration with Dr. Anu Lala (Mount Sinai), who will review analytic findings and provide specialized input on clinical decision-making related to cardiac devices.

Defining the analytic sample: We identified 270 individuals who received an LVAD during a hospitalization that qualified as an index stay, given that it took place during the timeframe of interest (7/01/2009-6/30/2010) and was followed by admission to home health care and a complete OASIS assessment. We identified a potential comparison group of 105,102 individuals who did not receive an LVAD but were hospitalized for heart failure during the index period, were discharged to home health care and had complete OASIS data. Given the imbalance between the size of the LVAD group and the potential comparison group, we selected a smaller subset of 5,400 patients without an LVAD in order to meet the statistical requirements for a logistic regression predicting a rare event. This allows for a total sample of 5,670 for modeling purposes, with roughly 5% of the sample having received an LVAD. In selecting the smaller subset for comparison, we also adjusted for the fact that the sample of LVAD recipients was skewed toward the younger end of the age distribution, with a much larger proportion receiving Medicare through the disability entitlement than the old age entitlement. We stratified the larger no-LVAD pool of 105,102 by age and randomly selected individuals within “age buckets” in order to generate a comparison group with a similar age distribution as the LVAD group. (In the cases of the youngest age brackets, it was necessary to select nearly all of the no-LVAD patients since there were so few individuals in these age brackets in the larger sample.)

Progress: Given the complexity of defining the sample and some data preparation issues that we have successfully addressed, the overall analytic timeline has been somewhat delayed. To date, we have completed the descriptive (bivariate) analyses comparing the characteristics of the LVAD group (N=270) with the age-stratified comparison group (N=5,400). Additionally, we have estimated logistic regression models to examine predictors of receiving an LVAD; we are currently refining these models and testing for multi-collinearity. Some key findings from the analyses thus far are summarized here.

First, it is notable that the LVAD group had fewer comorbidities that were not directly related to AHF. Presumably, having less clinical complexity in conditions not directly linked with heart failure might make a patient a better candidate for the LVAD procedure. Second, the length of stay for the index hospitalization was markedly longer for the LVAD group, with a mean of 38.8 days (SD=27.4) for the stay in which the LVAD surgery was performed. This is compared to a mean of 5.7 days (SD=4.8) for the HF-related index hospitalization in the no-LVAD group. In the LVAD group, the index hospital stay was less likely to have been initiated in the emergency room (17.4% vs. 75.4%; p<0.001), suggesting that most of the LVAD implantations occurred within the context of a planned admission. Third, the LVAD group had a significantly lower proportion who were of a racial minority (31.9% vs. 40.2%; p=0.006) and a significantly lower proportion who were eligible for Medicaid (27.0% vs. 53.1%; p<0.001). However, in preliminary multivariate logistic regressions, race was not a significant predictor of receiving an LVAD,
whereas patients who were eligible for Medicaid were significantly less likely to receive an
LVAD, controlling for other demographic and clinical factors. Thus far, the findings on race and
Medicaid eligibility have been consistent across different versions of the models. Finally, LVAD
recipients were more concentrated in the Northeast and Midwest U.S. Census regions, with less
representation in the South and West compared to non-recipients.

Next Steps and Deliverables: Having made significant progress toward completing Aim 1 and
having created the outcome variables and analytic plan for Aim 2, we expect to complete the
remaining analytic tasks during the first quarter of 2016. In January 2016 we will submit an
abstract for the AcademyHealth Annual Research Meeting. By the spring of 2016, we will have
prepared a manuscript for publication based on the analyses for Aims 1 and 2.

Project 3: Prospectively Identifying Older Adults with Serious Illness at Risk for High
Healthcare Utilization

Principal Investigator: Amy Kelley, MD, MSHS – Department of Geriatrics and Palliative
Medicine, Icahn School of Medicine at Mount Sinai  Co-Investigators: RS Morrison, MD; K
Ornstein, PhD, and E Bollens-Lund, MA (Department of Geriatrics and Palliative Medicine,
Icahn School of Medicine at Mount Sinai); P Deb, PhD (Department of Economics, Hunter
College)

Background and Specific Aims: Many healthcare reforms in the U.S. are focused on a small
proportion of the population with the highest healthcare costs. Notably, the majority (>80%) of
these patients are not in the last year of life. Despite the high spending among these complex
patients, care is often poorly coordinated, marked by inadequate symptom control, characterized
by low patient and family satisfaction, and frequently at odds with personal goals and
preferences. While high cost treatment may be entirely appropriate for some patients with serious
illness, it is a marker of poor quality for others. Predicting who is at risk for high cost, poor
quality care, however, has proven extremely difficult.

Building upon our prior work with the Health and Retirement Survey (HRS), and utilizing a
conceptual definition of serious illness derived from a recent survey of palliative care experts, we
developed operational descriptors of serious illness using combinations of medical conditions,
functional measures and prior healthcare utilization. These basic definitions performed well in a
preliminary analysis predicting high Medicare costs and hospital use over 1 year, but lacked the
precision to identify the subgroup of patients with persistently high utilization and the highest
costs. Notably, these basic definitions did not include several clinical and social elements (e.g.,
symptom burden, caregiver burden) that may be key predictors of high-cost, high-intensity
treatment. Therefore, this project specifically aims to: 1) Examine a wide range of clinical and
social factors that may predict high-cost, high-intensity treatment within the nationally
representative Health and Retirement Study (HRS), which contains extensive clinical, social and
financial survey data, and the National Health and Aging Trends Study (NHATS), which contains
a greater breadth of physical function and caregiver measures; and 2) Use innovative statistical
models to identify the most parsimonious, yet effective, set of predictors.

Progress/Status

This project has received funding from the National Palliative Care Research Center (NPCRC),
through the Pilot Project Support Grants Program. This grant will support 2 years of work,
beginning May 2015, including $77,000 in year 1 and $77,000 in year 2. Our preliminary work

Human Subjects and Data Protection reviews: This project requires the use of personal Medicare claims data and restricted elements of survey data. We have submitted our proposal for review and received approval from the Mount Sinai IRB, NHATS Data Confidentiality Committee, and the Centers for Medicare and Medicaid Data Privacy Board. We have received the restricted data elements from both NHATS and CMS and have successfully merged these data into a single analytic file.

Data Cleaning and Crosswalk: We are currently working on data cleaning steps and developing a code book and crosswalk file of variables in HRS and NHATS. Given our prior work with HRS, we are first comparing the HRS items the available items in NHATS and identifying those variables that are exact matches. When exact matches are not available, we are assessing candidate variables for construct validity and frequency, to select the closest match. Through this process, we are translating the basic HRS definitions to an NHATS definition item by item. In next steps, content areas such as caregiving, where NHATS offers measures beyond that available in HRS, candidate variables will be considered as a refinement or improvement to the specified definition.

Next Steps and Deliverables: Data Cleaning and Variable Identification: Once we have completed the data cleaning and crosswalk between HRS and NHATS data, we will replicate the basic definitions and sampling strategy used in HRS in the new NHATS cohort. We will compare these cohorts’ 1 year outcomes of hospitalization, Medicare costs, and mortality. Next, we will return to our conceptual definition of serious illness and explore additional variables in NHATS (i.e., caregiver measures, quality of life and symptom measures) that may improve upon the basic serious illness definition.

Analyses: We will then use the complete HRS and NHATS datasets and innovative statistical model techniques, including finite mixture and grade of membership models, to develop a parsimonious, yet effective definition of serious illness. The ultimate goal is to determine an efficient set of clinically applicable predictors to prospectively identify those seriously ill individuals who are most likely to benefit from specialized geriatric and palliative care services.

Deliverables: We plan to prepare 2 additional peer-reviewed publications to disseminate these results.

Project 4: Hospitalization-related stress and risk for adverse events after discharge

Principal investigators: Deena Goldwater, MD, PhD and Fred Ko, MD – Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai

Background and specific aims: After discharge from the hospital from either a medical or surgical admission, patients face a transient period of increased risk for adverse events such as rehospitalization and death, as well as enhanced susceptibility to infections, cardiovascular events, progressive deconditioning, debility, frailty, and cognitive decline. Allostasis defines a system functioning within normal stress-response parameters.
Extended stress exposure, however, results in abnormal hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS) activation, disrupting the finely tuned mechanisms of mind-body balance. This maladaptive state, termed allostatic overload, leads to cognitive deterioration, cardiovascular and immune system dysfunction, and functional decline, all components of post-hospital vulnerability. Allostatic load has been operationalized as the summation of a variety of hemodynamic, hormonal and metabolic factors, including blood pressure, lipid profile, glycosylated hemoglobin, cortisol and catecholamine levels and inflammatory markers. We hypothesize that a summative measure of hospitalization-related stress burden will provide insight into which patients are at highest risk for adverse outcomes post-discharge. Specific aim: to test the correlation between stress biomarkers during hospitalization and risk for rehospitalization and functional decline after discharge.

Methods: This pilot study will assess allostatic load as a composite index of known stress biomarkers. It will utilize a subset of data gathered by Dr. Sean Morrison and Dr. Fred Ko for a hip fracture study called Improving Pain and Function in Hip Fracture. This cohort is composed of individuals over 60 years of age who presented with an acute hip fracture to the emergency department and were admitted to the hospital for planned surgical repair. Stress biomarkers will be measured in blood serum samples previously collected on POD3. Concentrations of inflammatory (IL-6, TNF-alpha, fibrinogen, and CRP), metabolic (albumin) and hormonal (cortisol) biomarkers will be measured using Luminex multiplex technology. All of the biomarkers with the exception of glucose will be processed by the Human Immune Monitoring Core (HIMC) facility at Mount Sinai School of Medicine. Glucose levels will be assessed with a glucometer by the applicant. A modified allostatic load score will be determined as follows: results for each of the 7 biomarkers will be divided into quartiles; the score will be a sum of the number of parameters for which an individual has a value placing them in the top quartile (or bottom quartile for albumin) of that parameter within the cohort. This proposed study’s primary outcome is hospital readmission within 90 days of hospital discharge. The secondary outcomes are functional status 6 weeks post-operatively. Hospital readmission data were obtained from an electronic medical record database query. Functional status data were previously gathered by Dr. Ko. Functional status was measured preoperatively and 6 weeks post-operatively using the Function Independence Measure (FIM-motor).

Significance/Products: This proposed pilot study is the first to consider a summative measure of hospital-related stress and its relationship to post-discharge outcomes. The development of a tool to quantify hospital-induced allostatic overload may identify patients highly susceptible to adverse events after discharge, facilitate targeted post-discharge intervention, and ultimately improve outcomes. Project findings can be used in an NIH or federal application to proceed to next steps in testing of the approach (e.g., a multi-site trial or trial planning grant).

Project 5: Describing treatment-related symptom burden and determining patient- and provider-level factors associated with palliative care referral in older patients with advanced cancer undergoing palliative radiation therapy

Principal Investigator: Kavita V. Dharmarajan, MD, MSc, Assistant Professor, Radiation Oncology and Palliative Medicine Department of Radiation Oncology, Mount Sinai Hospital

Background and specific aims:
Palliative radiation treatment (RT) is commonly used in the setting of advanced cancer to alleviate cancer-related symptoms, improve function, and allow better quality of life. It may, however, also be associated with temporary periods of worsened symptoms as a result of acute treatment-related side effects. This may be particularly challenging in older patients leading to a higher number of ED visits, hospitalizations, and decreased quality of life. Access to palliative care resources within the timeframe of acute symptom development may add a layer of support that helps lesson the burden of symptoms related to palliative RT in these individuals, yet little is known about the characteristics and severity of symptoms experienced among older patients shortly after treatment or the current referral patterns to palliative care. In this proposal, I outline a descriptive pilot study to ascertain the burden of symptoms leading to ED visits and hospitalizations among older patients after a course of palliative RT as well as the factors impacting referral to palliative care services among these patients. Findings from these projects will inform future work that leads to designing and testing pilot interventions, in the context of NIH-funded K23 and later R01 trials, that leads to better quality of life of older patients with advanced cancer receiving palliative RT. My goal is to become an independent clinician-investigator at the intersection of aging, palliative care, and radiation oncology whose work improves the lives of older, advanced cancer patients undergoing palliative RT.

**Specific aims:** Between 2010 and 2030, a 67% increase in cancer incidence is anticipated for patients 65 years or older (1.0 million to 1.6 million instances). In approximately 30% of these, radiation treatment (RT) will be given in a palliative setting. RT can improve tumor-related symptoms and functional outcomes, but may also be associated with significant adverse outcomes such as fatigue, worsened pain, long hospital stays, and reduced independence, especially in the period immediately after radiation when patients experience acute toxicities. Some of these toxicities may be unexpectedly more pronounced in older individuals. Many patients may also hold unrealistic expectations of cure. The American Society of Radiation Oncology (ASTRO) has thus urged radiation oncologists to discuss goals of treatment, provide primary palliative care, and consider referral to specialty-level palliative care when initiating RT. Palliative care resources, when applied in conjunction with RT, may especially permit older patients undergoing palliative RT to maintain their quality of life and functional independence. Despite its clear strengths, palliative care services are underutilized for older patients with cancer. Moreover, little is known about the extent to which palliative care is accessed among older patients undergoing palliative RT. The goal of this project is to describe the burden of symptoms and consequent health care service utilization (such as ED visits and hospitalization) experienced by older patients after palliative RT and to determine the factors associated with the current referral practice to palliative care services for older patients receiving palliative RT. Pilot data generated through this investigation will lead to a more complete understanding of older patients’ unique experiences with palliative RT and inform optimal time points for palliative care referrals for these individuals.

**Project 6: Palliative Care for Patients with Hepatocellular Carcinoma**

**Principal Investigator:** Christopher Woodrell, MD, Brookdale Department of Geriatrics and Palliative Medicine
Background and specific aims:
The specific palliative care needs of patients with end-stage liver disease have not been well described. Patients with hepatocellular carcinoma (HCC) are an important subgroup of this population, as HCC is difficult to treat, carries a high rate of mortality, and has a rapidly rising incidence. Because most of these patients also have cirrhosis, the disease trajectory is difficult to predict. Further studies are needed to design models of care to meet the unique palliative care needs of this population. Mount Sinai Hospital, with a robust palliative care service and the largest HCC program in the country, provides the ideal platform to carry out this study. A secondary analysis of clinical databases will be performed, to determine which HCC patients were seen by palliative care and the demographic and disease severity characteristics associated with a palliative care consult. Rates of healthcare utilization will be measured for HCC patients who received an inpatient palliative care consult and for a matched group of patients who did not. Hospital readmission, intensive care unit admission, and emergency department visits will be measured at 30 days for comparison. This pilot study will aid in the design of a future prospective palliative care intervention for HCC patients. The work will be accompanied by career development activities, including mentorship and focused coursework, to facilitate the principal investigator’s development as an independent researcher.

Little is known about the palliative care needs of patients with hepatocellular carcinoma (HCC), which is difficult to treat and has a very poor overall five-year survival (15%). Curative treatments are limited to surgical resection and transplant in early-stage disease, though two-thirds of cases are identified at later stages. Furthermore, HCC has the fastest rising incidence of any solid cancer in the United States, attributable to the aging hepatitis C-infected cohort and rising rates of nonalcoholic steatohepatitis (NASH). Annual deaths from primary liver cancer (85–90% HCC) were projected to increase from 20,000 in 2010 to 51,000 by 2030, making liver cancer the third-highest cause of cancer-related death in the country. Driven in part by the increasing prevalence of HCC, the average age of patients awaiting liver transplant has risen dramatically in recent years. Increasing age is associated with higher pre- and post-transplant mortality. Almost all patients with HCC in the United States also have cirrhosis, thus the disease trajectory is likely an amalgamation of that of end-stage organ failure and cancer. This makes HCC unique and particularly difficult to predict and necessitates earlier palliative care involvement. In addition, care is often delivered by hepatologists and transplant surgeons, with whom supportive and palliative care programs have not been widely developed or implemented. In order to better integrate palliative care into the care of this growing population, it is important to effectively design models tailored for patients with HCC. The goal of this project is to lay the groundwork for future funding to implement a palliative care intervention to meet the needs of the aging population of patients with HCC. To this end, this pilot project will have two specific aims:

**Specific Aim 1:** Identify characteristics associated with patients with HCC receiving a palliative care consult. **Methods:** Combine two pre-existing Mount Sinai datasets to determine which HCC patients receive inpatient palliative care consults and the relationship of demographic and disease characteristics to referral.

**Hypothesis 1:** HCC patients are seen by palliative care in the setting of advanced age and late stage disease, as compared to those not seen by palliative care.

**Relevance:** These data will help determine the patient-based factors associated with HCC patients being referred to palliative care and thus help better tailor future interventions to meet these patients’ needs.
Specific Aim 2: Examine the effect of inpatient palliative care consultation on number of and time to readmissions, Emergency Department (ED) visits, and Intensive Care Unit (ICU) admission.

Methods: Use the dataset defined in aim 1 to create a cohort of hospitalized HCC patients referred to palliative care, propensity-score matched with a group of those who did not, and compare rates of healthcare utilization. Hypothesis 2: Patients who receive a palliative care consult will have fewer and longer times to readmissions, ED visits, and ICU admissions. Relevance: Describing healthcare utilization patterns of patients with HCC will help define the benefit of palliative care for this population and support a future palliative care intervention to improve their care.

Section III. Career Development

Analgesic Safety and Effectiveness in Older Veterans with Arthritis (EP-1); PI: Ula Huang; VA Merit Award

The Impact of Mental Illness on Veterans' Palliative Care Access and Outcomes (EP-2) PI: Melissa Garrido; VA Career Development Award

Effects of 30-day Bundled Payment of Hospital at Home on Outcomes, Satisfaction and Costs (EP-3). PI: Al Siu; CMMI innovation Award

Section IV. Publications:

Publications:


Xie K, Gelfman LP, Horton JR, Goldstein NE. Current State of Research on Palliative Care in Heart Failure as Evidenced by Published Literature, Conference Proceedings and NIH Funding. Circulation. Submitted for Review.


Book Chapters:

Gelfman LP, Goldstein NE. Palliative Care Services for Patients with Heart Failure. In: Miriam Johnson, Lehman Richard, and Karen J. Hogg, eds. Heart Failure and Palliative Care: A Team


Section 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). (5 years)

2. Vincent Mor, PhD - Florence Pirce Grant Professor of Community Health in the Public Health Program of the Brown University School of Medicine. (5 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 (5 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 (4 years)

Recognition and Awards:

The Bronx VA GRECC – Received a $1.3 million grant from the VA Office of Rural Health to sustain GRECC Connect in 2015-2016, a project to educate and provide clinical support to rural providers to improve geriatric care via telehealth means. The Bronx GRECC will continue to lead as the coordinating center for the project. Participating sites include Madison, WI; Rochester, NY; Seattle/Puget Sound, WA; Pittsburgh, PA; Bedford, MA; Durham, NC and San Antonio, TX, with a new site in Little Rock, AR. William Hung, MD, MPH directs the multisite project; other key staff includes Judith L. Howe, PhD; Kenneth S. Boockvar, MD; Ab Brody, PhD and Daniel Sun. October, 2015.

Nathan E. Goldstein, MD – Awarded an Endowed Professorship: Gerald J. and Dorothy R. Friedman Chair in Palliative Care. Presented to Dr. Goldstein at Convocation 2015, hosted by Dean Charney. October 1, 2015.
I. Description of Center

The theme of the Arkansas OAIC at UAMS is “Translational research on striated muscle (cardiac and skeletal) 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 striated muscle (skeletal 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 striated muscle (cardiac and skeletal) 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 striated muscle (skeletal 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 striated muscle (cardiac and skeletal) 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 striated muscle (cardiac and skeletal) 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
striated muscle (cardiac and skeletal) 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

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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 overall OAIC theme of maintaining function of striated muscle (including skeletal and cardiac) in the elderly. 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 (CTSA) 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 junior faculty trainees, both locally at UAMS, around Arkansas, and nationally. The LAC also facilitates the mentoring of postdoctoral fellows and predoctoral students. 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

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Progress towards RC1 Specific Aims:

Specific Aim 1. Assist investigators with designing research plans that are statistically sound and utilize efficient and secure data management procedures.

Dr. Roberson, Ms. Schrader, and Mr. Spencer 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 have recently assisted several Pepper Center members in submitting and resubmitting R01 applications. They assisted Dr. Wolfe plan and develop an R01 application titled “Amino acids and muscle protein metabolism” which was submitted in June 2016. They are also currently assisting Dr. Azhar plan and resubmit an R01 application titled “Cardiac and Vascular Contributors to Cognitive Aging” which will be submitted in July 2016. Dr. Roberson and Dr. Prior also participated in the review of pilot award applications.

Specific Aim 2. Assist investigators with the conduct of research through data management services and appropriate statistical analyses.

The statistical data analysis effort continued to increase this year as more projects completed data acquisition and moved into the analysis phase. Published manuscripts are listed elsewhere in this document. Analyses of several projects are nearing completion and manuscripts are being drafted. For example, analyses are almost complete for the pilot awards made to Dr. Masil George and Dr. Sakeena Raza. Manuscripts for both of these studies are in preparation. The Biostatistics component of this core also assisted with poster layout and data analysis for two medical students in Geriatrics (Stephen Foster and Dominic Picetti) and for a Pepper pilot
The Biomedical Informatics team developed a wearable sensor infrastructure and a unique algorithm to detect if the wearer has fallen. These tools have been used by three research research groups and are currently being evaluated by three additional investigators for future projects. The CRIS clinical trial management system continues to be evolved and adapted for specific trials.

**Specific Aim 3. Educate investigators in relevant areas of biostatistics and biomedical informatics.**

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. Dr. Roberson and Dr. Prior attend the monthly research seminars and participate in the monthly administrative meetings of the center. Ms. Schrader attended the Arkansans Promoting Education for Caregivers and Communities (APECC) meeting hosted at the UAMS Pepper Center in May 2015 to discuss designing a Caregiver Burden survey tool as well as provide an overview on the role of Biostatistics in aging research. The department of Biomedical Informatics launched a monthly lecture series dealing with topics of interest to the OAIC research community.

**Changes in Personnel (include biosketches for all new staff members working on the grant, even if paid from other sources):**

Dr. Topaloglu left UAMS for a position at Wake Forest University in July 2015. Fred Prior, PhD, was recruited from Washington University as the Chair of the newly created UAMS Department of Biomedical Informatics and assumed this position on October 1, 2015. At this time he also assumed the position of Co-leader of the RC1 of the UAMS OAIC. His biosketch is attached.

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

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The RC2 provides expertise, instrumentation, training, and evaluation in support of translational research. The RC2 supports 20 research protocols (see table).

**Progress towards RC2 Specific Aims:**

**Specific Aim 1. Provide standardization for comprehensive nutritional, metabolic, and functional assessments of study subjects.**  
There are currently 17 ongoing research protocols supported by this aim of RC2 (see table). Protocols require functional tests, as well as nutritional and metabolic evaluations. We have now hired a dietician, Amanda Dawson, MS, RD who is able to provide close oversight and control of nutritional studies.
Specific Aim 2. Facilitate performance of complex methodologies specifically derived to address the metabolic and functional implications of aging and its related health issues.

Five of studies will employ skeletal muscle biopsies and/or stable isotopes to evaluate macronutrient metabolism. RC2 is also assisting with analysis of body composition and coordination with the metabolic kitchen for all the projects.

Three projects looking at skeletal and/or cardiac functional outcomes will not use stable isotopes.

Specific Aim 3. Provide training opportunities for collaborative and translational research.

Training opportunities are available to investigators at all times for their specific protocols. 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. 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. 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.

Projects supported by the RC2 and the specific aims addressed in each project:

<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>
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<tbody>
<tr>
<td>Ferrando, AA</td>
<td>Substrate utilization, exercise performance, and skeletal muscle response to energy deficit and altitude acclimatization.</td>
<td>United States Army Environmental Research Institute</td>
<td>Glucose and protein metabolism</td>
<td>2 and 3</td>
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<td>Ferrando, AA</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>
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<td>Ferrando, AA</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</td>
<td>Tolerance of Enteral Formulas</td>
<td>Nestle Healthcare Nutrition</td>
<td>nutritional assessment</td>
<td>1 and 3</td>
</tr>
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<td>Study Goal</td>
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<td>---------------------</td>
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<td>Borsheim, E</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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<td>Lefler, LL</td>
<td>A Lifestyle Physical Activity Intervention for Older, Sedentary Women</td>
<td>NIH/National Institute for Nursing Research 1R15NR012832</td>
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<tr>
<td>Wolfe, RR</td>
<td>Is there a maximal anabolic response to beef intake?</td>
<td>National Cattlemen’s Beef Association</td>
<td>Metabolic kitchen, protein metabolism</td>
<td>1, 2, and 3</td>
</tr>
<tr>
<td>Wolfe, RR</td>
<td>Determination of the Optimal Infusion Rate of Amino Acids in Seriously Ill Patients.</td>
<td>Baxter Laboratories</td>
<td>Body composition, protein metabolism, glucose metabolism</td>
<td>1, 2, and 3</td>
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<tr>
<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>
</tr>
<tr>
<td>Baum, J</td>
<td>The role of leucine and -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>
</tr>
<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>
</tr>
<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 echo-cardiogram</td>
<td>1 and 3</td>
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<tr>
<td>Singh, S</td>
<td>Modulation by 4-hydroxyxnonenal (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>
<td>Harvest of mouse tissues; body composition, echo-cardiogram, insulin resistance</td>
<td>1, 2, and 3</td>
</tr>
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<td>Hauer-Jensen, M</td>
<td>Arginine supplementation reverses muscle wasting due to deficient de novo arginine synthesis</td>
<td>OAIC Pilot</td>
<td>Protein metabolism</td>
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<tr>
<td>Name</td>
<td>Project Title</td>
<td>PI</td>
<td>Training in aging research Functional Outcomes in CHF patients, with protein intake</td>
<td>1 and 3</td>
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<tr>
<td>George, M</td>
<td>Biologic Factors Influencing Cachexia in the Elderly</td>
<td>OAIC Pilot</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>
<td>Stable isotope determination of amino acid turnover</td>
<td>2 and 3</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>
<td>Cardiac function by Doppler echo-cardiogram</td>
<td>1 and 3</td>
</tr>
<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>
<td>2 and 3</td>
</tr>
<tr>
<td>Rnika, Abraham</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 regulation in response to tilt in heart failure patients; Functional Outcomes patients, and response to protein intake</td>
<td>1,2 and 3</td>
</tr>
<tr>
<td>Raza. Sakeena</td>
<td>Improvement in functional capacity of obese elderly with heart failure</td>
<td>OAIC Pilot</td>
<td>Training in clinical aging research, Functional Outcomes in Obese CHF patients, exercise and protein intake</td>
<td>1,2 and 3</td>
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**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-Young, 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:**

**Grant Awards/Applications resulting from RC2 support:**

1. 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)
2. NIH R15 AREA application (June 2015): Effects of High Speed Power Training in Mobility Limited Older Adults (Cody Sipe: Harding University, PI) (Submitted)

The following presentations were supported by the Pepper Center RC2:


2013 Protein Summit. Protein intake and public policy: A call to reason (R. Wolfe). Washington DC.
2013 Distinguished Lecturer, Dept of Food Science, University of Arkansas Fayetteville. Dietary recommendations for protein intake (R. Wolfe).


2014 Course Director, Tracer Methodology Workshop (5 days), Cleveland, OH (R. Wolfe).

4/28/2014 Leucine and omega-3 fatty acids act synergistically through mTOR to activate translation initiation in young and aged C2C12 myotubes (J. Baum, Poster Presentation). Experimental Biology, San Diego, CA.


7/14/2014 Protein Intake for Peak Performance (Invited – A. Ferrando). Florida Academy of Nutrition and Dietetics, Ft. Lauderdale, FL.

4/9/2014 Riddett Institute, Massey University. Dietary protein intake and protein quality (R. Wolfe - Invited). Palmerston North, New Zealand,


3/29/2015 Higher protein intake during mixed meal ingestion increases whole-body net protein accretion through a reduction in protein breakdown (IL Kim). Experimental Biology, Boston, MA.

6/12/2015 Determining Protein Metabolism (A. Ferrando - Invited). International Society of Sports Nutrition, Austin, TX.

7/13/2015 Protein Intake for Peak Performance (A. Ferrando - Invited). Florida Academy of Nutrition and Dietetics, Ft. Lauderdale, FL.


2015 Texas A&M College Station. Distinguished Lecture Series. Scholar Award (R. Wolfe - Invited). “Healthy aging through exercise and nutrition”.


II.D. RC-3: Analytical Core

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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.

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

| Projects Supported by Research Core 3 Utilizing Stable Isotope Tracer Methodology |
|---------------------------------|---------------------------------|---------------------------------|
| Investigator | Project Title | Sponsor |
| Wolfe, RR | Is there a maximal anabolic response to beef intake? | National Cattlemen’s Beef Association |
| Wolfe, RR | Lysine supplementation and glucose metabolism | TRI Pilot Grant |
| Wolfe, RR | Determination of the optimal infusion rate of amino acids in seriously ill patients. | Baxter Healthcare |
| Borsheim, E | Effects of amino acids on regional lipid metabolism | NIH R01 AG033761 |
| Ferrando, AA | Dairy macronutrient effects on the metabolic syndrome | Dairy Research Institute |
| Ferrando, AA | Effect of dietary protein intake distribution on protein metabolism and skeletal muscle | Dairy Research Institute, Egg Nutrition Center, National Cattlemen’s Beef Association |
| Ferrando, AA | Effect of bimagrumab in older adults with sarcopenia | Novartis Institute for BioMedical Research |
| Ferrando, AA | Overcoming TWEAK signaling to fully restore muscle mass and mobility function after total joint arthroplasty | NIH 1R01HD084124-01 (Co-I) |
| Ferrando, AA | The benefits of egg for breakfast | Egg Nutrition Center |
| Ferrando, AA | Tolerance of enteral formulas | Nestlé Healthcare Nutrition |
| Lefler, LL | A lifestyle physical activity intervention for older, sedentary women | NIH/National Institute for Nursing Research 1R15NR012832 |
| Raastad, T | Effect of protein intake on muscle protein synthesis and breakdown after exercise | The Norwegian School of Sport Sciences |
| Hamarsland, H | Role of amino-acid deficiency in aging-related muscle atrophy | OAIC Pilot |
| Ayyadevara, S | The role of leucine and omega-3 fatty acids in skeletal muscle function during aging | OAIC Pilot |
| Baum, J | Improvement of cardiovascular function in rats by arginine | OAIC Pilot |
| Csiszar, A | Improvement of cardiovascular function in rats by arginine | OAIC Pilot |
supplementation

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<tr>
<td>Washington, T</td>
<td>The effect of leucine supplementation on aged skeletal muscle regenerative capacity</td>
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I.I.E. RCDC - Research Career Development Core

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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 nanotechnology in advancing skeletal muscle translational research with Dr. Wolfe and his group.

Abraham Rtika M.D. is pursuing a second fellowship in endocrinology and working on the “Nutritional therapy for autonomic dysfunction in the elderly HF patients”. Dr. Rtika has had 2 publications during the past year and recently had another manuscript accepted in Aging Science, titled, “The metabolic health of nonagenarians and centenarians living in Arkansas”.
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.

Minority Researchers:

**Emmanuel Williams Ph.D.** (African American) is a post-doctoral researcher and a junior scholar. He completed his Ph.D. in 2016. His area of interest is mitochondrial bioenergetics and the aging endothelial cells. He has been very productive and has published 3 manuscripts on endothelial senescence and mitochondrial dysfunction in 2015 and is currently submitting a proposal to the American Heart Association (AHA).

**Elvin Price Pharm D., Ph.D.** (African American). Dr. Price is an Assistant Professor within the UAMS College of Pharmacy, new to the field of aging. He received pilot funding from the OAIC to study pharmacogenetics in the elderly. He will focus on differences between Caucasians and African Americans. He has received numerous awards, including a recent Geriatric Workforce Enhancement award (GWEP) and is planning to submit a Beeson award.

**Larry Robins Ph.D. M.D.** (c), is a junior scholar with an interest in differential expression of nitric oxide in heart failure patients. He is currently in medical school but is also leading a medical-student run clinic in an underserved African American neighborhood. He is collaborating with Dr. Sakeena Raza on a heart failure project. His long-term goal is to conduct translational and health disparity research.

**Jennifer Vincenzo Ph.D.** (Latino American) is an Assistant Professor in physical therapy at the University of Fayetteville, Arkansas. She is new to the field of aging. Her area of interest is rehabilitation of the elderly after stroke or other illness. She is also a recent recipient of the Geriatric Workforce Enhancement award (GWEP) and is testing different modalities of improving balance in elderly subjects.

**Allen Antino Ph.D.** (African American), is an Assistant Professor in the UAMS College of Pharmacy. His background is behavioral neuroscience in rodents. He is new to the field of aging and is collaborating with researchers in the OAIC to evaluate behavior of various transgenic mouse lines and in the process is also learning about aging physiology.

**Tyrone Washington Ph.D.,** (African American), is an Assistant Professor in the department of Health, Human Performance, & Recreation at the University of Arkansas at Fayetteville. His area of interest is skeletal muscle aging in rodents. He has been extremely productive and has 10 manuscripts and 8 abstracts in past year. He has also received pilot funding from the OAIC and is also funded by American Biosciences and a R15 award.

**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 Csizsar 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. Rtika 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 cardiac 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. Phenomenal Woman honoree, 2015 |
<p>| Cardiopulmonary resuscitation in elderly |                         |                        |                             |</p>
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Affiliation</th>
<th>Co-authors</th>
<th>Journal</th>
<th>Year</th>
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<tr>
<th>Author(s)</th>
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<tr>
<td><strong>Aging, cancer and effects on cardiac and skeletal muscle</strong></td>
<td><strong>Klimberg/Wei/Azhar/Zhang RCDC, RC2</strong></td>
<td><strong>Monthy Pepper meetings, weekly Oncology meetings, weekly lab meetings, journal club, IRB training and updates.</strong></td>
<td><strong>Klimberg/Wei/Azhar/Zhang RCDC, RC2</strong></td>
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<tr>
<td><strong>Nutritional therapy for autonomic dysfunction in the elderly HF patients.</strong></td>
<td><strong>Wei/Azhar/Roberson RCDC, RC2, RC1</strong></td>
<td><strong>AGS, monthly Pepper meetings, weekly endocrine seminars, weekly lab meetings, interdisciplinary geriatric seminars, journal club, IRB training and updates</strong></td>
<td><strong>Wei/Azhar/Roberson RCDC, RC2, RC1</strong></td>
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</tr>
<tr>
<td><strong>Rtika Abraham M.D</strong></td>
<td><strong>Wei/Azhar/Roberson RCDC, RC2, RC1</strong></td>
<td><strong>AGS, monthly Pepper meetings, weekly endocrine seminars, weekly lab meetings, interdisciplinary geriatric seminars, journal club, IRB training and updates</strong></td>
<td><strong>Wei/Azhar/Roberson RCDC, RC2, RC1</strong></td>
<td></td>
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</tr>
<tr>
<td>I Kim Young Ph.D</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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<tr>
<td>Bryce Marquis, Ph.D.</td>
<td>Wolfe/Ferrando /Reis RC1/RC3/RCD C</td>
<td>Monthly Pepper meetings, Weekly metabolomics lab meetings, weekly journal club, interdisciplinary geriatric seminars, IRB training and updates.</td>
<td></td>
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<tr>
<td><em>Metabolomics in the aging muscle</em></td>
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<tr>
<td>Tyrone Washington, Ph.D.</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>
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<tr>
<td>Name</td>
<td>Department</td>
<td>Events and Training</td>
<td>References</td>
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</table>
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>
<thead>
<tr>
<th>Pepper Center Pilot Awardees</th>
<th>Papers</th>
<th>Grants</th>
</tr>
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<tbody>
<tr>
<td><strong>Pilot P.I.</strong></td>
<td><strong>Support dates</strong></td>
<td><strong>Publication papers since award (citing P01)</strong></td>
</tr>
<tr>
<td>Anna Csiszar</td>
<td>02/12 -01/13</td>
<td>19 (13)</td>
</tr>
<tr>
<td>Martin Hauer-Jensen</td>
<td>12/11 - 11/12</td>
<td>36 (1)</td>
</tr>
<tr>
<td>Sharda P. Singh</td>
<td>03/12 - 03/13</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Jamie Baum</td>
<td>01/12 - 12/12</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Cody Sipe</td>
<td>11/12 - 10/13</td>
<td>0</td>
</tr>
<tr>
<td>Nukhet Aykin-Burns</td>
<td>04/12 - 03/13</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Masil George</td>
<td>06/12 - 05/13</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Sakeena Raza</td>
<td>11/11 - pres.</td>
<td>0</td>
</tr>
<tr>
<td>Srinivas Ayyadevara</td>
<td>6/12 - 5/13</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Tyrone Washington</td>
<td>03/13 - 02/14</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Valentina Todorova (2 pilots funded)</td>
<td>08/12 - 07/13, 09/14 – 08/15</td>
<td>2</td>
</tr>
<tr>
<td>Neil Il Young Kim</td>
<td>09/13 - 08/15</td>
<td>0</td>
</tr>
<tr>
<td>Vladimir Zharov</td>
<td>09/13 - 08/14</td>
<td>7</td>
</tr>
<tr>
<td>Andrew Gardner</td>
<td>02/14 - 09/15</td>
<td>10</td>
</tr>
<tr>
<td>Rtika Abraham</td>
<td>09/13 - 08/14</td>
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<td>Bryce Marquis</td>
<td>09/14 – 08/15</td>
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</tr>
<tr>
<td>Mani Ponnappan</td>
<td>09/14 – 08/15</td>
<td>1</td>
</tr>
<tr>
<td>Alexei Basnakian</td>
<td>09/14 – 08/15</td>
<td>3</td>
</tr>
<tr>
<td>Nicolas Hurren</td>
<td>09/14 – 08/15</td>
<td>0</td>
</tr>
</tbody>
</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.

Abstracts
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”.

III. UAMS OAIC 2015/2016 Publications

LAC:


RC3:


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


52. Tuvendorj D, Borsheim E, Sharp CP, Zhang X-J, Barone CM, Chinkes DL, Wolfe RR. Amino acid


64. Wolfe RR, Rutherford SM, Kim IY, Maoughan PJ. Protein quality as determined by the digestible indispensable amino acid score (DIAAS): Evaluation of factors underlying the calculation. Nutr Rev. IN PRESS

RCDC:


PESC:

133. Baum JI, Howard LR, Prior RL, Lee S-O (2016). The effect of Aronia melanocarpa (Black Chokeberry) supplementation on markers of obesity in mice. Accepted – Berry Research


165. Klimberg, VS. It’s Freezing to Death (Editorial). *Annals of Surgical Oncology*. Published online June 6, 2016.


221. Gardner AW, Parker DE, Montgomery PS, Blevins SM. Step-monitored home exercise improves ambulation, vascular function, and inflammation in symptomatic patients with peripheral artery...
disease: a randomized controlled trial. J Am Heart Assoc. 2014 Sep 18;3(5).
with additional on-line material.


IV. External Advisory Board Members

Dr. Elena Volpi is the Director of the Sealy Center on Aging and the UTMB Claude D. Pepper Older Americans Independence Center, and the Associate Director of the Institute for Translational Sciences and CTSA at the University of Texas Medical Branch at Galveston. She is an expert in clinical and translational research on sarcopenia and functional recovery in older adults. Her major scientific contributions to research on aging include discovery of novel metabolic pathways that lead to loss of muscle mass and strength with aging; the identification of therapeutic targets to improve muscle function; and testing in clinical trials novel nutritional, exercise and pharmacological interventions to improve physical function and independence in geriatric patients. Her research has been continuously funded by the NIH, and many of her mentees have also attained NIH funding. She has published more than 100 papers in peer-reviewed journals and has been involved in several national and international consensus panels on nutritional recommendations for older adults. She has participated in numerous NIH study sections and is currently the chair of the Aging Systems and Geriatrics Study Section. She also chairs the Fellowship Committee of the Gerontological Society of America. Dr. Volpi has served as Chair of the UAMS Donald W. Reynolds Institute on Aging’s External Advisory Committee since 2012.

Dr. Kevin E. Yaraskevi is the Assistant Director of the Biomedical Mass Spectrometry Research Laboratory, and professor of medicine in Cell biology & Physiology, and physical therapy at Washington University in St. Louis, Missouri. His research group focuses on the pathogenesis and treatments for metabolic, anthropomorphic, and cardiovascular syndromes associated with HIV-infection, advanced age, and cachectic conditions. We utilize interdisciplinary resources and translational approaches to address patient and disease-oriented issues. We utilize stable isotope tracer methods and mass spectrometry, radioisotope tracer methods and positron emission tomography to quantify and characterize defects in substrate utilization and sensing in humans. We utilize several radiologic techniques to quantify adipose, lean, and bone mineral content and distribution in humans. Once metabolic, anthropomorphic, or cardiovascular syndromes have been characterized, we sample human tissues (muscle, fat, CSF) and utilize mass spectrometry-based analyses to identify and characterize protein, complex lipid, DNA, and RNA expression profiles that are dysregulated and may provide mechanistic information. The goal is to understand and describe the underlying pathogenesis for
metabolic, anthropomorphic, and cardiovascular syndromes, so that safe and effective therapeutic interventions can be designed and tested. He serves on: Advisory Committees for the Clinical Nutrition Research Unit and General Clinical Research Center at WUMS; Study Sections for several national and international agencies; Conference Organizing Committees; and the Editorial Board for the American Journal of Physiology. He mentors several junior faculty investigators and post-doctoral research fellows, and is a collaborator/consultant on several research projects within and outside WUMS. **Dr. Yarasheski has served on the UAMS Donald W. Reynolds Institute on Aging’s External Advisory Committee for the 2015-2016 External Advisory Board Review.**

**Dr. Marcus M. Bamman** is the Director of the University of Alabama at Birmingham’s Center for Exercise Medicine, and his interdisciplinary, translational research program involves co-investigators from Neurology, Geriatric Medicine, Cardiology, Surgery, Physical Therapy, and Rheumatology. Dr. Bamman’s research program focuses on skeletal muscle and exercise biology and his primary research objectives span three, inter-related focus areas in human subjects: Objective 1) to determine the cellular and molecular mechanisms driving muscle regeneration following damage or injury, while identifying differences responsible for regeneration impairment in the aging muscle; Objective 2) to better understand the primary etiology of muscle atrophy in acute (burn, trauma) and chronic (sarcopenia, cachexia) conditions; and Objective 3) to determine key processes responsible for myofiber hypertrophy in response to mechanical overload, and to exploit these processes with countermeasures to promote muscle re-growth in atrophied patients. To meet these objectives, his research program is using genomic, proteomic, and in vitro approaches to study the molecular regulation of muscle protein synthesis, proteolysis, and stem (satellite) cell function in humans experiencing atrophy and resistance training-induced hypertrophy. This translational research program takes full advantage of cellular and molecular studies in our Core Muscle Research Laboratory and in vivo functional assessments during clinical trials in the UAB Center for Exercise Medicine. Additional appointments at UAB: Dr. Bamman holds secondary appointments in the Department of Nutrition Sciences and Department of Medicine (Division of Gerontology, Geriatrics, and Palliative Care). In addition to directing the UAB Center for Exercise Medicine, he holds appointments in the Comprehensive Cardiovascular Center, Comprehensive Neuroscience Center, Comprehensive Center for Healthy Aging, Comprehensive Arthritis, Musculoskeletal, Bone, and Autoimmunity Center, Nutrition Obesity Research Center, Comprehensive Diabetes Center, Center for Clinical and Translational Science, and Center for Biophysical Sciences and Engineering. **Dr. Bamman has served on the UAMS Donald W. Reynolds Institute on Aging’s External Advisory Committee for the 2015-2016 External Advisory Board Review.**
## Recognition and Awards (2015/2016)

### LAC:

**Jeanne Y. Wei**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event/Conference/Award</th>
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<tbody>
<tr>
<td>2016</td>
<td>Keynote Speaker, “Management of Heart Failure with Preserved Ejection Fraction (HFPEF) in the elderly,” at Best Care Practices in the Geriatrics Continuum 2016: Navigating successfully into a New Frontier: PA/LTC, Florida Medical Directors Association, Orlando, FL.</td>
</tr>
<tr>
<td>2016</td>
<td>University of Arkansas for Medical Sciences; Graduate School; Mentor Award</td>
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<tr>
<td>2016</td>
<td>Distinguished Speaker, The George Randolph and Patricia Scott Lectureship, Mayo Clinic, Rochester, MN.</td>
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<tr>
<td>2014-Present</td>
<td>Fellow, Gerontological Society of America (GSA), Washington, DC</td>
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<tr>
<td>2014-Present</td>
<td>Secretary, Biological Sci Section, GSA, Washington, DC.</td>
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**Robert R. Wolfe**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event/Conference/Award</th>
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<tbody>
<tr>
<td>2015</td>
<td>Invited Lecture; International Society of Sports Nutrition; R. Harris Keynote Lecture in Basic Science. &quot;Is there an upper limit to protein intake to maximize the anabolic response?&quot; Austin, TX.</td>
</tr>
<tr>
<td>2015</td>
<td>Distinguished Lecture Series, Scholar Award. Texas A&amp;M University</td>
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<tr>
<td>2015</td>
<td>Peter B Raven Lecture, American College of Sports Medicine</td>
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### RC1:

**Paula K. Roberson**

(Leader, RC1; Professor and Chair of the UAMS Department of Biostatistics) was elected to a three-year term on the Board of Directors for the American Statistical Association (ASA). The ASA is the world’s largest community of statisticians and supports excellence in the development, application and dissemination of statistical science in industry, government and academia. Dr. Roberson has been active in the ASA since 1974. Her term runs January 1, 2016 – December 31, 2018.

(Leader, RC1; Professor and Chair of the UAMS Department of Biostatistics) was inducted as an elected fellow by the American Association for the Advancement of Science (AAAS) in February 2015. AAAS, perhaps best known as the publisher of *Science*, is the world’s largest general scientific society, and is dedicated to advancing science, engineering, and innovation throughout the world for the benefit of all people.
Gohar Azhar
2015 University of Arkansas for Medical Sciences; Dean’s Research Incentive Award

Jamie I. Baum
2016 Selected to participate in the Institute of Food Technologists Emerging Leader Network
2016 University of Arkansas, Division of Agriculture Alumni Society Outstanding Advising Award
2015 National Institute on Aging Butler-Williams Scholar
2015 Accepted into the National Institute on Aging Butler-Williams Scholars Program
2015 Outstanding Mentor Award, University of Arkansas

Arny Ferrando

Il–Young Kim
2016 Jan The review paper: “Applications of stable, nonradioactive isotope tracers in in vivo human metabolic research” (Kim IY, SH Suh, I-K Lee, and RR Wolfe) has been featured as a Research Summary in the Journal Experimental & Molecular Medicine Website (http://www.nature.com/emm/latest.html) on Jan 16th 2015.
Elisabet Borsheim


Il-Young Kim


2016 Jan The review paper: “Applications of stable, nonradioactive isotope tracers in in vivo human metabolic research” (Kim IY, SH Suh, I-K Lee, and RR Wolfe) has been featured as a Research Summary in the Journal Experimental & Molecular Medicine Website (http://www.nature.com/emm/latest.html) on Jan 16th 2015.


2016 April The 2016 New Investigator Award, The American Physiological Society Endocrinology & Metabolism Section, American Physiological Society (Selected for the 2016 recipient).

Robert R. Wolfe

2015 Invited Lecture; International Society of Sports Nutrition; R. Harris Keynote Lecture in Basic Science. "Is there an upper limit to protein intake to maximize the anabolic response?" Austin, TX.

2015 Distinguished Lecture Series, Scholar Award. Texas A&M University

2015 Peter B Raven Lecture, American College of Sports Medicine

RCDC:
Gohar Azhar


2015 University of Arkansas for Medical Sciences; Dean’s Research Incentive Award

Jeanne Y. Wei

2016 Keynote Speaker, “Management of Heart Failure with Preserved Ejection Fraction (HFPEF) in the elderly,” at Best Care Practices in the Geriatrics Continuum 2016: Navigating successfully into a New Frontier: PA/LTC, Florida Medical Directors Association, Orlando, FL.

2016 University of Arkansas for Medical Sciences; Graduate School; Mentor Award

2016 Distinguished Speaker, The George Randolph and Patricia Scott Lectureship, Mayo Clinic, Rochester, MN.

2014-Present Fellow, Gerontological Society of America (GSA), Washington, DC

2014-Present Secretary, Biological Sci Section, GSA, Washington, DC.

Robert R. Wolfe

2015 Invited Lecture; International Society of Sports Nutrition; R. Harris Keynote Lecture in Basic Science. "Is there an upper limit to protein intake to maximize the anabolic response?" Austin, TX.

2015 Distinguished Lecture Series, Scholar Award. Texas A&M University

2015 Peter B Raven Lecture, American College of Sports Medicine

PESC:

Jamie I. Baum

2016 Selected to participate in the Institute of Food Technologists Emerging Leader Network

2016 University of Arkansas Division of Agriculture Alumni Society Outstanding Advising Award

2015 National Institute on Aging Butler-Williams Scholar

2015 Accepted into the National Institute on Aging Butler-Williams Scholars Program

2015 Outstanding Mentor Award, University of Arkansas
2015  Travel award from the American Federation for Aging Research

2015-2016  ASN – Chair-Elect, Nutrient-Gene Interactions RIS

Arny Ferrando


Il–Young Kim


2016 Jan  The review paper: “Applications of stable, nonradioactive isotope tracers in in vivo human metabolic research” (Kim IY, SH Suh, I-K Lee, and RR Wolfe) has been featured as a Research Summary in the Journal Experimental & Molecular Medicine Website (http://www.nature.com/emm/latest.html) on Jan 16th 2015.


2016 April  The 2016 New Investigator Award, The American Physiological Society Endocrinology & Metabolism Section, American Physiological Society (Selected for the 2016 recipient).

Susan Klimberg

2016  Professional Recognition – Selected for recognition in “America’s Top Doctors”, Selected by Castle Connolly Medical, Ltd.

2016  Professional Recognition – Selected as a “2016 Top Doctor of Little Rock”, by Castle Connolly Medical, Ltd.

2016  Professional Recognition – Selected to be featured as one of “American’s Top Doctors for Cancer: 2016”, by Castle Connolly Medical, Ltd.

2016  Professional Recognition – Selected as one of the “2016 Best Doctors in Arkansas”. The Best Doctors list is being excerpted in the February 2016 issue of Arkansas Times.


2015 Professional Recognition – Selected for inclusion in “Arkansas’ "Best Doctors" list, compiled by Best Doctors Inc. and published by the weekly newspaper Arkansas Times.

2015 Professional Recognition – One of America’s Top Doctors for Cancer Treatment, 10th Edition, Selected by Castle Connolly Medical, Ltd.


Bryce Marquis

2015 KL2 (KL2TR000063) Amino acid supplementation for improved physical function in geriatric heart failure patients. $185,000

Robert J. Shmookler Reis

2015 Chair, CAVHS, Research & Development Committee
## Minority Research

### A. Activities with minority trainees

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Race / Ethnicity / gender / other issues</th>
<th>Participated in Research/ any award</th>
<th>Publications &amp; areas of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emmanuel Williams Ph.D., post-doc</td>
<td>African American, M</td>
<td>Junior scholar</td>
<td>Mitochondrial &amp; aging vessels</td>
</tr>
</tbody>
</table>

| Elvin Price Pharm D., Ph.D. | African American, M | Yes (PESC) KL2 award ; PRIDE award, GWEP award, Beeson applicant, Jonathan J. Wolfe and Donna M. Wolfe Annual Endowed Award For Faculty Excellence Grants: NIH P30 AG028718 (“Pharmacogenetics in Elderly Patients), ASTA award 15-B-30 (“Novel Genetic Biomarkers to Improve Cardiometabolic Outcomes Among | Pharmacogenetics, health disparity |
Arkansans”


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<tr>
<th><strong>Leybi Ramirez, M.D. Research Associate</strong></th>
<th>Latino American, F</th>
<th>Yes (junior scholar)</th>
<th><strong>Aging Metabolism</strong></th>
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<tr>
<th><strong>Larry Robins, Ph.D. M.D. (c)</strong></th>
<th>African American, M</th>
<th>Yes (summer scholar)</th>
<th><strong>Nitric oxide in aging</strong></th>
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<tr>
<th><strong>Reeshema Britt, MPH (c) pre-doc</strong></th>
<th>African American, F</th>
<th>Yes (junior scholar), APHA abstracts 2015, 2016</th>
<th><strong>Healthcare disparity</strong></th>
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<tr>
<th><strong>Jennifer Vincenzo Ph.D., Assistant professor</strong></th>
<th>Latino American, F</th>
<th>Yes, GWEP award</th>
<th><strong>Physical rehabilitation and falls</strong></th>
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**T. Washington Assistant professor Ph.D.**

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<tr>
<th>African, American, M</th>
<th>PESC Grants: American Biosciences Institute (Cancer Cachexia and Leucine Supplementation), R15 AR064481 (Engineering a Muscle Mimetic Biomaterial)</th>
</tr>
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</table>

**Skeletal muscle inflammation, molecular biology**


Western diet-induced obesity and partially restored by moderate physical activity in mice. Physiological reports, 3(7), p.e12470.


11, No. 3, p. 18).


<table>
<thead>
<tr>
<th>Jennifer Vincenzo Ph.D., Assistant professor Latino American, F</th>
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<tbody>
<tr>
<td>2015, Adopt-A-Doc Award</td>
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<td>2016, Junior Faculty Development Award</td>
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<td><strong>Active Grants:</strong></td>
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<tr>
<td>1. HRSA, DHHS 2016 GWEP award</td>
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</table>

**Physical rehabilitation and falls**


B. Research focusing on hypotheses dealing with minority health

Elvin Price, Ph.D. has received support to participate in the NHLBI funded Programs to Increase Diversity among Individuals Engaged in Health-Related Research (PRIDE) Cardiovascular Genetic Epidemiology program at the Washington University in St. Louis School of Medicine Division of Biostatistics. Dr. Price received a prestigious UAMS Translational Institute KL2 scholar award. As a KL2 scholar Dr. Price received a competitive Arkansas Science and Technology Authority (ASTA) Basic Science Research grant. He is also currently a Geriatric Workforce Enhancement Program (GWEP) grant recipient and is planning to reapply for the Beeson award.

Dr. Price has been involved in healthcare disparity research as part of the PRIDE program when he helped analyze data from two of the NHLBI’s Family Blood Pressure Program studies: 1) The Hypertension Genetic Epidemiology Network (HyperGEN) and 2) The Genetic Epidemiology Network of Arteriopathy (GENOA). The data constituted 2.5 Million genetic variants from approximately 3000 subjects respectively from both studies. Using these rich data sets, he identified novel candidate genes that could be plausible contributors to the pathogenesis of hypertension in the elderly with differential expression between Caucasians and African Americans. His hypothesis is that candidate polymorphisms in genes (LXRA, THR, ESR1, NR6A1), might influence the pharmacologic responses in the elderly African Americans. This could partially explain the higher morbidity and mortality that African American populations experience with hypertensive heart disease and end-organ damage.
He is currently involved in developing the “The Arkansas Family Heart Study” that will recruit ethnically diverse patients statewide to help develop personalized medicine approaches that reduce the burden of hypertension and help reduce cardiovascular healthcare disparity in the State of Arkansas.

**ReeShema T. Britt, M.P.H (c)** has been a junior scholar. The focus of her master’s degree in on Health Behavior and Health Education in minority populations. She is also interested in rural health and health policy. Her abstract, the “Impact of GMOs on Health Outcomes for African Americans”, was presented at the American Public Health Association 143rd Annual Meeting in Chicago, Illinois on November 1, 2015. A more recent abstract, “Raising awareness in the Elderly: Nutritional Needs for African Americans”, has been accepted for Roundtable presentation at the APHA, 2016 meeting in Denver.

**Emmanuel Williams, Ph.D.** has been a junior scholar and is participating in the assessment of biometrics & body composition of adults, the young and the elderly. His primary focus is on community dwelling African Americans residing in South Central Arkansas and the underserved Delta Region in the Eastern portion of Arkansas.
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
Debra Saliba, MD, MPH  
Director, The Anna and Harry Borun Center for Gerontological Research  
Email: saliba@rand.org

Administrator:
Lucio Arruda  
Email: larruda@mednet.ucla.edu

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  
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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  
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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
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David Geffen School of Medicine at UCLA
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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  
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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:

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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:
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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 10 (JULY 2015 – JUNE 2016)

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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<tr>
<td>Theodoros Kelesidis, MD, PhD</td>
<td>Ex vivo/in vitro studies of novel therapeutics for HIV-related accelerated aging</td>
<td>To define the direct effects of oxidized lipoproteins (present in chronic treated HIV) on mechanisms important for aging such as cellular senescence, apoptosis and mitochondrial function using T cells from HIV-1-infected and uninfected older persons.</td>
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<tr>
<td>Ramesh Halder, PhD</td>
<td>Impact of Aging on Hydrocarbon Oil-induced Pulmonary Vascular Inflammation and Alveolar Hemorrhage</td>
<td>Does the age of mice influence the immune and clinical-pathological outcome of exposure to certain hydrocarbon oils? Are older mice better models to study immune inflammatory effects of hydrocarbon oils, and for inflammatory disorders that are generally more severe and have poorer outcomes in elderly humans?</td>
</tr>
<tr>
<td>Zhenqi Zhou, PhD</td>
<td>The role of DJ1 in regulating metabolic homeostasis, adiposity, and inflammation with aging</td>
<td>Test the role of DJ1 in adipogenesis and inflammation in white adipose tissue during aging. (DJ1 is a loss-of-function gene mutation in one of the familial Parkinson’s genes, DJ1. This mutation is associated with a wasting phenotype marked by a reduction in muscle and adipose tissue mass) Investigate the role of DJ1 in adipose tissue browning with aging.</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 1750 patients in 4 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

   **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 health care 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.
<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>FORMER AWARDEES</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. |

UCLA OAIC CDA Awardees (Current Cycle 2011 – Present)
IV. PUBLICATIONS (2015 – 2016)


20. Hoffman RM, Lake JE, Wilhalme HM, Tseng CH, Currier JS. Vitamin D Levels and Markers of Inflammation and Metabolism in HIV-Infected Individuals on Suppressiv


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)
Lee A. Jennings, MD, MS

- UCLA Research Conference on Aging, Poster Competition Winner, May 2016
- Junior Faculty Hamolsky Award Finalist, Society of General Internal Medicine, 2015
- Outstanding Research Mentor, UCLA Medical Student in Aging Research (MSTAR) Program, 2015
- Merck/American Geriatrics Society, 2016 New Investigator Award

Jordan Lake, MD

- Rising STAR Award, The University of Texas System, 2016

David B. Reuben, MD

- National Associate, National Academies of Sciences, Engineering, and Medicine - Health and Medicine Division

Catherine A. Sarkisian, MD, MS

- Best Poster Award in the category of Behavioral and Social Sciences, at the UCLA Research Conference on Aging, presented on May 10th, 2016.
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 2015-2016:

- **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.
Linguistic and Cultural Adaptation of the Geriatric Depression Scale and the PROMIS® Physical Function Item Bank to be used in Under-Served African American and Latino Elders (PI: Paz).
OAIC RRC facilitated recruitment through the Theresa Lindsay Multi Purpose Senior Center to recruit and the Mexican American Opportunity Foundation to recruit African Americans and Latino older adults.

Publications (2015-2016)


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
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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:**
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The Research Education Component (REC) identifies, supports, and nurtures talented junior investigators who will become national leaders in aging research through the REC Scholars Program and Advanced Scholars Program. The REC 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 REC 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 Education Component also sponsors a diversity supplement program to increase the number of faculty members from underrepresented and diverse backgrounds conducting aging research at UCSF.

Current REC Scholars:
Elizabeth Dzeng, MD, MPH, Assistant Professor, Division of General Internal Medicine
Dr. Dzeng was chosen because of her innovative research focused on communication about end of life treatments in older adults. As a REC scholar she will conduct mixed methods research on moral distress among physicians regarding futile treatments in older adults at the end of life. She aims to explore the influence of hospital culture on ethical thinking and end of life practices in older adults.

Jane Jih, MD, MPH, Assistant Professor, Division of General Internal Medicine
Dr. Jih is a General Internist in the UCSF Division of General Internal Medicine and a GEMSSTAR R03 awardee. Her work examines the contribution of food insecurity to multiple chronic conditions in diverse older adults. As a REC scholar, she will use the Health and Retirement Study (HRS) to determine: 1) the prevalence of food insecurity among older adults with multi-morbidity; 2) sociodemographic and health predictors of food insecurity; and 3) associations of food insecurity with functional limitations, health care costs, and family structure.

Current REC Advanced Scholars:
Elena Portacolone, PhD, MBA, MPH, Assistant Professor of Nursing
Dr. Portacolone is a Social Scientist in the School of Nursing’s Institute for Health & Aging who received an NIA K01 in September 2015. As a REC Advanced Scholar she will conduct a mixed-methods study to examine the lived experience of older adults from ethnic/racial minorities living alone with cognitive impairment. Dr. Portacolone is collecting data on social isolation of older residents in high-crime neighborhoods focusing on: 1) factors associated with social isolation; 2) the optimal methodology for recruiting truly isolated older adults; and 3) effects on participants of receiving a diagnosis of cognitive impairment.
**Raquel Gardner, MD.** Assistant Professor, Department of Neurology
Dr. Gardner is a Neurologist and Beeson Scholar who has developed an innovative focus studying the predictors and outcomes after traumatic brain injury (TBI) in older adults. As a REC Advanced Scholar, she will use the multi-site Transforming Research and Clinical Knowledge in TBI study and the Brain Aging in Veterans study to define cognitive, motor, mood/behavioral, and functional trajectories and predictors of trajectories in 1) older adults with acute TBI and 2) older adults with remote TBI.

**Anne Suskind, MD, MS.** Assistant Professor, Department of Urology
Dr. Suskind is a Urologist, a UCSF K12 awardee and a GEMSSTAR R03 awardee. Her innovative research focuses on outcomes in older adults undergoing urologic procedures. As a REC Advanced Scholar, she will use the Minimum Data Set (MDS) linked to Medicare data to examine outcomes following common urologic procedures in nursing home residents in the U.S. She aims to study 1) immediate (30-day) outcomes following urologic procedures (e.g., cystoscopy, transurethral resection and incision of the prostate, prostate biopsy, etc.) among nursing home residents and determine factors associated with outcomes; and 2) long-term (1-year) functional and cognitive outcomes following common urologic procedures among nursing home residents and determine factors associated with outcomes.
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.

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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 three External Projects. The first external project comprises a study done by Nursing PhD student Lauren Hunt evaluating pain in older adults with dementia, using data from the National Health and Aging Trends Study, with mentoring and support provided by Drs. Covinsky and Yaffe. Findings from this study were published in the Journal of the American Geriatrics Society. The second external project is a continuation of a series of epidemiologic studies by Dr. Amy Byers on late-life suicidal behavior in older veterans, funded by an IIR from the VA CSR&D service and by an R01 from NIMHD. Dr. Covinsky provided Dr. Byers support with design and interpretation of her studies to incorporate geriatric and functional considerations, while Dr. Boscardin from the RDAC core provided assistance in the use of the National SPAN, Veteran Suicide Archive, NPCD, and CMS data to conduct the first comprehensive longitudinal examination of suicidality in older Veterans. The third external project is an ongoing R01 by Margot Kushel, MD of the UCSF Division of General Internal Medicine evaluating geriatric syndromes in a cohort of older homeless adults; Dr. Walter has provided Dr. Kushel with extensive methodologic advice and support on measurement and interpretation of geriatric syndromes and conditions. Finally, we have also provided external project support to the San Francisco VA Health Care System’s QUERI program, which has several projects on which we have provided close advice and support.

Core Leaders:
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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:
**Rebecca Brown, MD**: Factors Associated with Early Versus Late Life Homelessness in a Cohort of Older Homeless Adults

**Meredith Greene, MD**: Addressing Medical Complexity for Older Adults Living with HIV infection: Development of an Integrated HIV Geriatric and Palliative Care Program

**Julene Johnson, PhD**: a) Music as Symptom Management: a Pilot Study; b) The Effects of the Arts on Health, Function, and Cognitive Outcomes – Secondary Data Analysis

**Margot Kushel, MD**: Symptoms and Their Management in Older Homeless Adults – a Qualitative Study

**Eleni Linos, MD, DrPH**: Involving Older Adults in Decision Making for Skin Cancer

**Carmen Peralta, MD**: Associations of Blood Pressure with Adverse Outcomes in Persons 65 Years who are Considered to be in the Complex Aging Process

**Christine Valdez, PhD**: Spanish Translation and Adaptation of a Trauma Cognitions Measure for Posttraumatic Stress Disorder: Validation in Latinos across the Adult Lifespan.

**Maya Vijayaraghavan, MD, MAS**: Development of a Tobacco Control Intervention for Older African American Homeless Adults

**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 (ImPacTT): A Pilot Study

Previous 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

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

Core Leader:
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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
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: Year 3**

In Year 3, we designated 3 External Projects that merited particularly close support and which reflect the key aims of our resource cores:

The first external project comprises a study done by Nursing PhD student Lauren Hunt evaluating pain in older adults with dementia, using data from the National Health and Aging Trends Study, with mentoring and support provided by Drs. Covinsky and Yaffe. Findings from this study were published in the Journal of the American Geriatrics Society.

The second external project is a continuation of a series of epidemiologic studies by Dr. Amy Byers on late-life suicidal behavior in older veterans, funded by an IIR from the VA CSR&D service and by an R01 from NIMHD. Dr. Covinsky provided Dr. Byers support with design and interpretation of her studies to incorporate geriatric and functional considerations, while Dr. Boscardin from the RDAC core provided assistance in the use of the National SPAN, Veteran Suicide Archive, NPCD, and CMS data to conduct the first comprehensive longitudinal examination of suicidality in older Veterans.

The third external project is an ongoing R01 by Margot Kushel, MD of the UCSF Division of General Internal Medicine evaluating geriatric syndromes in a cohort of older homeless adults; Dr. Walter has provided Dr. Kushel with extensive methodologic advice and support on measurement and interpretation of geriatric syndromes and conditions. Finally, we have also provided external project support to the San Francisco VA Health Care System’s QUERI program, which has several projects on which we have provided close advice and support.
C. Pilots:

**Year 3 Pilots: 2015-2016**

**PES-1: Factors Associated with Early Versus Late Life Homelessness in a Cohort of Older Homeless Adults** (Project Leader: Rebecca Brown, MD, Assistant Professor, UCSF Division of Geriatrics and San Francisco VA Medical Center). The aim of this study is to describe life course events in a cohort of older homeless adults, and to identify characteristics associated with experiencing a first episode of homelessness in early versus later adulthood. This pilot has been using data from a large cohort study of homeless adults aged 50 and older, the HOPE HOME Study (Health Outcomes in People Experiencing Homelessness in Older Middle age), which includes extensive data about key life course events that may contribute to homelessness.

**PES-2: Addressing Medical Complexity for Older Adults Living with HIV infection: Development of an Integrated HIV Geriatric and Palliative Care Program** (Project Leader: Meredith Greene, MD, Assistant Professor, UCSF Division of Geriatrics and San Francisco VA Medical Center) Within the San Francisco General Hospital’s Positive Health Program “Ward 86,” this study seeks to develop an integrated geriatric and palliative care clinic and study its outcomes to address this knowledge gap. It is examining the impact of geriatric and palliative care services on patient reported outcomes such as satisfaction with care and quality of life, as well as the impacts on medication prescribing and service utilization within this large urban clinic.

**PES-3: 3a) Music as Symptom Management: a Pilot Study.** This study examines the effect of an iPad application that involves music-associated autobiographical memory as a possible intervention for symptom management in severely ill patients receiving palliative care services.  
**3b) The Effects of the Arts on Health, Function, and Cognitive Outcomes – Secondary Data Analysis.** This study utilizes the new Arts and Culture module from the Health and Retirement Study to examine the cross-sectional associations between engagement in various arts activities and health, function, and cognitive outcomes in a sample of approximately 2,000 older adults, including those from diverse racial/ethnic backgrounds.  
(Project Leader for both pilots: Julene Johnson, PhD, Cognitive neuroscientist and Professor at the UCSF Institute for Health & Aging)

**PES-4: Symptoms and Their Management in Older Homeless Adults – a Qualitative Study.** (Project Leader: Margot Kushel, MD, Professor of Medicine in the Division of General Internal Medicine at the Zuckerberg San Francisco General Hospital and Trauma Center). This study is using in-depth interviews to examine how older homeless adults are affected by their symptoms (shortness of breath, constipation/diarrhea, pain, insomnia, fatigue, guilt, regret), and their management strategies (including but not limited to their use of the health care system (primary care, emergency care), alternative and complementary strategies, substance use, environmental changes, etc). It also examines their ideas as to what would be most useful in mitigating symptomatology. Dr. Kushel has had the opportunity to engage learners at various stages in her research and is partnering with medical students to do this research. By involving trainees, she hope to engage trainees in aging research.
PES-5: Involving Older Adults in Decision Making for Skin Cancer. (Project Leader: Eleni Linos, MD, DrPH, Assistant Professor, Department of Dermatology). More patients are diagnosed with basal and squamous cell carcinoma (collectively termed non-melanoma skin cancer or NMSC) in the US than all other cancers combined: more than 3.6 million NMSCs vs. 1.7 million other cancers each year. Over a quarter of patients report problems related to treatment of NMSC and over 100,000 NMSCs are treated annually in persons who ultimately die within one year. The central hypothesis of this research is that there is significant procedure overuse for NMSC in patients with limited life expectancy, and that patients want to know the risks and benefits associated with management options including active surveillance. The rationale underlying this research is that these are ubiquitous, slow-growing tumors, and that patients should be informed of the risks and benefits of all management options, in order to make choices consistent with their clinical characteristics, values and preferences. This study aims to understand expert and practicing physicians’ perspectives on skin cancer care at the end of life, which will lay the groundwork for future funding to develop and test the effect of decision tools on treatment utilization and patient-reported outcomes in patients with limited life expectancy.

PESC-6: Associations of Blood Pressure with Adverse Outcomes in Persons 65 Years who are Considered to be in the Complex Aging Process. (Project Leader: Carmen Peralta, MD. Associate Professor, Division of Nephrology, UCSF Department of Medicine). The long-term goal of this study is to reliably identify elderly persons in whom blood pressure treatment is beneficial and those in whom treatment is ineffective, by defining subpopulations of similar health status. Specifically, the study aims to identify factors from four domains (functional, cognitive/mental, self-rated health, and physiologic) that can identify elderly persons in whom high blood pressure is strongly associated with higher risk for death and cardiovascular events, using data from three NIH-funded cohorts: Cardiovascular Health Study (CHS), Health Aging and Body Composition (Health ABC) and Sacramento Area Latino Study on Aging (SALSA).

**Partnership with Tideswell™ at UCSF**

PESC-7: Paired Integrative Home Exercise for Seniors with Dementia and their Caregivers: A Pilot Study (Project Leader: Wolf Mehling, MD. Associate Clinical Professor, UCSF Department of Family and Community Medicine). Few resources are available to help people living in the community with dementia maintain independence and quality of life. This study has adapted and pilot-tested an integrative exercise program called PLIÉ, originally designed for the adult day care setting, so that it can be performed at home in pairs by affected individuals and caregivers (Paired PLIÉ). Paired PLIÉ is a unique integrative exercise program that could be widely disseminated at relatively low cost and could substantially improve function and quality of life in people living with dementia and their care partners.

PESC-8: Social Isolation of Older Americans Living in High-Crime Neighborhoods: Root Causes and Possible Solutions. (Project Leader: Elena Portacolone, PhD, MBA, MPH. Assistant Adjunct Professor, UCSF Institute for Health & Aging). Very little is known about the experience of older residents of high-crime neighborhoods. It is important to expand our knowledge on this population because older residents of high-crime neighborhoods are likely to be socially isolated and at risk for poor health outcomes. This study aims to build knowledge of culturally-sensitive clinical interventions to (1) improve understanding of isolated elderly; and (2) identify potential strategies that will increase the quality of life of this vulnerable population.
PESC-9: Improving Palliative Care Access in Nursing Homes Through Technology (ImPAcTT). (Project Leader: Caroline Stephens, PhD, MSN, APRN, Assistant Professor, Community Health Sciences, UCSF School of Nursing). Nursing homes are increasingly becoming the place of care and site of death for frail older adults living and dying from multiple chronic illnesses. This vulnerable population has had little access to formal palliative care expertise outside of hospice services. Palliative care services have not kept pace with the growing demand, so alternative workforce strategies are needed to expand the reach of palliative care to nursing homes. Telehealth, or remote monitoring of patients through information and communication technologies, may allow palliative care specialists to efficiently reach individuals with advanced illness and unmet symptom management needs.

Supplemental Funding with the Center for Aging in Diverse Communities

PESC-10: Spanish Translation and Adaptation of a Trauma Cognitions Measure for Posttraumatic Stress Disorder: Validation in Latinos across the Adult Lifespan. (Project Leader: Christine Valdez, UCSF Postdoctoral Scholar). The PI has co-developed the Posttraumatic Information Processing Scales (PIPS), a measure of trauma cognitions that assesses positive and negative trauma cognitions linked to trauma-focused therapy goals. The PIPS is undergoing preliminary validation in English-speaking student and online samples. This study will translate the PIPS into Spanish and validate it with a Latino population that is at high risk for trauma and negative reactions. The aims of this study are to: 1) translate and adapt the PIPS for Spanish-speaking therapy clients; 2) conduct a psychometric evaluation of the PIPS with Latino older adults seeking specialized clinical services for trauma-focused therapy; and 3) pilot test the use of PIPS with Latino clients in trauma-focused therapy.

PESC-11: Development of a Tobacco Control Intervention for Older African American Homeless Adults. (Project Leader: Maya Vijayaraghavan, MD, MAS. Assistant Professor, UCSF San Francisco General Division of General Internal Medicine). The aim of this study is to develop an intervention to increase smoking cessation among older, African American homeless smokers. We will recruit a sub-group of 30 African American current smokers from an established cohort of 350 homeless adults, of whom 80% are African American (The Aging Homeless Cohort Study, PI, Margot Kushel, MD), to conduct in-depth, semi-structured interviews to identify new tobacco control strategies for this population.
Section III. Career Development: funding subsequent to Pepper pilot funding

**Research Career Development Core (RCDC) / Research Education Component (REC) Scholars**

**Sei Lee, MD, MAS**  
VA HSR&D Locally Initiated Project grant, Understanding and Improving Diabetes Care in VA Community Living Centers  
R01 AG047897, NIA/NIH, Developing prognostic models for life expectancy and geriatric outcomes

**Alex Smith, MD, MPH**  
K23 AG040772, Late Life Disability: Epidemiology, Symptoms, Quality of Life  
R01 AG047897, NIA/NIH, Developing prognostic models for life expectancy and geriatric outcomes  
National Palliative Care Research Center, Prognosis Communication with Disabled Elders

**Brie Williams, MD, MS**  
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 – 2015  
National Palliative Care Research Center Pilot Grant, Bringing Advanced Care Planning to Prisons – 2016

**Ryan Greysen, MD**  
KL2 National Center for Advancing Translational Sciences  
K23 AG045338 Functional, Cognitive, and Social Vulnerabilities and Hospital Readmission

**Jennifer Lai, MD**  
K23 AG048337 Frailty and Functional Status in Older Liver Transplant Patients

**Raquel Gardner, MD**  
R21 HD089081, NICHD, Defining Clinical Trajectories after Traumatic Brain Injury  
K23 NS095755, NINDS, Traumatic Brain Injury And The Aging Brain: Predictors Of Clinical Trajectories

**Jane Jih, MD, MPH**  
R03 AG050880 (GEMSSTAR), NIH/National Cancer Institute, Identifying and Assessing Food Insecurity In Older Diverse Primary Care Patients
UCSF Pilot in Integrative Medicine (Co-I), Osher Center. Pilot RCT of integrative nutritional counseling to improve diet self-management among Chinese Americans with type 2 diabetes

Anne Suskind, MD, MS  
SUFU Research Foundation, The Study of Overactive Bladder and Urgency Urinary Incontinence  
R03 AG050872 (GEMSSTAR), NIH-NIA, Immediate and Long-Term Outcomes of Common Urologic Procedures in Nursing Home Residents

Elena Portacolone, PhD, MBA, MPH  
K01AG04910201, NIA, Living Alone in Older Age with Cognitive Impairment Alzheimer’s Association, Living Alone in Older Age with Alzheimer’s disease

Pilot and Exploratory Studies Awardees

Rebecca Brown, MD  
KL2, CTSI, Epidemiology and Outcomes of Premature Geriatrics Syndromes  
K23 AG045290, Epidemiology and Outcomes of Premature Geriatric Syndromes  
QUE 15-283, Department of Veterans Affairs Quality Enhancement Research Initiative (QUERI), Implementation of Standardized Measurement of Functional Status for Older Veterans.

Meredith Greene, MD  
Tideswell at UCSF, Addressing Medical Complexity for Older Adults Living with HIV infection: Development of an integrated HIV Geriatric and Palliative Care Program

Julene Johnson, PhD  
AROHA-2015-13180, Aroha Philanthropies, Roadmap to Accelerating Arts-Based Research for Older Adults

Margot Kushel, MD  
R01 AG041860, Aging among the homeless: geriatric conditions, health and healthcare outcomes  
R01 AG050630, Family-assisted Housing for Older Homeless Adults  
K24 AG046372, Mentoring Researchers in Aging in Vulnerable Populations

Eleni Linos, MD  
UCSF Cancer Center Impact grant, Melanoma Prevention Using Social Media

Rebecca Sudore, MD  
Tideswell at UCSF Grant Award, Developing a toolkit to empower IHSS workers to engage disenfranchised older adults in advance care planning – 2015  
National Palliative Care Research Center Pilot Grant, Developing a Toolkit to Empower Medicaid-Paid Caregivers to Manage Common Palliative Care Symptoms – 2016  
Gordon and Betty Moore Foundation Award, English and Spanish advance directives customized for all 50 United States – 2016
OptumCare License Agreement, Evaluating the effectiveness of OptumCare collaboration using PREPARE’s new reporting functions to measure uptake – 2016
Section IV. 2015-2016 Publications:


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 performed their most recent site visit in March 2016.

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)
Ken Covinsky, MD, MPH
Harold S. Luft Award for Mentoring in Health Services and Health Policy Research – 2015

Louise Walter, MD
Inducted into the UCSF Chapter of the Alpha Omega Alpha Honor Medical Society – 2016
Named a Top Doctor in Marin County for Geriatrics in 2016

Kristine Yaffe, MD
Invited to serve on the Alzheimer Association National Medical Scientific, 2015
American College of Psychiatrists Award for Research in Geriatric Psychiatry, presented at the National Academy of Sciences Symposium on Aging, 2015

Mike Steinman, MD
Mid-career Mentoring Award, Society of General Internal Medicine – 2015
Appointed to the Diabetes Overtreatment Expert Work Group convened by the National Center for Quality Assurance (NCQA) and Mathematica, Inc. – 2016
Appointed to the Research Committee of the American Geriatrics Society – 2016

Christine Ritchie, MD, MSPH
Selected as member of the Palliative Care and End of Life Standing Committee of the National Quality Forum (NQF) – 2016
Named a Top Doctor in Marin County for Geriatrics in 2016

Brie Williams, MD, MS
Nominee, The Distinction in Mentoring Award, UCSF – 2015

Alex Smith, MD, MPH
Best scientific poster award at the Annual Older Americans Independence Centers annual meeting – 2016

Sei Lee, MD, MAS
Selected as the Vice-Chair for the American Geriatrics Society Quality and Performance Measurement Committee (AGS-QPMC) – 2016

Rebecca Brown, MD
American Geriatrics Society Outstanding Junior Investigator of the Year Award - 2016
American Geriatrics Society Outstanding Junior Research Manuscript Award - 2016
Society for General Internal Medicine Best Published Research Award - 2016
Ryan Greysen, MD
Society of Hospital Medicine Fellow in Hospital Medicine (FHM) – 2015
Society of Hospital Medicine Junior Investigator Award (Inaugural) – 2015
Society of General Internal Medicine Junior Investigator of the Year – 2016
American Geriatrics Society Outstanding Junior Investigator – 2016

Rebecca Sudore, MD
AGS Outstanding Scientific Achievement for Clinical Investigation Award – 2015
Inducted into American Society for Clinical Investigation – 2016
PREPARE website was a winning innovation in the Let’s Get Healthy California Innovation Challenge – 2016
PREPARE website named UCSF Dept of Medicine Tech Challenge's Top 12 ideas – 2016

Jennifer Lai, MD
American Geriatrics Society New Investigator Award – 2015
Clinical Science Career Development Award by the American Society of Transplantation – 2016

Joaquin Anguera, PhD
U CSF Young Innovator Award - 2015

Julene Johnson, PhD
Invited speaker at the National Advisory Council on Aging for the Task Force on Minority Aging at the NIA – 2016

Margot Kushel, MD
Invited speaker at the National Association of Science Writers Annual meeting in Cambridge, MA – 2015

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

Jane Jih, MD, MPH
Selected to participate in National Institute on Aging Butler-Williams Scholars Program - 2015

Anne Suskind, MD, MS
AGS New Investigator Award – 2016

Eleni Linos, MD
Cancer Center Impact Award – 2016
Nominated Department Diversity Leader for Dermatology
Assistant Editor, JAMA Dermatology

Meredith Greene, MD
Plenary speaker for the New York State Clinical Conference on HIV and Hepatitis C – 2016

Caroline Stephens, RN, PhD, GNP
Best Health Information Technology Study Award - AGS Presidential Poster Session - 2015
General Brief Description of Minority Activities:
The UCSF OAIC developed an active collaboration with the UCSF Center for Aging in Diverse Communities (CADC)—an NIA Resource Center for Minority Aging Research—led previously by Dr. Eliseo Perez-Stable and since 2015, by Dr. Anna Napoles. After the launch of the UCSF OAIC, Dr. Covinsky presented the mission and work of the UCSF OAIC to the CADC faculty and trainees, and we developed a process to make OAIC core resources available to the CADC. We collaborated with the CADC on their pilot studies RFA in 2014, supporting Dr. Joaquin Anguera, and in 2015, supporting Drs. Maya Vijayaraghavan and Christine Valdez. In 2016, we are collaborating with the CADC for the third year to co-fund a pilot award to Dr. Maria Ventura focused on dance therapy to address Parkinson’s Disease symptoms in ethnically diverse patients.

Minority Trainees/Investigators:
The RCDC and PESC seek to encourage diversity among investigators by outreach programs that encourage applications from women and minority investigators. In year 3, all five of the RCDC funded investigators and 8 of the PESC funded investigators were women. One of our pilot awardees is from a group included in the NIH definition of persons underrepresented in biomedical research. (Dr. Peralta-Hispanic/Latina.) Over the life of our Center, 82% of our PESC awardees have been women and 24% under-represented minorities. Among our RCDC scholars/advanced scholars, 75% have been women and 17% under-represented minorities.

Minority-Related Research Projects:
PESC Awardee, Christine Valdez, PhD, was awarded a joint award between the UCSF Pepper Center and the UCSF Center for Aging in Diverse Communities in 2015. Dr. Valdez has co-developed the Posttraumatic Information Processing Scales (PIPS), a measure of trauma cognitions that assesses positive and negative trauma cognitions linked to trauma-focused therapy goals. The PIPS is undergoing preliminary validation in English-speaking student and online samples. This study is translating the PIPS into Spanish and validating it with a Latino population that is at high risk for trauma and negative reactions. The aims of this study are to: 1) translate and adapt the PIPS for Spanish-speaking therapy clients; 2) conduct a psychometric evaluation of the PIPS with Latino older adults seeking specialized clinical services for trauma-focused therapy; and 3) pilot test the use of PIPS with Latino clients in trauma-focused therapy.

PESC Awardee, Maya Vijayaraghavan, MD, MAS, was awarded a joint award between the UCSF Pepper Center and the UCSF Center for Aging in Diverse Communities in 2015. Dr. Vijayaraghavan is developing an intervention to increase smoking cessation among older, African-American homeless smokers. She is recruiting a sub-group of 30 African-American current smokers from an established cohort of 350 homeless adults, of whom 80% are African-American (The Aging Homeless Cohort Study, PI, Margot Kushel, MD), to conduct in-depth, semi-structured interviews to identify new tobacco control strategies for this population.
In Year 4, the UCSF OAIC will co-fund a joint award with the UCSF Center for Aging in Diverse Communities to Maria Ventura, PhD. Dr. Ventura’s project will seek to describe perceptions of community-based dance among diverse older adults with Parkinson’s Disease (PD) and identify barriers and facilitators to dance engagement. She will describe attitudes, beliefs, and opinions about dance in racial/ethnic minorities. Four small focus groups, each consisting of 5 participants from the same racial/ethnic group (e.g., African-American, Asian, Latino, and White), will be conducted with men and women with PD aged 50-80. Questions will focus on experiences and knowledge of dance, and beliefs about the benefits of dance. This will identify racial/ethnic preferences for specific dance styles and identify strategies to engage racial/ethnic minorities in alternative arts-based treatment strategies such as dance.

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.

Alex Smith MD, MPH, a Years 1 & 2 RCDC Advanced Scholar, 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 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, many of the RCDC scholars and PESC awardees are conducting research using populations or datasets that include large proportions of women and ethnic minority subjects.
2015-2016 Publications Pertaining to Minority Research:


Previous Year Publications Pertaining to Minority Research:

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 function 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
The current Junior Scholars are:
Brian Ahn, Ph.D., ARNP, ANP-BC  hcahn@ufl.edu
Assistant Professor
College of Nursing
Department of Family, Community and Health System Science

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

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

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

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

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

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

Clinical Research Core (RC 1)
Leader: Steve Anton, Ph.D.
Phone: 352-273-7514  Fax: 352-294-5836  Email: santon@ufl.edu

Co-Leader: Marco Pahor, M.D.
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/or VA funding, who also have established track records as mentors for career development, lead each one of these goals.

Metabolism and Translational Science Core (RC 2)
Core Leader: Christiaan Leeuwenburgh, Ph.D.
Phone: 352-294-5825 Fax: (352) 294-5836 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 (Western blot and Quantitative-PCR, quantitative-Real-Time PCR, enzyme-linked immunosorbent assays, multiplex immunoassays), high resolution respirometry, and selected measures of metabolism (i.e., ATP measures and enzymes of metabolism) that will address a set of genetic and biological themes focused on causes for sarcopenia and disability. The Core utilizes this state-of-the-art technology to determine specific mechanisms of sarcopenia and the cause of reduced physical function present in elderly populations. The Core provides support for numerous independently funded studies, development projects, pilot studies and exploratory studies. Analyses of levels of biomarkers or cell signaling molecules will help to identify specific biological pathways of aging implicated in the development of sarcopenia. If the precise mechanisms underlying age-associated cellular deterioration can be identified, it will explain the loss of muscle mass and function with age and provide us with potential targets for intervention. In this context, we will also test if specific rehabilitation, physical activity and dietary interventions can attenuate biological pathways leading to sarcopenia and functional impairment. In addition, the Core supports preclinical phenotyping of various domains of function include: Cognition, Motor, Sensory, Hearing. Each of these measures is currently in use in our laboratories and are sophisticated procedures requiring expert oversight and the use of highly trained technicians. These assessment methodologies are conceptually similar to those used in humans and highly translatable. 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 using The UF & Shands Academic Health Center’s new electronic medical record system (EPIC), which has gone live with new modules planned through the next few years. This includes the implementation of a clinical data warehouse (CDW). The CDW is the foundation for the development of a research data repository whereby researchers and junior scholars and faculty may have unfettered access to anonymized data for clinic research.

Data Science Core (RC 6)
Core Leaders: Todd Manini, Ph.D. and Sanjay Ranka, Ph.D.
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)
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The Pilot/Exploratory Studies Core serves to develop key information needed to select and design future, original and independently funded studies that can advance our insight into sarcopenia and prevention of disability in older Americans. Specifically, the core fosters the Pilot and Exploratory studies by ensuring the availability of optimal infrastructure, environment, funding, expertise, and instrumentation. Pilot and Exploratory studies foster Junior Scholars in their efforts to develop research careers in aging by providing opportunities for meaningful participation in well-designed research studies and by collecting the needed preliminary data for independent research applications. Furthermore, these studies will allow investigators already accomplished in aging research to gather data that will extend and broaden their focus of research. Finally, these studies will also be a vehicle to encourage and facilitate experienced investigators traditionally working in other research fields to focus on aging.

B. RESEARCH

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

The current research development projects are:

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

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

The past research development projects are:

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

The loss of muscle mass occurring with aging is accompanied by concomitant increases in whole body adiposity and excessive storage of lipids around and into the 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.

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 establish test-retest reliability of these techniques in healthy older and PAD patients. The completion of project will provide the CRC a thorough evaluation of O2 delivery and utilization in a single package thus reducing participant burden while maximizing cost effectiveness.

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

This development project is evaluating interventional models that modulate adiposity in aged rats for assessing effects on physical function, inflammation, oxidative stress, apoptosis, and sarcopenia. This study will set the basis and methodologies for preclinical testing of other weight lowering interventions on relevant age-related outcomes. The central hypothesis of this development project is that increased adiposity with age contributes to two age-related outcomes: 1) a decline in physical performance; and 2) changes in muscle quality as measured by increased oxidative stress, inflammation, and subsequent apoptosis in skeletal muscle. We have established several relevant interventional strategies to reduce or increase adiposity in the Fischer 344/Brown Norway (F344xBN) rat, a well-established animal model of aging. F344xBN rats demonstrate declining physical performance, occurring in the context of a steady increase in body weight and adiposity into early senescence followed by a decline, similar to what occurs in humans (1). We will employ one paradigm that elevates adiposity (fat-feeding) and should further reduce physical performance in aged rats, and two interventions that reduce adiposity (mild 8% caloric restriction and POMC gene therapy) and should restore physical performance. Subsequently, we will assess muscle quality, in the context of each of these interventions. We are addressing the following specific aims: 1) Does high-fat feeding exacerbate the already elevated oxidative stress/inflammatory status with age and accelerate the decline in physical performance? 2) Aged rats are obese and, similar to obese humans are profoundly leptin resistant. Therefore, does activation of the central melanocortin pathway (through POMC gene therapy) circumvent leptin resistance and evoke weight loss in aged-obese rats, ameliorate the elevated oxidative stress/inflammatory status with age and lead to improved physical performance? 3) Does short-term, mild (8%) CR prevent the decline in physical performance with age? Thus, these studies will compare the effects of either adiposity inducing or reducing interventions in a model of age-related physical decline, and link these outcomes to dysregulation of muscle quality. The first phase of the developmental project was completed in the first year, in which the responses of aged rats to high-fat (HF) feeding were examined. Results indicated aged rats ate more food, gained more fat and weight compared with young. In addition, high-fat feeding decreased the tendency for wheel running, suggesting the propensity for inactivity with age and high-fat feeding may contribute to the accelerated 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 metabolic 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 tAGMENTAL area or hypothalamus was effective at deterring 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:

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**CLINICAL**

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

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

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

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

Sepsis in the intensive care unit (ICU) is a significant problem which carries significant morbidity, mortality and costs. Project Title: The acute development and persistence of frailty, comorbidity and disability in critically ill patients after intra-abdominal sepsis: “Induced Frailty”. Project Leader: Scott Brakenridge, M.D.

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

Project Title: Knee Pain and Transcranial Direct Current Stimulation in Older Asian Americans
Project Leader: Hyochol Ahn, Ph.D., ARNP, ANP-BC

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

Project Title: Pain and mobility function in older adults
Project Leader: Yenisel Cruz-Almeida, Ph.D.

There are 17.3 million Asians in the United States, and Asian American was the fastest growing ethnic group in the United States between 2000 and 2010. Ethnic group disparities in pain and disability in the United States are often reported in the literature, but few studies have examined differences in pain and disability
between Asian Americans and other ethnic groups. While it is generally believed that Asian Americans’ pain experiences do not differ from those of whites, our current findings suggest Asian Americans display increased pain and disability compared to non-Hispanic whites. Osteoarthritis (OA) of the knee affects 16% of the population above 45 years old, and leads to a chronic pain state that decreases physical performance and mobility. Because pharmacologic modalities for pain may increase the risk of adverse effects, researchers are becoming interested in therapeutic approaches to pain that target the central nervous system and do not depend on pharmacologic agents. In particular, clinical studies of Transcranial Direct Current Stimulation (tDCS) have shown promising preliminary results for other types of chronic pain; however, these studies are limited in number and have not focused on older adults or ethnic minorities. In addition, a small number of studies reported that outcomes following pain treatment may differ by ethnic group. Therefore, the overall goal of this proposed study is to examine ethnic differences in pain and mobility disability among older Asian Americans and non-Hispanic whites with knee OA, and to evaluate the efficacy of tDCS on pain and disability in this population. We also propose to explore ethnic group differences in biological and psychosocial factors and their contribution to pain sensitivity, and to investigate whether tDCS effects differ by ethnic group. This will be one of the first studies to characterize ethnic group differences and underlying mechanisms of pain and mobility disability in Asian Americans and non-Hispanic whites with knee OA, and to test the efficacy of the innovative pain treatment tDCS in older adults with knee OA. Moreover, this study will evaluate the role of ethnicity in determining pain sensitivity and pain treatment outcomes in individuals with OA.

**Project Title:** A Pilot Study to Evaluate the Role of Brain Integrity on Post-Hospital Sarcopenia

**Project Leader:** Adam Woods, Ph.D., Todd Manini, Ph.D.

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

Project Leader: Thomas Buford, Ph.D.

With persons aged > 65 years representing the fastest growing segment of the U.S. population, the prevention of age-related functional decline and disability is an important public health priority. The loss of functional abilities in advanced age is associated with not only the onset of disability and the loss of independence but also with increased rates of morbidity and mortality. Compared to normotensive counterparts, older persons with hypertension experience accelerated functional decline. To date, physical exercise is the primary strategy for preventing functional decline. Yet despite the general benefits of training, exercise alone appears to be insufficient for preventing this decline. Thus, alternative or adjuvant strategies are needed to optimize the functional benefits of exercise for seniors with hypertension. Our preliminary data suggest that angiotensin converting enzyme inhibitors (ACEi) are efficacious in enhancing exercise-derived improvements in function.

Despite these promising initial findings, the hypothesis that ACEi improve older adults’ functional responses to exercise has not to our knowledge been tested in a randomized controlled trial (RCT). The long-term goal of this research is to conduct a RCT to appropriately test the hypothesis that ACEi improve older adults’ functional responses to exercise. The specific objective of this proposal is to provide proof-of-mechanism to strengthen the rationale for the future trial. A total of 36 sedentary men and women > 65 years of age with physical limitations and hypertension will be recruited to participate in a 12 week intervention study. Participants will be randomly assigned to one of three conditions: (1) ACEi plus exercise training, (2) thiazide diuretic plus exercise training, or (3) AT1 receptor antagonist plus exercise training. The exercise intervention will include both multi-modal, center-based training and home-based walking. The specific aims are to: (1) assess the relative effect of the interventions on changes in exercise capacity, (2) characterize the effect of the interventions on circulating concentrations of angiotensin-related peptides, and (3) evaluate the impact of the interventions on relevant molecular and cellular skeletal muscle characteristics.

Project Title: Effects of Oxytocin on Physical and Cognitive Functioning in the Elders

Project Leader: Natalie Ebner, Ph.D.

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

Project Leader: Stephen Anton, Ph.D.

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

PRE-CLINICAL

Project Title: Critical role of Sirtuin 1-Mitofusin 2 axis in aged livers

Project Leader: Sooyeon Lee, Ph.D.

Ischemia-Reperfusion (I/R) injury commonly occurs during liver surgery, trauma, hemorrhagic shock and liver transplantation. Sirtuin 1 (SIRT1) is an NAD+-dependent deacetylase that induces longevity, stress resistance and tumor suppression. Growing evidence indicate that SIRT1 also serves important roles in cytoprotection against ischemia/reperfusion-mediated injury. In our recent studies, we have identified a novel target of SIRT1-a mitochondrial protein Mitofusin-2 (MFN2), that interacts with SIRT1 and is potentially deacetylated by this enzyme. In this study, we will extend our original findings that SIRT1-MFN2 interaction directly impacts multiple essential processes during I/R in young cells, and investigate how the status of this SIRT1-MFN2 axis is impacted by aging. Our principal hypothesis is that premature SIRT1 loss by short ischemia in old hepatocytes precipitates an accelerated sequential chain of defective mitophagy, mitochondrial permeability transition (MPT) onset and hepatocyte death after I/R. Furthermore, we will establish whether MFN2 acetylation is a critical signal that bridges SIRT1-mediated cytoprotection with autophagy and/or mitophagy. To test our hypothesis, we will use three age groups (young, middle aged, and old) mice and isolate primary hepatocytes from both SIRT1 wild type (WT) and knockout (KO) mice and characterize the cellular mechanisms including defective mitophagy, and onset of the MPT and cell death after I/R. These studies will provide novel mechanistic knowledge regarding the role of aging and increased susceptibility for liver damage from I/R, and will establish new directions for therapeutic strategies for improving I/R-mediated liver failure.
**Project Title:** A Novel Rodent Model of Age-related Motor-Cognition Dual-Task Deficits  
**Project Leader:** Sara Burke, Ph.D.

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

The completed pilot/exploratory projects are:

**Project Title: A new adaptive physical activity technology in nursing home older adults**  
**Project Leader:** Vincenzo Valiani, M.D.

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

**Project Title: Age related post-transcriptional regulation of translation in skeletal muscle**  
**Project Leader:** Luciano Brocchieri, Ph.D.

Sarcopenia, a muscle atrophy condition associated with weakness and loss of strength leading to a decline
in physical capacity, is commonly observed in the elderly population. A progressive increase with age in the concentration of damaged macromolecules, especially proteins, is likely to play a central role in senescent decline. Classic studies in diverse organisms, including humans, have established a link between the aging process and the regulation of protein synthesis and degradation. Eukaryotic cells must invest in an extensive network of factors, comprising ~800 proteins in human cells (~200 chaperones and co-chaperones and ~600 ubiquitin-proteasome and autophagy components), which cooperate to maintain the conformational integrity of the proteome. Thus, to understand the causalities of loss of proteostasis with aging requires a global understanding of how regulation of the quantities and quality of the protein product is affected by aging.

Recent applications of the newly developed deep-sequencing technique of “ribosome profiling” have demonstrated on a transcriptomic level how protein production strongly depends on stress-related posttranscriptional mechanisms of translational control. The purpose of this study will be to provide first-time characterization of how age-related muscle function decline (sarcopenia) is regulated and affected by the deterioration of control of translational processes. We will use a well established rat model of mammalian translational control of individual genes in muscle tissue at different stages of aging in comparison to young animals and to modifications induced in muscle cell by mild and severe oxidative stress treatment, a known condition associated with aging. Using the transcriptomewide information provided by ribosome profiling we will be able to identify age and stress related mechanisms of translational control, to quantify gene-by-gene translational activities, and to formulate hypotheses on how failure of translational control may lead to proteostasis collapse with aging. muscle aging to investigate modifications in

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

Sarcopenia, the age-related loss of functionality of skeletal muscle, is characterized by high levels of apoptosis, by accumulation of oxidative damage, and by mitochondrial (mt) DNA abnormalities. In addition, aging muscle shows decreased levels of the mitochondrial transcription factor A (TFAM), a 25 KDa 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 344xBrown Norway rats. Repair kinetics of base excision repair enzymes will be measured on mtDNA sequences (D loop, common deletion sequence) containing specifically positioned single-base modifications, abasic sites, or nucleotide gaps. 2) Measure binding efficiency of TFAM to damaged and undamaged mtDNA sequences in skeletal muscle. Our molecular analyses will be supported by measurements of functional activities on animals of different age groups, thus providing us with a comprehensive view of how molecular deficiencies affect muscle function. Our studies for the first time will provide a comprehensive analysis of DNA repair and DNA maintenance mechanisms in an animal model system that most closely resembles the sarcopenia observed in humans. This innovative approach will bring a new level of scientific discovery to the unresolved question of how muscle mass and function declines with sarcopenia.

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

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

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

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

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

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

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

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

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

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

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

Project Title: Epigenetic model of accelerated late life obesity and decline in muscle quality  
Project Leader: Philip Scarpace  
Obesity, including age-related obesity has become a national problem (1). Age-related obesity is a major link to insulin resistance, diabetes, increased cardiac risk, atherosclerosis, and stroke, ultimately leading to impaired physical performance and disability (2). Obesity in males and females over 70 years of age dramatically increases by nearly two-fold the number of remaining years spent disabled (3). There are several potential causes of obesity, including genetic and epigenetic factors, as well as lifestyle factors (6). A relatively small number of preclinical (mostly rodent) studies have examined the role of maternal obesity on the susceptibility of offspring to develop obesity. Most have studied the offspring at a young age, but the implications of the maternal environment for later life susceptibility to dietary obesity remain unexplored. Aging is associated with a number of factors that may contribute to a decline in physical performance with age (4), two of which are obesity and a decline in muscle quality, and these may be interdependent as HF-feeding contributes to a decline in muscle function (Fig 5). We discovered that with increasing age, rats demonstrate a greater susceptibility to high fat (HF) diet-induced weight gain and this is related to the presence of leptin resistance (5). Our umbrella hypothesis is that maternal HF-induced obesity predisposes the offspring to accelerated age-related dietary obesity and the associated decline in muscle quality. Put simply, at every age, offspring from obese dams will demonstrate greater susceptibility to diet-induced obesity (DIO) than corresponding offspring from lean dams, and this will accelerate the age-related decline in muscle quality leading to loss of physical function at an early age. The underlying mechanisms are hypothesized to be maternal leptin resistance hastens the onset of age-related leptin resistance in offspring, thus increasing the susceptibility to DIO.
Project Title: A Network Based Analysis of Systemic Inflammation  
Project Leader: Paul Borsa, Ph.D.
This exploratory study will examine the temporal response of gene expression in the innate immune system following acute muscle injury. In this exploratory project we will evaluate with newly developed micro-array technology the gene expression of inflammation biology in low functioning and high functioning old age-matched subjects in response to acute muscle injury (pre and 24-hours post-injury). We will use a novel technology that combines genomics, statistics and precise signaling transduction pathways of inflammation, which will allow us to visualize and understand the complexity of the inflammation responses and may provide us with additional biomarkers to monitor inflammation in humans. We will correlate biomarkers of inflammation (gene expression) with measures of muscle function (ROM, strength) to evaluate the inflammatory response and rate of recovery between subjects. This exploratory study will generate pilot data that will be used to determine variances and effect sizes for sample size calculations for a future large-scale clinical study.

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

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

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

**Project Title: Autophagy and Sarcopenia in a Transgenic Mouse Model**  
**Project Leader: Stephanie Wohl, 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 myocites. Thus, studies are needed to investigate the potential molecular links between obesity, weight loss, and systemic levels of inflammation and oxidative stress. Findings from these studies may identify novel therapeutic targets and therapies for improving health and decreasing the incidence of age-related diseases associated with obesity and sarcopenia. The proposed study will utilize a large sample of obese, older adults (N = 100) from rural communities to examine: 1) the dose response relation between weight loss programs of varying intensity on changes in markers of systemic inflammation (i.e., CRP, IL-6, and TNF-alpha), oxidative stress levels (i.e., oxLDL, 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 regrowth and improved function in old animals following a period of muscle disuse. The rationale for the proposed work is based on the role that Hsp70 may play in enhancing protein synthesis and activating satellite cells. Furthermore, muscles from adult rats increase Hsp70 expression during reloading and completely regrow, whereas the ability of muscles from old rats to increase Hsp70 is significantly compromised. To test this central hypothesis, we cast immobilized rats for 10 days to cause significant skeletal muscle atrophy and then used gene transfer to overexpress Hsp70 in the soleus muscle of one limb, with the contralateral limb serving as a control. Hsp70 overexpression significantly enhanced skeletal muscle fiber regrowth in old rats. In a separate group of rats we tested “physical performance” via incline plane and a swim test prior to cast immobilization, immediately following 10 days of cast immobilization, and following 10 days of cast immobilization plus 10 days of reloading. Overexpression of Hsp70 increased the mean time to failure on the incline plane test in old rats but not young rats and increased the swim distance during repeated swim trials in young rats but not old rats. Ongoing biochemical analyses will determine whether Hsp70 overexpression enhances markers of protein synthesis and/or satellite cell activation during muscle regrowth.
Biological Effect of Weight Loss and Exercise in Elders
Project Leader: Stephen D. Anton, Ph.D.
This study will lay the groundwork for a randomized controlled trial (RCT) of the effects of weight loss plus exercise (WL+E) on inflammation, oxidative stress, apoptosis, body composition, intramuscular fat, sarcopenia, muscle strength, and physical functioning in obese older adults.

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

Testosterone Trial IVR Pilot
Project Leader: Marco Pahor, M.D.
The purpose of the study was to learn about the use of questionnaires about general health and feelings of well-being in men who are ≥ 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 FOXO3A). This research is significant because it is expected to result in the development of a novel and practical intervention that promotes muscle growth in the absence of high-intensity exercise. However, prior to widespread use of this modality the first step is to investigate an acute bout of exercise to evaluate the potential underlying responses that will help in developing a conceptual model for the mechanisms of action. Once these data are available chronic low intensity exercise coupled with blood flow restriction can be studied in older adults for enhancement of skeletal muscle health in older adults at risk of muscle atrophy.
The Influence of Resistance Exercise on Physical Function Depression, Quality of Life, Muscle Morphology and Bone Metabolism in Stroke Patients  
**Project Leader: Kevin Vincent, M.D.**

Stroke is associated with musculoskeletal adaptations that result in decreased bone mineral density (BMD), 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 BMD, 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 BMD, 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>
<thead>
<tr>
<th>OAIC Junior Scholar Publications and Grants from 2010 to 2015</th>
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<tr>
<td>Stephen Anton, PhD</td>
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<tr>
<td>Thomas Buford, PhD</td>
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<tr>
<td>David Clark, PhD</td>
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<td>Yenisel Cruz-Almeida, PhD</td>
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<td>Vonetta Dotson, PhD</td>
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<td>Natalie Ebner, PhD</td>
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<td>Philip Eron, MD</td>
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<td>Anna Maria Joseph, PhD</td>
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<td>Andrew Judge, PhD</td>
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<td>Todd Manini, PhD</td>
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<tr>
<td>Joe Nocera, PhD</td>
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<tr>
<td>Kimberly Sibille, PhD</td>
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<tr>
<td>Shinichi Someya, PhD</td>
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<td>Bridgitt Rahim-Williams, PhD</td>
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<td>Kevin Vincent, MD</td>
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<td>Stephanie Wohlgemuth, PhD</td>
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<td>Adam Woods, PhD</td>
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<td>Jinze Xu, PhD</td>
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<td>Zvinka Zlatar, PhD</td>
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Total # | 347 | | 17 | 40 | 12 | 10 | 6 | 9 | 5 | 4 |

| % of Junior Scholars | 89% | 52% | 32% | 47% | 26% | 21% |

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

IV. PUBLICATIONS


82. Altman M, Cahill Holland J, Lundeen D, Kolko RP, Stein RI, Saelens BE, Welch RR, Perri MG, Schechtman KB, Epstein LH, Wilfley DE. Reduction in food away from home is associated with improved child relative weight and body composition outcomes and this relation is mediated by changes in diet quality. J Acad Nutr Diet. 2015


**Section V. External Advisory Board**

Jeffrey Halter, MD (1 year)
Professor, Internal Medicine
Research Professor, Institute of Gerontology
University of Michigan Geriatrics

Debra I. Diz, PhD (3 years)
Professor and Director, Hypertension & Vascular Research Center
Professor, Department of General Surgery and Department of Physiology and Pharmacology Wake Forest School of Medicine

Roger Fielding, PhD (3 years)
Senior Scientist and Director
Nutrition, Exercise Physiology, and Sarcopenia Laboratory
Tufts University

Mary McGrae McDermott, MD (3 years)
Mary McDermott, MD
Jeremiah Stamler Professor
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I. CENTER DESCRIPTION

The overarching UM-OAIC goal is to build on the sciences and therapeutic applications of exercise and rehabilitation by: 1) advancing our understanding of the mechanisms by which exercise and activity-based rehabilitation interventions directed at specific impairments affect multiple body systems underlying functional performance; and 2) developing and testing interventions to restore function and minimize disability following acute disabling events and gradual declines related to serious chronic diseases.

The functional impairments and disabilities that occur in older people emanate from acute events, such as stroke, heart attack, and hip fracture, or reflect the progression of chronic diseases. Older people aging with chronic diseases have a reduced aerobic capacity and develop sarcopenia, weakness, fatigue, and neuromotor and cognitive impairments that reduce their physiological reserve, impair their ability to function independently, and increase their level of medical care and risk for institutionalization and death. This pathway of how disease leads to disability has been discussed extensively by Nagi, made more operational by Verbrugge and Jette, and extended further to include socio-environmental elements by the IOM and WHO. More recently, further commentary debates how best to understand functioning and disablement.

The UM-OAIC mission embodies the process by which function is lost and the multiple factors identified thus far that affect the onset and progression of disability. Building on these important perspectives, the UM-OAIC focuses on the restoration of function in order to improve function in those with impairments, and prevent or delay further progression in those who are already disabled. This has been aptly referred to as enablement. (10, 11)  The UM-OAIC will continue to focus its research on the processes involved in enablement by identifying the deficits or impairments associated with specific disabling conditions, investigating the mechanisms and pathophysiology leading to the impairments, developing exercise and other activity-based interventions that target these mechanisms and deficits, testing them in clinical laboratories/centers under carefully controlled conditions, and then adapting them for implementation and further testing in community settings outside the medical center.

The specific aims of the UM-OAIC are to:

1. Conduct research that examines the mechanisms underlying the functional impairments associated with stroke, hip fracture, and prevalent chronic diseases in older people;
2. Design novel, efficacious exercise and activity-based rehabilitation interventions that produce clinically relevant outcomes and study the mechanisms underlying them;
3. Translate the most efficacious interventions developed in UM-OAIC clinical laboratories and in other clinical centers for implementation and rigorous evaluation outside the clinic (e.g., home, senior center, gym).
4. Support pilot and exploratory studies (PESs), UM-OAIC junior scholar research, development projects (DPs), and externally funded projects (EP) that examine the mechanisms underlying disability and the processes of recovery, and that design and test interventions for the restoration and maintenance of function in clinical laboratories and settings outside the medical center.
5. Foster the career development of junior faculty/scholars from multiple disciplines into independent, academic scientists with expertise in the study of older persons with disabling diseases through mentor-based, bench-to-bedside translational research training that includes didactic and experiential/practical-applied training in conducting independent, aging research.

The UM-OAIC has three resource cores (RC): Biostatistics, Informatics and Translational Science (RC-1); Applied Physiology and Tissue Mechanisms (RC-2); and Neuromotor Mechanisms and Rehabilitation (RC-3), that serve as a resources for the conduct of innovative exercise and activity-based rehabilitation research. An enhanced Research Education Core (REC) (formerly RCDC) will provide didactic and experiential training under the guidance of an interdisciplinary mentoring team to prepare the next generation of scientists committed to careers in aging research. Center aims will be accomplished by: 1) using multidisciplinary research working groups (RWGs) to provide mentoring and guide REC and PES investigators and faculty scholars in designing and conducting their projects, reporting results, and developing future investigations; 2) supporting studies that
determine the mechanisms underlying functional impairments and implement exercise and activity-based rehabilitation interventions to improve clinically relevant outcomes; and 3) translate safe and efficacious interventions into randomized clinical trials outside the medical center with the goal of changing practice for those with disabling diseases and conditions. The restoration of functional independence through an integrated approach that includes exercise and activity-based rehabilitation will transform the care of older people with disabling diseases and conditions.

II. RESEARCH, RESOURCES AND ACTIVITIES
A. CORES

1. Biostatistics, Informatics and Translational Research (RC1)
Core Leader: John D. Sorkin, M.D., Ph.D., (Telephone: 410-605-7119, E-mail: jsorkin@grecc.umaryland.edu), Core Co-Leaders: Laurence Magder, Ph.D., (Telephone: 410-706-3253, E-mail: lmagder@epi.umaryland.edu) and Michael Terrin, M.D., C.M., M.P.H., (Telephone: 410-706-6139, E-mail: mterrin@epi.umaryland.edu)

RC1 provides biostatistical and informatics support to investigators, to help design interventions that prevent functional decline, promote restoration and maintenance of function, and to facilitate the translation of interventions from laboratory to clinic and community. We will participate in Research Working Groups (RWGs), a forum in which investigators from multiple disciplines collaborate on the design and conduct of studies. Our informatics system (GERI) will provide an infrastructure that helps us manage studies, and facilitates the flow of information and data. RC-1 draws on the resources and statistical expertise of the UM Department of Epidemiology and Public Health’s Divisions of Biostatistics and Bioinformatics, and Gerontology. We share resources and personnel with the biostatistics cores of the Baltimore VA Geriatrics Research, Education, and Clinical Center (GRECC), the VA RR&D Maryland Exercise and Robotics Center of Excellence (MERCE), and the UM Nutrition Obesity Research Center (NORC). The resultant synergy saves money and makes the whole more than the sum of its parts. Statistical methods, hardware purchased and software developed by one center are used by all centers.

The specific aims of RC-1 are to:
1. Provide a centralized, user-friendly information management system (GERI) that:
   a) Facilitates submission of requests for core services, schedules and tracks use of core resources
   b) Facilitates recruiting of subjects
   c) Monitors study progress by tracking recruiting efforts and subject progress through studies
   d) Informs investigators and OAIC leadership of adverse events
   e) Facilitates data management
   f) Ensures confidentiality, physical security, and logical integrity of data
   g) Promotes data completeness, accuracy, and validity
   h) Improves laboratory quality control, and automates the review of study data.

2. Provide biostatistical expertise to UM-OAIC investigators by:
   a) Planning studies that are optimally designed, adequately powered, statistically efficient and that lead to valid, unbiased estimates of parameters
   b) Randomizing subjects
   c) Analyzing data
   d) Helping investigators with the interpretation and presentation of results
   e) Helping investigators and clinicians get access to, and provide analytic support for “big data” science.

3. Participate in Research Working Groups (RWGs) that will assist UM-OAIC investigators:
a) Design and conduct studies, analyze and interpret data, and publish study results
b) Optimize treatment fidelity and translate studies from the laboratory to the clinic and community.

4. Provide training to UM-OAIC faculty, trainees, and staff in biostatistics and epidemiology.

2. Applied Physiology and Tissue Mechanisms (RC2)
Core Leader: Alice Ryan, Ph.D., (Telephone: 410-605-7851, E-mail: aryan@grecc.umaryland.edu) and Core Co-Leader: Leslie I. Katz, 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 and activity-based rehabilitation can improve multiple physiological systems in older, mobility limited individuals leading to improved functional performance, reduced cardiometabolic disease risk, and prevention of functional decline. By determining the composition, molecular, and metabolic abnormalities in skeletal muscle, adipose tissue, and vascular endothelium, and response to exercise rehabilitation, we can optimize exercise interventions to improve muscle structure, function, metabolism, and CVD risk profiles in older adults with these chronic conditions. Exercise interventions may potentially reduce risk and delay chronic disability in older adults. To achieve this goal, RC2 implements specific aims that:

1. To facilitate the conduct of musculoskeletal and tissue mechanistic exercise rehabilitation and preventive biomedical research in aging and disability across the UM-OAIC pilot projects, OAIC scholars’ research, Development Projects (DPs), and external NIH and VA funded research through:
   a.) Patient recruitment, the performance of medical assessments and cardiovascular screening of research volunteers to ensure patient safety and eligibility for research protocols;
   b.) The development and testing of novel exercise-based interventions (aerobic, resistance, multi-modal training) and collaborations with rehabilitation science in RC-3;
   c.) The clinical, cardiometabolic and functional profiles at the whole body and tissue level before and after exercise training.
2. To provide research support, mentoring, and training to OAIC scholars, junior faculty, and OAIC researchers in the performance of aging research relevant to exercise and rehabilitation-based restoration of function and the prevention of functional declines in older people with chronic disabling diseases through:
   a.) Mentoring in research working groups (RWGs) to provide educational and consultative resources to OAIC junior and senior investigators in the design and implementation of their research;
   b.) Clinical applied training in the conduct of translational research and the assessment of cardiovascular and physiological outcomes of exercise rehabilitation in aging; and
   c.) Laboratory training in standardized core methodologies in order to gain expertise in the performance of cardiovascular and metabolic testing, exercise testing, and cellular and molecular assays at the bench to facilitate their bedside to bench translational research.

The characterization of the clinical and metabolic phenotype(s) of individuals with stroke, hip fracture and other chronic disabling diseases in RC-2 has allowed UM-OAIC investigators to develop successful specific exercise rehabilitation strategies to improve functional and clinical outcomes. Thus this core, in collaboration with the other OAIC cores will continue to support innovative research studies examining the mechanisms and physiological effects of multisystem rehabilitation and preventive strategies on functional and physiological outcomes in older adults aging with chronic disabilities with translation of these outcomes in novel clinical trials.
3. Mobility Function and Neuromotor Plasticity (RC3)
Core Leader: Mark Rogers, Ph.D., P.T., (Telephone: 410-706-0841, E-mail: mrogers@som.umaryland.edu) and 
Core Co-Leader: George Wittenberg, M.D., Ph.D., FASNR (Telephone: 410-706-4456, E-mail: 
gwittenberg@som.umaryland.edu)

The combination of physical impairments and a sedentary lifestyle with aging and chronic conditions such as 
stroke, hip fracture, metabolic syndrome and Parkinson’s disease, results in multi-system brain, neuromotor, 
physiological, behavioral, and cognitive deficits that precipitate loss of functional independence and disability. 
The central hypothesis of Resource Core-3 (RC-3) Neuromotor Mechanisms and Rehabilitation is that 
appropriately-selected functional activity and exercise-based rehabilitation interventions can promote beneficial 
changes in brain [central nervous system (CNS) structure, connectivity, and physiology] and neuromotor 
mechanisms to improve motor performance and function and minimize chronic disability in older people.

RC-3 provides support, guidance, and mentoring to UM-OAIC investigators using a multi-system approach 
focused on whole-body balance, locomotion, and upper limb activities to address the mechanistic bases upon 
which to build novel rehabilitation strategies to improve motor function and independence and promote 
recovery in older people with chronic disease-associated disabilities. Through this framework, functional 
activity and exercise-mediated brain and neuromotor plasticity can be identified to guide condition-specific and 
individual-specific rehabilitation approaches for minimizing disability. The complementary and collaborative 
relationship between RC-3 and RC-2 -- which focuses on muscle, metabolic, and cardiovascular mechanisms of 
aging with disability -- forges a strong and comprehensive inter-core synergy for understanding the bases for 
designing and testing effective new rehabilitation programs to restore and sustain functional independence and 
quality of living among older individuals.

The specific aims of RC-3 are:
1. To develop, enable, and support the investigation and identification of brain and neuromotor mechanisms 
associated with functional performance for the development of novel and effective activity and exercise-based 
rehabilitation interventions to enhance whole-body balance, mobility, and upper limb motor functions and 
minimize disability among people with chronic health conditions of aging.
2. To assist, mentor, and support trainees, junior faculty, and UM-OAIC investigators through research 
working groups (see REC) in the design and conduct of functional activity and exercise-based rehabilitation 
interventions that will be translated from the laboratory to the clinic and into the community to improve 
functional independence in older individuals with chronic disease-associated disability.
3. To perform testing and assessments using the core repertoire of methodologies to quantify the brain and 
neuromotor mechanisms of balance, postural control, mobility, upper limb activities, and disability phenotype 
that characterize the processes of adaptive plasticity underlying structured activity and exercise-derived 
functional gains across UM-OAIC rehabilitation-based interventions.

The brain and neuromotor changes and accompanying impairments of chronic medical conditions of aging that 
limit functional performance and lead to disabilities will be investigated in RC-3. This knowledge will form the 
mechanistic bases for the development and testing of functional activity and exercise-based rehabilitation 
interventions to improve functional outcomes and alleviate disability. In collaboration with the other cores, RC- 
3 will advance the overall UM-OAIC goal to build on the sciences and therapeutic applications of exercise and 
rehabilitation to restore function and minimize disability due to acute disabling conditions and long-term 
declines related to chronic conditions of older age.

4. Leadership and Administrative Core (LAC)
Core Leader: Jay Magaziner, Ph.D., M.S.Hyg., (Telephone: 410-706-2406, E-mail: 
jmagazin@epi.umaryland.edu) and Co-Directors: Leslie I. Katzel, M.D., Ph.D., (Telephone: 410-605-7248, E-
The Leadership and Administrative Core (LAC) will ensure that the UM-OAIC provides support for training the next generation of scientists pursuing research careers in aging, and the conduct of novel research in older adults directed at the UM-OAIC goals of: 1) advancing our understanding of the mechanisms by which exercise and activity-based rehabilitation interventions directed at specific functional impairments affect multiple body systems underlying functional performance; and 2) developing and testing interventions to restore function and minimize disability following acute disabling events and gradual declines related to serious chronic diseases.

The LAC will foster ongoing discussion among core leaders and faculty scholars to ensure that research and research training are carried out in a cohesive, coordinated and integrated manner. The LAC will also engage scientists and educators from across the University of Maryland Baltimore (UMB) community so that research and research training can take full advantage of the breadth and depth of experience in aging and other relevant areas to facilitate collaborations that advance UM-OAIC goals.

The LAC will receive input and guidance and discuss program operations in the Core Leadership Executive Committee (CLEC) of resource core (RC) leaders; the UM-OAIC Research and Education Advisory Committee (REAC) charged with reviewing proposed Development and Pilot/Exploratory Studies; an Internal Advisory Committee (IAC) charged with evaluating UM-OAIC progress and accomplishments and advising on ways to extend research on aging to other university centers and departments; and an External Advisory Board (EAB) that will provide guidance to the program and report progress annually to the NIA. In addition, the LAC will support an Internal Data and Safety Monitoring Board (I-DSMB) that will review the conduct of clinical protocols to ensure patient safety, and an External Data and Safety Monitoring Board (DSMB) that will provide another layer of review by experienced scientists who can remain impartial as they monitor data quality and safety, and report to the NIA annually (Figure 1).

Specific Aims of the Leadership and Administrative Core are to:
1. Coordinate and oversee all aspects of the UM-OAIC, establishing collaborations with other centers, investigators and institutions that contribute to UM-OAIC goals.
2. Enrich the cadre of basic, clinical and population scientists conducting translational research in aging by recruiting outstanding junior and senior faculty and research staff to become involved in the UM-OAIC.
3. Advance the careers of junior faculty from multiple disciplines to become independent investigators and academic leaders in aging research.
4. Develop resources that support the conduct of basic, clinical, and translational research designed to advance UM-OAIC goals.
5. Ensure independent review and oversight of UM-OAIC research and scholar training, data quality, and safety for studies undertaken by pilot study investigators and faculty scholars.
6. Manage the UM-OAIC budget and distribution of funds, assure adherence to federal regulations and NIA policies, and report scientific progress and resource use annually to 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) and Core Co-Leaders: Glenn Ostir, Ph.D., (Telephone: 410-706-3907, E-mail: gostir@epi.umaryland.edu) and Marc Hochberg, M.D., M.P.H., MACP, MACR, (Telephone: 410-706-6474, E-mail: m hochber@umaryland.edu)

The purpose of the UM-OAIC Pilot and Exploratory Studies Core (PESC) is to provide critical, initial funding for pilot and exploratory studies that are consistent with the Center’s overall goal, which is to build the
sciences and therapeutic applications of exercise and rehabilitation by: 1) advancing our understanding of the mechanisms by which exercise and activity-based rehabilitation interventions directed at specific impairments affect multiple body systems underlying functional performance; and 2) developing and testing interventions to restore function and minimize disability following acute disabling events and gradual declines related to serious chronic diseases.

To meet this objective, the PESC will provide research support and mentoring of investigators with high quality pilot and exploratory research proposals designed to acquire preliminary data needed for future crucial studies congruent with the Center’s focus: examination of the mechanisms underlying mobility limitation, physical disability, and recovery from disability in vulnerable older adults, and assessment of functional and clinical responses to novel exercise and activity-based rehabilitation interventions.

The specific aims of the PESC are:

1. Solicit and select high quality, innovative pilot and exploratory studies (PES) that are relevant to the UM-OAIC goal.
   a.) Identify talented junior faculty and other investigators interested in conducting studies to advance the UM-OAIC goal.
   b) Review, select and fund the highest quality pilot and exploratory studies that have the potential to acquire preliminary data required for future studies of innovative rehabilitation interventions that will optimize the recovery of older individuals who are disabled by stroke, hip fracture, Parkinson’s disease, or other chronic metabolic, neuromuscular or musculoskeletal diseases.

2. Support the implementation of innovative and promising pilot and exploratory studies and facilitate their development into independently funded grant applications through establishment of multidisciplinary Research Working Groups (RWGs), in coordination with the Research Education Core (REC), Resource Cores (RCs) and Leadership and Administrative Core (LAC).
   a) Assist pilot and exploratory study investigators in the conduct of their research and in accessing resources from UM-OAIC cores, research programs and centers at the University of Maryland Baltimore (UMB), and nationally through collaboration with other OAICs;
   b) Ensure and monitor adherence to ethics, safety, privacy and protection of human subjects enrolled in PESC studies; and
   c) Monitor and evaluate the progress of pilot and exploratory studies.

The PESC will support five innovative studies involving multidisciplinary rehabilitation research in the first year of this competitive renewal. The preliminary data obtained in these studies will form the basis for larger, investigator-initiated studies. Thus, PESC leadership will attract investigators to study exercise and activity-based rehabilitation and recovery in older adults with disabling chronic conditions, stimulate new studies in aging rehabilitation research through targeted funding, encourage new interdisciplinary collaborations, and translate efficacious therapies across the spectrum from bench to clinical laboratory to community practice. This will advance the UM-OAIC research goal of expanding impairment specific and activity-based therapies in the broadest context of geriatric rehabilitation that emphasizes restorative and preventive medicine to promote the recovery and health of older adults with disabilities.

6. Research Career Development Core
   Co-Core Leaders: Jay Magaziner, Ph.D., M.S.Hyg., (Telephone: 410-706-2406, E-mail: jmagazin@epi.umaryland.edu) and Mary-Claire Roghmann, M.D., M.S., (Telephone: 410-706-0062, E-mail: mroghman@epi.umaryland.edu)

The purpose of the Research Education Core (REC) is to foster the career development of junior faculty from
multiple disciplines into academic scientists in gerontology and geriatrics, focusing on the theme of exercise and activity rehabilitation and recovery research. The REC supports mentor-based research training and education to promote the career development of REC Scholars as well as other junior faculty, fellows, and students pursuing research careers in aging. The UM-OAIC has a successful history of mentored training that crosses traditional disciplinary boundaries to develop novel research for improving function and independence in older persons. This has enriched the cadre of scientists at UM and elsewhere conducting aging research in exercise and rehabilitation science.

The specific aims of the REC are to:

1. Recruit, select and support REC 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. This is accomplished by:
   a.) Recruiting and selecting talented junior faculty whose research and career goals are congruent with the UM-OAIC goals and
   b.) Ensuring support for the REC Scholars by departmental commitment to protected time for research training and mentoring, access to resources for the conduct of pilot and exploratory studies, and career development opportunities.

2. Mentor REC Scholars and Affiliated Scholars. Provide a multidisciplinary team approach for individual and group mentoring to REC Faculty Scholars and Affiliated Faculty Scholars and trainees conducting research congruent with the UM-OAIC, but receiving salary from other career development funding mechanisms. This is accomplished by:
   a.) Building interdisciplinary Research Working Groups (RWGs) that include the Scholar, the PI’s primary mentor, a scientist from each core, and ad hoc experts to provide mentoring and guidance on the design, implementation, and conduct of their studies. RWGs ensure comprehensive mentoring and career development, guidance in the application of best practices for the conduct of their research, access to collaborations, and the infrastructure to guide the investigator’s academic development.

   Over 20 years, the UM-OAIC has provided 35 Faculty Scholars and many postgraduate trainees with a rich learning environment for their career development, exposure to gerontology and geriatrics, and resources for pursuing independent research related to the theme of the UM-OAIC. This approach has resulted in 23 of our former 35 REC Scholars attaining independent funding and academic advancement.

3. Provide Career Development Opportunities in Areas Relevant to Aging Research. The REC training program is tailored to meet the individual and group needs of REC Scholars and other trainees. This is accomplished by:
   a.) Developing an individualized career development plan (CDP) that leverages the strengths of the UM-OAIC and institutional career development resources to meet the needs of each REC Scholar. Scholars develop a working CDP for didactic and experiential, applied training with their mentor in the classroom, laboratory and clinic that meets their academic needs. All receive training in the Responsible Conduct of Research (RCR) with an emphasis on ethical and safety issues in studying older people.
   b.) Providing opportunities to REC Scholars, REC Affiliated Scholars, fellows, and students for additional instruction and collaboration in scholar-driven RWG meetings and data reviews, journal clubs, Center on Aging seminars, mock study sections, and research methods seminars presented in conjunction with the other UM campuses and the Johns Hopkins OAIC, and the NIA Gerontology Research Center. Proximity to NIH allows easy access to other aging-related seminars.

4. Evaluate the Activities of the REC. This will be achieved by an evaluation team that measures the short term and long term success of the REC aims using established quantitative and qualitative metrics, informal focus groups and individual meetings to track the needs and accomplishments of Scholars, success of our trainees and meetings to provide feedback to REC Scholars, other trainees, mentors, and UM-OAIC leadership and advisory committees.

   The REC’s comprehensive research training program has developed junior scholars trained with skills at
the bench and in the conduct of clinical research, posed to translate clinical problems into mechanistic studies, and laboratory findings into clinical application in the elderly. This is why our Scholars are so successful in the receipt of federal career development awards (NIH Ks and VA CDAs), and subsequent independent research funding and academic promotion.

UM-OAIC Career Development Awardees
Currently Funded Awardees:

- 2014-2017: **Kelly Westlake, Ph.D., MSc, PT** Assistant Professor, Department of Physical Therapy and Rehabilitation Sciences, School of Medicine, University of Maryland Baltimore
  “Probing the Neural Basis and Influence of Cognitive Changes on Impaired Balance in Older Adults”
  A. Research Progress Report: Dr. Westlake investigates the neural underpinnings and cognitive contribution to reach, grasp and balance responses in older adults at low and high risk of falling by evaluating the spatiotemporal transitions between cognitive brain networks and reactive balance responses following platform perturbation during gait and tests of neurocognitive function. Data collection and analysis for the first phase of this research is completed (10 young adults, 11 older non-fallers, 12 older fallers). The findings provide preliminary evidence of the cognitive deficit in attention shifting away from an ongoing working memory task that underlies delayed and inaccurate protective reach to grasp responses in older adult fallers. Results have been presented at 4 meetings, 1 manuscript has been accepted, and 1 is under review.
  B. Mentoring [Core use]: Rogers (primary), Wittenberg, Adali (RC-1, RC-3)
  C. Goals for career progression by the end of the UM-OAIC Award: Preparation for a 3rd manuscript regarding the neuroimaging findings is currently underway. Plans for 2016 include an NIH R21 grant submission to further probe the mechanisms and possible treatment options for impaired protective arm responses in older adults.

- 2014-2017: **Rishi Kundi, M.D.**, Assistant Professor, Department of Surgery, School of Medicine, University of Maryland Baltimore
  “Functional Benefit of Exercise Therapy after Endovascular Intervention in Older Patients with PAD”
  A. Research Progress Report: Little data exists regarding the degree to which surgical outcomes and mobility function deficits can be improved by the addition of adjuvant exercise therapy to standard endovascular revascularization in older people with peripheral arterial disease (PAD). This study seeks to define these improvements and explore the mechanisms underlying them. The underlying hypothesis is that the addition of neuromuscular electrical stimulation to a structured exercise rehabilitation program after standard revascularization in older PAD patients will improve function and quality of life, compared to standard revascularization, through mechanisms including increases in target vessel flow, angiogenesis and beneficial alterations in muscle ultrastructure and metabolism. The preliminary results obtained through preoperative testing of 10 patients have demonstrated significant deficits in functional mobility and in measures of distal perfusion responses to exercise. Enrollment into the intervention continues. Four abstracts have been accepted for presentation at national meetings. Additional funding ($15,000) has been obtained from a Society for Vascular Surgery Foundation Seed Grant. Career development award applications was submitted to the VA in the spring of 2016
  B. Mentoring [Core Use]: Lal (Primary), Ryan, Prior, Goldberg, Alon (RC-2)
  C. Goals for career progression by the end of the UM-OAIC Award: Revise and resubmit CDA. Enrollment of subjects will be complete by spring of 2016 and the results written up for publication by the end of 2016.

- 2015-2018: **Derik Davis, M.D.**, Assistant Professor, Department of Diagnostic Radiology & Nuclear Medicine, School of Medicine, University of Maryland Baltimore
  A. Research Progress Report: Dr. Davis began his position as a scholar in July 2015. He has rapidly established
his RWG, CDP and research plan.

Project 1 (Male Hip/Ancillary CT Study; PI: Dr. Terrin; additional mentors: Drs. Magaziner, Goldberg, Ryan)
2) Winter/Spring 2016: Initial start to secondary analysis began in March 2016. Outcome variables: LEGS total score, SPPB total score, LEGS subcomponents, SPPB subcomponents. Primary independent variables: truncal fat mass, age, sex + other independent variables
3) Spring 2016: April/May 2016 beginning image analysis for CT scan calculation of visceral adiposity mass, followed by additional analysis. Outcome variables: LEGS total score, SPPB total score, LEGS subcomponents, SPPB subcomponents. Primary independent variables: visceral adiposity mass (VAT), subcutaneous fat adiposity mass (SAT), age, sex + other independent variables

Project 2 (Health ABC Study; Mentors: Drs. Terrin, Goldberg, Ryan; External Health ABC co-authors: Drs. Stephen Kritchevsky – Wake Forest, Denise Houston – Wake Forest)
1) February 2016: Application for use of Health ABC Study for secondary analysis.
2) March 2016: Application approved by Health ABC executive committee. Current working title: “Examining Sarcopenia as an Independent Risk Factor for Low Bone Density in Older Adults in the Health ABC Cohort”
3) March /April 2016: Apply for U of Maryland IRB approval
4) Spring / Summer: Begin analysis

B. Mentoring [Core Use]: By project above


**UM-OAIC Junior Scholars (Research supported by the UM-OAIC):**

<table>
<thead>
<tr>
<th>Year</th>
<th>Name</th>
<th>Title</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001-2004</td>
<td>Larry Forrester, Ph.D.</td>
<td>Associate Professor, Department of Physical Therapy, School of Medicine, University of Maryland Baltimore</td>
<td></td>
</tr>
<tr>
<td>2001-2004</td>
<td>Marianne Shaughnessy, Ph.D., CRNP</td>
<td>Program Analyst, Office of Geriatrics Programs, Veterans Health Administration</td>
<td></td>
</tr>
<tr>
<td>2001-2004</td>
<td>Denise Orwig, Ph.D.</td>
<td>Associate Professor, Department of Epidemiology and Preventive Medicine, School of Medicine, University of Maryland Baltimore</td>
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<tr>
<td>2004-2006</td>
<td>Jacob Blumenthal, M.D.</td>
<td>Assistant Professor, Department of Medicine, School of Medicine, University of Maryland Baltimore</td>
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<tr>
<td>2004-2006</td>
<td>Eun-Shim Nahm, Ph.D., RN</td>
<td>Professor, Department of Organizational Systems and Adult Health, School of Nursing, University of Maryland Baltimore</td>
<td></td>
</tr>
<tr>
<td>2004-2006</td>
<td>Federico Villagra, Ph.D., PT</td>
<td>Visiting Physiologist, Hospital Universitario Virgen del Rocio, Pamplona Spain</td>
<td></td>
</tr>
<tr>
<td>2004-2007</td>
<td>Kris Ann Oursler, M.D.</td>
<td>Associate Professor, School of Medicine and Research Institute, Virginia Tech/ Salem VA Medical Center</td>
<td></td>
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<tr>
<td>2004-2007</td>
<td>Ram Miller, M.D., CM, MSc, MBA, FRCPC</td>
<td>Director of Clinical Development, Muscle Metabolism Discovery Performance Unit, GlaxoSmithKline</td>
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<tr>
<td>2005-2008</td>
<td>Sandy McCombe Waller, Ph.D.</td>
<td>Associate Professor, Department of Physical Therapy and Rehabilitation Sciences, School of Medicine, University of Maryland Baltimore</td>
<td></td>
</tr>
<tr>
<td>2009-2011</td>
<td>Kathleen Michael, Ph.D., RN, CRRN</td>
<td>Assistant Professor, Interim Chair- Department of Organizational Systems and Adult Health, School of Nursing, University of Maryland Baltimore</td>
<td></td>
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<tr>
<td>2011-2014</td>
<td>Douglas Savin, Ph.D.</td>
<td>Assistant Professor, Department of Physical Therapy and Rehabilitation Sciences, School of Medicine, University of Maryland Baltimore</td>
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<tr>
<td>2011-2014</td>
<td>Avelino Verceles, M.D.</td>
<td>Assistant Professor, Department of Medicine, School of Medicine, University of Maryland Baltimore</td>
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</table>
2012-2015  **Michael Dimyan, M.D.,**  Assistant Professor, Department of Neurology, School of Medicine, University of Maryland Baltimore

2014-present  **Kelly Westlake, Ph.D., MSc, PT,**  Assistant Professor, Department of Physical Therapy and Rehabilitation Sciences, School of Medicine, University of Maryland Baltimore

2014-present  **Rishi Kundi, M.D.,**  Assistant Professor, Department of Surgery, School of Medicine, University of Maryland Baltimore

2015-present  **Derik Davis, M.D.,**  Assistant Professor, Department of Diagnostic Radiology & Nuclear Medicine, 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.

<table>
<thead>
<tr>
<th>Major Grants Associated with the UM-OAIC</th>
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<tbody>
<tr>
<td>Research Projects</td>
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<tr>
<td>UM-OAIC Scholar Projects</td>
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<tr>
<td>Association of visceral and truncal adiposity with functional recovery after hip fracture in a longitudinal 12-month study</td>
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<tr>
<td>Functional Benefit of Exercise Therapy after Endovascular Intervention in Older Patients with PAD</td>
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<tr>
<td>Probing the Neural Basis and Influence of Cognitive Changes on Impaired Balance in Older Adults</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 Neuropathy</td>
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<td>Task-Specific Effects of Two Different Balance Training Regimens</td>
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<tr>
<td><strong>Year 1 UM-OAIC Pilot Projects: 2011-2012</strong></td>
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<tr>
<td>Improving walking symmetry and functional mobility in stroke survivors with split-belt treadmill training.</td>
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<tr>
<td>Aerobic exercise (AEX) to improve regulation of Endothelial Progenitor Cells (EPCs) and Vascular Function in T2DM.</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>
</tr>
<tr>
<td>Resistance training (RT) and protein (Pro) supplementation to improve muscle physiology and reduce fatigue in breast cancer survivors</td>
</tr>
<tr>
<td>A high-density Electroencephalography (EEG) neural Decoding study of Dynamical Cortical Mapping of Gait in Humans after Stroke.</td>
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<tr>
<td><strong>Year 2 UM-OAIC Pilot Projects: 2012-2013</strong></td>
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<tr>
<td>Comparison of Reactive Step Training and Voluntary Task-Oriented Training to Induce Neuromotor Changes for</td>
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<tr>
<th>PI</th>
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<tbody>
<tr>
<td>D. Davis, MD</td>
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<tr>
<td>R. Kundi, MD</td>
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<tr>
<td>K. Westlake, PhD, PT</td>
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<tr>
<td>M. Rogers, PT, PhD, FAPTA; 7/1/14-6/30/17</td>
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<tr>
<td>J. Barton, PhD; 10/01/11-09/30/16</td>
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<tr>
<td>A. Bastian, PhD/D. Hanley, PhD</td>
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<tr>
<td>S. Prior, PhD</td>
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<tr>
<td>E. Streten, MD/H. Ortmeyer, PhD</td>
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<tr>
<td>M. Serra, PhD</td>
</tr>
<tr>
<td>J. Contreras-Vidal, PhD</td>
</tr>
<tr>
<td>D. Savin, PhD, MPT</td>
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<tr>
<th>Improving Balance and Preventing Falls</th>
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<tr>
<td>Development of a Rehabilitation Strengthening and Mobility Program for Ventilator Dependent Older Patients</td>
</tr>
<tr>
<td>Probing the Neural Basis and Influence of Cognitive Changes on Impaired Balance in Older Adults</td>
</tr>
<tr>
<td>Using Self-Triggered, Sensory-Enhanced Gaze Shift to Improve Axial Turning Deficits in Persons with Parkinson’s Disease</td>
</tr>
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</table>

**Year 3 UM-OAIC Pilot Projects: 2013-2014**

| Early Mobilization of Older Adults after Emergency Surgery | L. Buchanan, MD |
| The Effect of Voluntary Exercise on Microglial Activation Phenotypes in the Aged Injured Brain | D. Loane, PhD |

**Year 4 UM-OAIC Pilot Projects: 2014-2015**

| Ambulatory Activity in Elderly Patients in a Shock Trauma Center | I. Berges, PhD |
| Targeting Corticostriatal Plasticity for Parkinson’s Disease Treatment | B. Mathur, PhD |
| Modulation of Interhemispheric Interactions and Arm Activity after Stroke | M. Dimyan, MD |
| Circulating MicroRNAs in Older Adults | J. Deiuliis, PhD |
| Multimodal Rehabilitation and High Protein Supplementation to Minimize ICU-Associated Sarcopenia in the Elderly | A. Verceles, MD/C. Wells, PhD, PT, CCS, ATC |

**Year 5 UM-OAIC Pilot Projects: 2015-2016**

| Muscle and Functional Assessment in Leakage Study | T. Sanses, MD |
| The Development of a New Biomarker for the Diagnosis of Concussion | N. Badjatia, MD, MSc, FCCM |
| Towards Next-Generation Phenotyping in Parkinson Disease: Quantitative Analysis of Gait and Balance Using a Portable Biosensor Device | R. von Coelln, MD |
| Can Lateral Step Training Improve Initial Postural Adjustments in Stroke? | V. Gray, PT, PhD |
| Functional Benefit of Exercise Therapy after Endovascular Intervention in Older Patients with PAD | R. Kundi, MD |

1. **Exercise and Weight Loss to Improve Mobility in Veterans with PAD**

   **PI: O. Addison, D.P.T., Ph.D.**
   **VA CDA**
   **06/01/2016-05/31/2021**

   This study will determine whether weight loss and exercise will improve mobility function to a greater extent than exercise alone and determine the mechanisms underlying these improvements by measuring muscle microvascular perfusion, inflammation, quality and composition in older obese veterans with PAD.

   **Supported by RC 1, 2 and 3**
2. Modulation of Interhemispheric Interaction and Arm Activity after Stroke  
PI: M. Dimyan, M.D.  
K23 NS088107  
07/01/2014-06/30/2019  
The goal of this study is to investigate interhemispheric interaction dynamics across multiple time-points during arm muscle activity and determine the pathological changes that occur with aging and after stroke.  
Supported by RC 1 and 3

3. Adaptive Ankle Robot Control System to Reduce Foot-Drop in Chronic Stroke  
L. Forrester  
VA Merit  
06/01/2015-05/31/2019  
In subjects with chronic stroke, this study will compare the effects of using an adaptive control system to integrate modular ankle robotic training with treadmill exercise vs. regular treadmill training without the robotic support. The hypothesis is that the robotics + treadmill approach will mediate greater gains in paretic leg propulsion, gait biomechanics, and balance control than the treadmill only approach.  
Supported by 1, 2 and 3

4. Improving Balance and Function in Older Veterans  
PI: L. Katzel, M.D., Ph.D.  
VA SPIRE Pilot Study  
04/01/2015-03/31/2017  
This VA SPIRE pilot study is a small randomized clinical trial comparing the effect of multimodality training versus Tai Chi on balance and functional performance on older adults at risk for falls.  
Supported by RC 1, 2 and 3

5. Exercise for Prevention of PTS through Enhanced Resolution of Thrombus  
PI: B. Lal, M.D.  
VA Merit  
07/01/2014-06/20/2018  
The goal of this study is to determine whether a therapeutic exercise program prevents post-thrombotic syndrome in patients with acute deep vein thrombosis, and to assess the effects of exercise therapy on fibrinolysis and thrombus resolution, as well as venous hemodynamics and exercise capacity.  
Supported by RC 2

6. Early Exercise to Improve Muscle and Cardiometabolic Health after Stroke  
PI: R. Macko, M.D.  
R01 HD068712  
04/01/2011-03/31/2016  
This study examines whether exercise started early after stroke can improve muscle structure and function and in so doing, improve cardiovascular health to prevent or reverse diabetes. We choose Jamaica as the study site because they have no rehabilitation (or exercise) after stroke, so we can truly understand the added benefits of exercise over best medical care, giving hope to stroke survivors and enabling us to know how to provide better care for our African-American minorities that suffer more from stroke in the U.S.  
Supported by RC 2
7. Community Ambulation Following Hip Fracture  
   PI: J. Magaziner, Ph.D., MS Hyg  
   R01 AG035009-01A1  
   09/01/2010-08/31/2017

This randomized controlled multi-center study will evaluate the effect of a 4 month, home delivered multi-component intervention on survival and the ability to ambulate independently in the community among older men and women who have sustained a hip fracture. The project also will investigate precursors to community ambulation and the cost effectiveness of delivering the program to this frail and disabled population of older persons.

Supported by RC 1, 2, 3

8. The Effects of Multi-Modal Exercise Intervention Post Hip Fracture  
   PI: J. Magaziner, Ph.D., MS Hyg  
   R37 AG009901  
   09/01/2011-08/31/2018

The goal of this study is to evaluate some of the key mechanisms on the pathway to changes in community ambulation in response to a Multi-Modal Intervention delivered to this frail and disabled group of older persons. This is being done as an ancillary study to a Phase III randomized clinical trial (1R01AG035009).

Supported by RC 1

   PI: G. Ostir, Ph.D.  
   CareFirst  
   05/01/2016-04/30/2017

The purpose of the telemedicine program is to provide nursing home residents with access to emergency medicine expertise and resources via telemedicine consultation. Major objectives of the telemedicine program are to improve communications between health care providers and reduce potentially avoidable transfers of nursing facility residents to emergency departments.

10. Exercise Training, CACs and Vascular Function in Older Veterans with IGT  
    PI: S. Prior, Ph.D.  
    VA Merit  
    10/01/2013-09/30/2017

This study tests the hypotheses that a) 6-month aerobic exercise training will improve circulating angiogenic cell (CAC) mobilization and function in older Veterans with IGT by increasing angiogenic growth factor levels and reducing inflammation and CAC oxidative stress, and b) the improvements in CAC mobilization and function will translate to better vascular function and insulin sensitivity in these older Veterans.

Supported by RC 1 and 2

11. Post-Revascularization Rehabilitation to Improve Function in Veterans with PAD  
    PI: S. Prior, Ph.D.  
    VA SPIRE  
    01/14/2016-12/31/2017

This study will test the hypothesis that a supervised rehabilitation program will improve mobility function, ambulatory capacity, and QOL more than standard care, and these improvements occur through mechanisms including increases in angiogenesis, capillary density, and muscle perfusion in veterans with PAD after revascularization.
12. Protective Balance and Startle Responses to Sudden Drop Perturbations in Aging
PI: M. Rogers, Ph.D., PT, FAPTA
R21 AG049615
08/01/2015-05/31/2017
The project’s focus is on understanding the causes of age-associated falls and on the development of effective interventions for minimizing the devastating economic, societal, and personal consequences of falls among older people.
Supported by RC 1, 2, 3

13. Transmission of Antibiotic-Resistant Gram-Negative Bacteria (R-GNB) in Nursing Homes
PI: MC.Roghmann, M.D., MS
R03 AI122223
03/01/2016-02/28/2018
Healthcare associated infections (HAI) are common in nursing homes and are often caused by multidrug-resistant organisms (MDRO) such as MRSA and antibiotic resistant Gram-negative bacteria (R-GNB). These MDROs colonize residents and can be spread from resident to resident by healthcare personnel. The use of gowns and gloves can prevent this spread decreasing the risk of HAI; however, their use detracts from a home-like environment which is an important priority for nursing homes.
Supported by: RC 1

14. 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
This study tests the hypothesis that resistive training+protein supplementation will be more effective than resistive training+placebo for restoring lean tissue and stimulating muscle protein synthesis within the myostatin regulatory network in those disabled by stroke.
Supported by RC 1 and 2

15. Aerobic Training to Improve Energy Utilization and Antioxidant Capacity in Stroke
PI: M. Serra, Ph.D.
VA Career Development Award-2
04/01/2014-03/31/2019
This study examines how six months of treadmill and nutritional rehabilitation versus stretching control affects fatigue, metabolic flexibility, and local and skeletal muscle oxidative stress in chronic stroke survivors.
Supported by RC 1 and 2

16. Investigating Parkinson Disease Genetics in a Longitudinal PD Database
PI: L. Shulman, M.D.
Private Donor- Euginia Brin
07/01/2014-06/30/2018
The primary objective is to investigate the genetics of subtypes of Parkinson disease (motor, cognitive, behavioral). The secondary objective is to investigate patient and family attitudes about genetics analyses in PD and to explore best practices for patient-clinician communication about genetics testing.
Supported by RC 1
17. Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial
   PI: M. Terrin, Ph.D.
   R01 AG037120
   08/15/2011-07/31/2016
   The primary aim of this multi-site clinical trial is to determine if doxycycline (100mg bid) will inhibit by at least 40% the increase in greatest transverse diameter of small abdominal aortic aneurysms over a 24-month period of observation in comparison to a placebo-treated control group.
   Supported by RC 1

18. The Multimodal Rehabilitation of Older Ventilated Survivors of Critical Illness
   PI: A. Verceles, M.D.
   R03 AG045100
   08/15/2013-07/31/2016
   This pilot study tests the hypothesis that an MRP, which combines strength, endurance training, and functional retraining for older, mechanically ventilated survivors of critical illness, can improve functional mobility, strength, endurance, weaning from prolonged mechanical ventilation and discharge status compared to usual care in a long term acute care hospital facility mechanical ventilation weaning unit.
   Supported by RC 1 and 2

19. Rehabilitation, NMES and High Protein to Reduce Post ICU Syndrome in the Elderly
   PI: A. Verceles, M.D.
   R21 AG050890
   08/01/2015-07/31/2017
   This study tests the hypothesis that preventive therapy involving the addition of neuromuscular electrical stimulation and high protein feeding to mobility-based physical rehabilitation program early and throughout the ICU hospital stay will mitigate PICS-associated sarcopenia, malnutrition, and immobility to confer valuable health benefits in older patients requiring mechanical ventilation.
   Supported by RC 1 and 2

20. Driving Cortical Plasticity for Rehabilitation of Reaching after Stroke
   PI: G. Wittenberg, M.D., Ph.D.
   R01 HD061462
   06/20/2011-04/20/2016
   The parameters of TMS stimulation timing that best support practice related plasticity in the motor cortex will be determined.
   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
   This project will apply a single optimized intervention, robotic upper extremity training with repetitive task practice and measure predictive biomarkers for clinically significant improvement.
   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 Vasoaicity 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 Vasoreactivity 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 Katzel, 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 Katzel, 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 Katzel, 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, M.D.C.M., 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**
Kris Ann Oursler, M.D., Assistant Professor, (410) 605-7000 ext.7194 & Heidi Ortmeyer, PhD, Assistant Professor, (410) 605-7000 ext. 5419 (Charlene Hafer-Macko M.D., Alice Ryan Ph.D., Andrew Goldberg, M.D., Mentors)
UM-OAIC & MERCE Joint Pilot Collaboration

**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, M.D., 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)

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)

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)

Circulating MicroRNAs in Older Adults
Jeffrey Deiuliis, Ph.D., Assistant Professor, (410) 328-4096 (Alice Ryan, Ph.D., Mentor)

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)

Multimodal Rehabilitation and High Protein Supplementation to Minimize ICU-Associated Sarcopenia in the Elderly
Avelino Vercel, MD, Assistant Professor, (410) 328-8141 (Andrew Goldberg, M.D. and Michael Terrin, M.D., Mentors)

Year 21 (2015-2016)
Muscle and Functional Assessment in Leakage Study
Tatiana Sanses, M.D., Assistant Professor, (410) 328-2385 (Alice Ryan, Ph.D., Mentor)
The primary aims of the study are to assess muscle quality and functional status in older women with urinary incontinence. Aim 1. To characterize functional status in women ≥ 70 years of age with symptoms of UI and correlate these findings with severity of UI. Hypothesis: Women with worse functional status based on specific objective evaluation will have worse symptoms of UI assessed by validated questionnaires. Aim 2: To phenotype women ≥ 70 years of age with symptoms of UI assessed by validated questionnaires. Hypothesis: Women with decreased quality (atrophy and fatty infiltration) of pelvic floor musculature and lower extremities will have decreased functional status and worse symptoms of UI.

The Development of a New Biomarker for the Diagnosis of Concussion
Neeraj Badjatia, M.D., M.Sc., FCCM, Associate Professor, (410) 328-4515 (Alan Faden, M.D., Mentor)
Circulating microRNAs (miRs) have not yet been examined to determine if they can be used as biomarkers of concussion. miRs are a large class of endogenous, small, non-coding RNAs that regulate gene expression at the
post-transcriptional level and are thought to be involved in regulating expression of more than 30% of messenger RNAs. The expression of individual clusters of miRs appears to be cell and tissue specific and altered in disease specific patterns. Detectable levels have been isolated in serum, plasma, and cerebrospinal fluid. In the CNS the action of miRs have been shown to play key roles in neurodevelopment and are likely to be important mediators of plasticity as well as neurodegeneration. Specific to TBI, several recent studies in models of moderate and severe TBI have shown a differential expression of miRNAs corresponding to neurodegeneration and cell death. Studies from the Faden laboratory have further shown experimental evidence of a cluster, miR-711, that rise in blood plasma, mirroring time lapsed changes seen in injured cortex. Further experiments have demonstrated this miRNA cluster to be important regulators of neuronal apoptosis. We believe expression of miR-711 in plasma may represent a novel biomarker for the assessment of the neuronal injury associated with brain injury after concussion, and may aid in the future development of diagnostic and therapeutic interventions for concussion. We have begun a pilot study investigating the association between the miR-711 biomarker and clinical diagnosis of concussion in subjects age 21 – 50. This age range was originally chosen as a method by which to control for any impact aging may have on miR-711 expression; however, additional funding would allow us to assess the ability of this biomarker to 1) diagnose mild TBI in an aging population and 2) compare any age related differences that may exist in the expression of miR-711. Our hypotheses for a cohort of elderly subjects, defined as age > 51 years old are noted below.

Hypotheses: 1) Non – hemorrhagic concussion (NHC) results in neuronal injury reflected by an acute elevation of plasma levels of miR-711; 2) The level of acute rise of plasma miR-711 after NHC corresponds to post concussive symptoms and cognitive deficits.

Aims: 1) To demonstrate an increase in plasma levels of miR-711 in within 6 hours of injury in subjects sustaining a NHC as compared to healthy controls; 2) To measure the association between plasma levels of miR measured within 6 hours of NHC and performance on post concussive questionnaires and cognitive testing as evaluated by the Rivermead Post Concussion Questionnaire12 and Montreal Cognitive Assessment (MOCA) Scale13, 14, respectively, 24 hours after injury.

Towards Next-Generation Phenotyping in Parkinson Disease: Quantitative Analysis of Gait and Balance Using a Portable Biosensor Device

Rainer von Coelln, M.D., Assistant Professor, (410) 328-7809 (Lisa Shulman, M.D., Mentor)

Impairment of gait and balance are key determinants of disability in PD. Clinical scales of PD symptom severity, including gait and balance, have been used to define motor subtypes of PD, e.g., the "Postural Instability and Gait Difficulty" subtype. However, these scales are limited by their subjective and semi-quantitative nature. Objective and quantitative analysis of gait and balance with a new generation of portable biosensor devices offers the opportunity to investigate mechanisms of disability due to gait and balance impairment in PD in great detail with minimal additional effort, compared to the standard clinical assessment. I propose to use a small light-weight portable whole-body biosensor device called Dynaport Hybrid for quantitative gait and balance analysis in PD. I will focus on the following aspects: 1) To establish re-test reliability of gait and balance measures performed with the Dynaport in PD patients; 2) to examine the Dynaport's potential to discriminate between levels of disease severity defined by conventional clinical scales; 3) to evaluate whether the Dynaport's potential to identify patients with increased risk of stumbling and falling is superior to conventional scales of PD severity.

The goal is to establish biosensor-based gait and balance analysis as a practical and valid tool in PD phenotyping. This project will provide preliminary data that will be instrumental for my application for an NIH career development award, focused on the use of biosensor-based phenotyping in refining motor subtypes and identifying PD phenotype-genotype correlations.
Can Lateral Step Training Improve Initial Postural Adjustments in Stroke?
Vicki Gray, P.T., Ph.D., Post-Doctoral Fellow, (410) 706-3778 (Mark Rogers, Ph.D., P.T., Mentor)

Sensorimotor and balance deficits after stroke increase risk of falling. Most falls after stroke occur during ambulation and transfers when weight is shifted laterally. There are an equal number of falls during planned voluntary actions as during unexpected disturbances, such as a slip, trip, or push. Balance is usually recovered with a protective step and the sensorimotor deficits impair one’s ability to recover a loss of balance. We have previously found impairments in both voluntary and reactive reflex-like protective forward steps in people affected by stroke. It is likely the two forms of steps involve mechanisms that are differentially affected by a stroke.

Current rehabilitation practices mainly focus on intentional voluntary actions rather than reactive balance training. Voluntary movements involve a cognitive component to plan and initiate the movement and low connectivity in the dorsolateral prefrontal cortex may inhibit motor learning. An increase in connectivity and activity of the primary motor cortex, primary sensorimotor cortex supplementary motor area brain stem and cerebellum midline may contribute to the motor recovery after stroke.

The purpose of this study is to compare the effects of two exercise training approaches, voluntary lateral step training and reactive lateral step training on lateral balance control in persons with chronic stroke, as assessed by an earlier initiation time of the center of pressure displacement and muscle activation of the leg and hip muscles, and a reduced response duration. Participants will also undergo functional MRI to determine if the anatomical connectivity, specifically the primary sensorimotor cortex, dorsolateral prefrontal cortex, primary motor cortex, and supplementary motor area, and the brain stem, and cerebellum midline can predict those individuals that will have motor gains after step training. The anatomical and functional connectivity of the primary sensorimotor cortex, dorsolateral prefrontal cortex, primary motor cortex, and supplementary motor area, and the brain stem, and cerebellum midline will be assessed after training to determine if those individuals in the reactive group show greater improvements in connectivity and activity in the brain stem, motor cortex and cerebellum. This research will provide improved understanding of the brain connectivity and motor changes that result from voluntary and reactive reflex-like training.

Functional Benefit of Exercise Therapy after Endovascular Intervention in Older Patients with PAD
Rishi Kundi, M.D., Assistant Professor, (410) 328-5840 (Brajesh Lal, M.D., Mentor)

Aim 1 will determine the effects of an exercise program implemented after endovascular intervention on lower extremity perfusion and patency of the revascularized lesion.

We will assess lower extremity perfusion and durability of the intervention compared to control over 6 months of follow-up. The primary outcome measures will be noninvasive vascular laboratory measurement of ankle-brachial index and primary patency of the revascularized lesion. Secondary measures will be digital perfusion pressure, segmental Doppler ultrasound waveform assessment, secondary patency, and reoperation rate.

Aim 2 will determine the effects of post-intervention exercise therapy on physical function and quality of life in older adults with PAD.

We will achieve this by assessing physical function and quality of life in the intervention group over 6 months of follow-up. The primary outcome measure will be the short physical performance battery (SPPB), SF-36 and VascuQoL-6 score; secondary measures will be the modified PTT, walking impairment score (WIS) and initial and absolute distances to claudication during a treadmill test.

Aim 3 will examine vascular, angiogenic, and muscular mechanisms through which post-intervention exercise may improve perfusion, limb function, general functional capacity and quality of life.

A) We will determine treated artery flow and distal perfusion. Blood flow in the revascularized arterial segment will be assessed through contrast-enhanced Duplex ultrasound and MRI. Gastrocnemius needle biopsy will allow quantification of muscle capillarization and expression of VEGF and bFGF via RT-PCR and multiplex ELISA.

B) We will determine the effect of post-intervention exercise therapy on limb muscle mass, muscular strength, and muscle fiber size. Muscle mass will be assessed via DEXA scan and limb strength through exercise testing.
Needle muscle biopsy will allow quantification of myofibril size and strength and provide tissue for RT-PCR and Western Blot quantification of PGC-1α expression. Collectively, the proposed studies will define the role of a program of supervised exercise following endovascular intervention for lower extremity arterial disease as a novel adjunct in older patients with peripheral arterial disease.

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 RR&D Merit Pilot Project: Adaptive Ankle Robot Control System to Reduce Foot-Drop in Chronic Stroke (Co-PI Forrester)
- 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)
- VA Merit: Veterans with Stroke Translating Exercise Programs (VET STEP) (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)
- M01: RR016500: 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”
- 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
- VA Merit: Resistive Training Combined with Nutritional Therapy after Stroke (PI Ryan)
- 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 (Co-PI Shaughnessy)
- VA Merit: Veterans with Stroke Translating Exercise Programs (VET STEP) (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)
• 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 AG045100: 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)
• R21 AG050890: Rehabilitation, NMES and High Protein to Reduce Post ICU Syndrome in the Elderly

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 on Interhemispheric Interactions and Arm Activity after Stroke

David Loane, Ph.D., Assistant Professor, Department of Anesthesiology, University of Maryland Baltimore
• P30 AG028747: The Effect of Voluntary Exercise on Microglial Activation Phenotypes in the Aged Injured Brain
• R01 NS082308: Microglial Activation Phenotypes and Mechanisms of Repair in the Aged TBI Brain

Tatiana Sanses, M.D., Assistant Professor, Department of Obstetrics and Gynecology, University of Maryland Baltimore
• P30 AG028747: Muscle and Functional Assessment in Leakage Study
• BIRCWH Institutional K12: Pelvic Floor Muscle Function in Aging Women with Pelvic Floor Disorders

Brian Mathur, Ph.D., Assistant Professor, Department of Pharmacology, University of Maryland Baltimore
• P30 AG028747: Targeting Corticostriatal Plasticity for Parkinson’s Disease Treatment
• K22 AA021414: Targeting Corticostriatal Plasticity for Parkinson’s Disease Treatment

Jeffrey A. Deiuliis, Ph.D., Assistant Professor, Department of Medicine, University of Maryland Baltimore
• P30 AG028747: Circulating MicroRNAs in Older Adults
• K01 DK099475: Adipose microRNAs (miRs) in Insulin Resistance
Danielle Beatty, Ph.D., Assistant Professor, Department of Psychology, University of Maryland Baltimore County
K01 AG043581: Race, Childhood Social Disadvantage, and the Adult Brain

IV. PUBLICATIONS

2015-2016


Klyushnenkova EN, Sorkin JD, Gallicchio L. Association of Obesity and Sleep Problems among Breast Cancer Survivors: Results from a Registry-Based Survey Study. Support Care Cancer. 2015. PubMed PMID: 25773672; PubMed Central PMCID: PMC4569517. [RC1]


Prior SJ, Goldberg AP, Ortmeyer HK, Chin ER, Chen D, Blumenthal JB, Ryan AS. Increased Skeletal Muscle Capillarization Independently Enhances Insulin Sensitivity in Older Adults after Exercise Training and Detraining. Diabetes. 2015;64(10):3386-95. PubMed PMID: 26068543; PubMed Central PMCID: PMC4587640. [RC2, PESC]


V. EXTERNAL ADVISORY BOARD MEMBERS

Karen Bandeen-Roche, PhD
Professor
Department of Biostatistics
Johns Hopkins Bloomberg School of Public Health

Rebecca (Becky) Craik, PT, PhD, FAPTA
Professor and Chair, Physical Therapy
Department of Physical Therapy
Arcadia University

Thomas M. Gill, MD
Professor of Medicine, Epidemiology & Public Health
Yale University School of Medicine

Bret Goodpaster, PhD
Senior Investigator
Translational Research Institute for Metabolism and Diabetes
Florida Hospital, Burnham Medical Research Institute

Alan M. Jette, PT, PhD
Director, Health & Disability Research Institute
School of Public Health
Boston University Medical Campus

Stephen Kritchevsky, PhD
Director, Sticht Center on Aging
Wake Forest University Baptist Medical Center

R. Sean Morrison, MD
Director, National Palliative Care Research Center
Brookdale Department of Geriatrics & Adult Development
Mount Sinai School of Medicine

Mark Redfern, PhD
Co-Director, Medical Virtual Reality Center
Department of Otolaryngology
University of Pittsburgh
Mary Rodgers, P.T., Ph.D., F.A.P.T.A., F.A.S.B. received the John H.P. Maley Award for Outstanding Contributions to Leadership in Research, Section on Research, American Physical Therapy Association.

Mary Rodgers, P.T., Ph.D., F.A.P.T.A., F.A.S.B. was elected Chair, Research-Intensive Physical Therapy Programs Consortium (RIPPT), Academic Council of Academic Physical Therapy (ACAPT).

Brian Mathur, Ph.D. was elected President of the Society for Clastrum Research for a 2 year term.

Shari R. Waldstein, Ph.D. was named the 2015-2016 Lipitz Professor of the Arts, Humanities, and Social Sciences at UMBC.

Shari R. Waldstein, Ph.D. was elected to the Executive Council of the Academy of Behavioral Medicine Research.
UM-OAIC Minority Research  
2015-2016

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:  
PI: Jay Magaziner, Ph.D., M.S.Hyg.  
Project Title: Effects of Multi-Modal Exercise Intervention Post Hip Fracture  
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.
University of Michigan
Claude D. Pepper Older Americans Independence Center

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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 (MICHRI, 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 database 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

Raymond Yung, M.D., Program Director 734-647-9746 ryung@umich.edu
Jeffrey Halter, M.D., Co-Program Director 734-764-3493 jhalter@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 myotrogen 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

Year 06 1994-1995
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 aualitative 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
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

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

The effect of vibrotactile tilt feedback on postural and gait stability in older adults
Kathleen Sienko, Ph.D., Assistant Professor of Mechanical Engineering, College of Engineering

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 (SWN) 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

Hypothalmic regulation in crowded litter mice: early life control of aging an d 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

Year 27- 2015-2016

Autophagy activity and adipose tissue mediated inflammation in aging
Amiya Kumar Ghosh, Ph.D., Research Investigator, Internal Medicine – Geriatrics and Palliative Medicine

Cognitive, functional, & behavioral risks for hospitalization of older adults
Donovan Maust, M.D., Assistant Professor, Psychiatry
Genomic analysis of multi-drug resistant organism transmission within and between nursing homes
Evan Snitkin, Ph.D., Assistant Professor, Internal Medicine – Division of Infectious Diseases

Olfactory social cues as regulators of mouse aging
Michael Garratt, Ph.D., Assistant Professor, Pathology

Hearing aid receipt by geographical, socioeconomic status, and health literacy
Michael McKee, M.D., Assistant Professor, Family Medicine

Intracortical biomarkers for promoting neural plasticity post-stroke
Sean Meehan, Ph.D., Assistant Professor, Kinesiology

SECTION III. Career Development (Listing from 2004-2016). Current academic titles are provided. All at University of Michigan, unless noted otherwise.

James Harper, Ph.D., Research Investigator, Pathology (2006-2008)
Grants Awarded

Allison Aiello, Ph.D., Professor and Social Epidemiology Program Leader, Epidemiology, Gillings School of Global Public Health, University of North Carolina (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 Grolleau-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., Assistant Research Scientist, 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, School of Medicine, University of Mississippi (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, School of Medicine, University of Alabama at Birmingham (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., Associate 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, Ohio State University (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., Assistant Professor, 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


R01 AG047178 (Min, PI) Optimizing Treatment of Older Adults with Hypertension: A Net Benefit Analysis of Falls Injury vs Cardiovascular Outcomes 9/1/2015-4/30/2020

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., Assistant Professor, Department of Microbiology and Immunology, Montana State University (2012-2013)

Kathleen H. Sienko, Ph.D., Arthur F Thurnau 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., Assistant Professor, Internal Medicine – Infectious Diseases (2014-2016)

Marianna Sadagurski, B.Sc., Ph.D., Research Assistant Professor, Internal Medicine – Geriatrics and Palliative Medicine (2014-2016)

Carrie Karvonen-Guiterrez, Ph.D., Research Assistant Professor, Epidemiology (2015-2016)

Vikas Kotagal, M.D., Assistant Professor, Neurology (2015-2016)
Grants Awarded
SECTION IV. PUBLICATIONS: Provide only those that are a direct result of Pepper Center resources and list publications published in the 2015-2016 funding year only (7/1/15 – 6/30/16).


Jepsen KJ, Bigelow EMR, Ramcharan M, Schlecht S, Karvonen-Gutierrez C. Moving toward a prevention strategy for osteoporosis by giving a voice to a silent disease. J Women’s Midlife Health 2016;2:3


Langa KM. Is the risk of Alzheimer’s disease and dementia declining? Alzheimer’s Research and Therapy. 2015; 7(1): 34. PMC4374373

Langa KM, Cutler D. Opportunities for insights on the life-course risks and outcomes of cognitive decline in the Kavli HUMAN Project. Big Data. 2015; 3(3): 189-192. PMC4605212


Levine D, Kabeto M, Langa KM, Lisabeth L, Rogers M, Galecki A. Does stroke contribute to racial differences in cognitive decline? Stroke. 2015; 46(7): 1897-1902. PMC4480064


of the health benefits seen in global GHR-/mice. Aging 7:500-512. 2015; PMID: 26233957 PMC4543039.


**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 2015-2016 grant year included:
Raul Mostoslavsky, M.D., Ph.D., Associate Professor of Medicine, Harvard Medical School / Massachusetts General Hospital
Daniel Goldstein, M.D. Professor of Internal Medicine/Cardiology, Yale University

Other recent external reviewers include:
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 2016.

- David Lombard, former pilot grant awardee and RCDC participant: promoted to Associate Professor with tenure; 2016 Elected Member, American Society for Clinical Investigation (ASCI)

- Lillian Min, former pilot grant and RCDC awardee: promoted to Associate Professor with tenure

- Lona Mody, director of the PESC, promoted to Professor with tenure and selected by the Department of Internal Medicine to receive the Amanda Sanford Hickey Professorship.

- Vineet Chopra, former pilot grant and RCDC awardee: 2016 Jerome Conn Award (outstanding junior faculty investigator in the UM Dept of Internal Medicine)

- Jeffrey Halter, OAIC Director: Selected to be the Parkway Visiting Professor in Geriatrics, Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore
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 and is mentored by Dr. James Ashton-Miller, Co-Leader of the Biomechanics Core).

Vicky Johnson-Lawrence, Ph.D., Assistant Professor, Department of Public Health and Health Sciences, University of Michigan at Flint will be a KL2 scholar in the Research Career Development Core in the coming year. Her research interests are socioeconomic determinants of multimorbidities and racial/ethnic health disparities over the life course.

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. Langa is also mentoring Elena Byhoff, a Robert Wood Johnson Clinical Scholar, whose research focuses on racial and ethnic differences in Medicare expenditures.

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:

Nnodim JO, Yung RL. Balance and its Clinical Assessment in Older Adults - A Review. *J Geriatr Med Gerontol.* 2015;1(1). PMCID: PMC4773046


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

Our specific aims 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-l’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: 412692-2023, 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 α estimation, where α describes the structure of dependence. But controversies remain about the method of estimation of α. 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 α=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 α. 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 α 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: 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 2: 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. 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 3: Neuroimaging Motor Skill, Learning and Adaption for Walking
Project Leaders: Jessie VanSwearingen, PhD, PT, FAPTA (Assoc Prof, Physical Therapy); Co-Investigator Andrea Rosso, PhD (Asst Prof, Epi);

Significance: The proposed work will form the scientific basis necessary to: 1) evaluate neuroplastic effects of motor learning interventions for walking; 2) derive and test further novel approaches to achieve both walking efficiency and neural efficiency; and 3) incorporate motor learning exercise into standard interventions to prevent or treat age-related walking problems. Our findings could establish a link between age-related changes in gait and greater brain activity in a broad network of cortico-cortico regions; the loss of neural efficiency for walking. The link to central neural functional mechanisms would be a substantial departure from the more commonly held explanations for gait dysfunction of aging – muscle weakness, joint biomechanical limitations, cardiorespiratory deconditioning and skeletal muscle mitochondrial damage. The proposed work is also important to advance knowledge of motor learning and neural correlates of motor skill in older adults. The ability of older adults to learn new motor skills is known, but little has been described about the functional neural circuitry correlates of compensated walking performance in older adults with age-related loss of motor skill in walking.

Approach: We will recruit older adults (n=10) enrolled in the motor learning based exercise (Standard-Plus, Task Specific Timing and Coordination Intervention) arm of our partnering NIA funded clinical trial (R01 AG045252) to participate. Older adults in the RCT parent study are ≥ 65 years old, and walk slower than the usual (range, 0.60m/s to 1.2m/s), representative of a range of age-related loss of motor skill in walking. The target population is older adults with age-related loss of motor skill in walking, excluding stroke or progressive neurological diseases. The critical exclusion criteria: 1) non-neurological related (e.g., arthritis, cardiovascular disease, cardiopulmonary obstructive disease, peripheral vascular disease) slowing of gait, and 2) health problems that prohibit safe participation in walking tasks and neuroimaging. B.2.1 Timeline (Table).We will
enroll approximately 3 subjects a month for ~3.5 months, total 10 subjects. All subjects will be enrolled and all testing completed by month 6.

**PES 4: Reversal of Chondrocyte Aging by 3D Cytoskeletal Re-organization**  
Project Leaders: Rocky S. Tuan, PhD (Prof, Ortho), Hang Lin, PhD (Research Instructor, Ortho)

Significance: To our knowledge, there have been no studies on the effect of cytoskeletal disruption on aging chondrocytes. We therefore hypothesize here that a 3D re-organization of the cytoskeleton will rejuvenate aging chondrocytes back to a stable phenotypic state comparable to that of young chondrocytes. To test our hypothesis, in Aim 1 we will first analyze how cytoskeletal organization relates to the phenotypic state of chondrocytes and test the effect of different cytoskeleton-disrupting agents and treatment regimens on proliferation capacity and phenotype of aging chondrocytes. The goal is to identify the best cytoskeleton-disrupting agent(s) and conditions in reversing the senescent state, which will be used to rejuvenate aging chondrocytes in following studies. In Aim 2, rejuvenated chondrocytes generated from optimized treatment will be culture expanded, loaded within a chondrosupportive hydrogel scaffold developed in our lab and transplanted subcutaneously into mice to assess their cartilage formation capacity. Untreated aged chondrocytes and cells isolated from young cartilage will serve as negative and positive controls, respectively.

Approach: As presented above, cytoskeletal organization is closely related to the cellular age of chondrocytes. We hypothesize that elongated and stressed microfilaments and dense microtubules accompany the aging progress, and that disrupting these cytoskeletal structures is able to halt or reverse chondrocyte aging state. We will first investigate the direct relationship between cytoskeletal structure alteration and cellular aging, i.e., relative gene expression of collagen type II/I, aggrecan/versican. Senescence-associated (SA) β-galactosidase (SAG), a marker of cell senescence, will also be analyzed. With IRB approval (University of Washington/University of Pittsburgh), we have regular access to surgical wastes, including knee joints, from patients that have undergone total joint arthroplasty. Articular cartilage will be harvested from macroscopically asymptomatic areas of the knee articular surface, and human chondrocytes isolated by collagenase II digestion. The state and organization of microfilaments, microtubules and intermediate filaments will be visualized by epifluorescence microscopy using fluoroprobe-tagged phalloidin, and anti-tubulin and anti-vimentin antibodies, respectively, using standard protocols in our lab. Chondrocytes will be treated with different agents for 1 or 3 days, including microfilament-disrupting and microtubule-disrupting agents, at concentrations similar to published dosages: (1) microfilament disrupting agents - Cytochalasin D, 1 μM; latrunculin B, 1 μM; dihydrocytochalasin B, 3 μM; staurosporine, 1 μM; (2) microtubule disrupting agents – nocodazole, 10 μM; Myoseverin: 25 μM. After 3 days of additional culture, single cells will be harvested by using a collagenase II-containing enzyme mixture reported before, and cytoskeletal structure, proliferation capacity and gene expression will be assessed as described above. Based on these results, best-performing agents/conditions for microfilament and microtubule disruption will be identified.
**PES 5: Exercise improves aging tendons by inducing cellular and molecular changes**

Project Leaders: James H-C. Wang, PhD (Prof, Ortho); MaCalus Hogan, MD (Asst Prof, Ortho)

Significance: With an increase in the aging population, aging-related musculoskeletal tissue problems have become a huge healthcare concern. In particular, aging decreases the mechanical properties of tendons and as a result, predisposes tendons to injury. Aging also impairs tendon healing, and is a major risk factor for tendinopathy or degenerative changes in tendons. Thus, aging impairs the quality of life among millions of aging population in the United States. Treatment of such injuries cost billions of health care dollars every year.

This study is highly innovative because: a) This is the first study to test a novel hypothesis that moderate exercise improves the biological and biomechanical properties of aging tendons by rejuvenating TSCs and thus improves tendon matrix structure and function; and b) this is also the first comprehensive study to determine how moderate exercise regulates tendon cell senescence and therefore moderate exercise may be used to treat degenerative changes in the tendons of aging patients in clinical settings.

Approach: The experimental design for this aim consists of an MTR group and a control group, each with 54 male aging mice (20 months). Mice in the MTR group will be subject to a regimen of treadmill running 13 m/min, 50 min/day, 5 days/week/. After treadmill running, mice will be scarified, and patellar and Achilles tendons will be harvested for the following analyses. 1) Detecting senescent cells by staining for SA-β-gal on tendon sections (6 mice). 2) Using Western blot analysis to measure CCN-1, p53 and p16 expression (12 mice); 3) applying qRT-PCR, ELISA, and Western blot to detect the senescence-associated secretory phenotype (SASP) including the expression of collagen I and III; MMP-1, MMP-3, MMP-13, IL-6 and IL-8 (20 mice); and 4) by immuno-staining CD31, a marker for angiogenesis (4 mice), to reveal the role of angiogenesis in the remodeling of degenerative aging mouse tendons due to MTR.

Functional evaluation of aging tendons before and after MTR – Mechanical testing will be performed to evaluate the impact of MTR on tendon function. A total of 12 mice in each group will be used for the testing. Both the structural and mechanical properties of the mouse patellar tendon (e.g. stiffness and ultimate tensile strength) will be determined.

**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.
RECs Scholars 2015-2016:

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. She became a Pepper Scholar in August 2014 to look at the association between insomnia, falls and mobility with Dr. Buysse as her primary mentor. In this way, Dr. Tyagi continued as a K 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 began 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 became the basis of her KL2 proposal in 2015. Specifically, with Dr. Kirk Erickson, she is examining 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 (2016-2017) to further develop a career in translational research.

<table>
<thead>
<tr>
<th>Name</th>
<th>Dates</th>
<th>Dept</th>
<th>Grants</th>
<th>Current Position</th>
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<tr>
<td>Jennifer Brach, PT, PhD</td>
<td>2004-05</td>
<td>PT</td>
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<td>Assoc Prof PT, Pepper Core Director</td>
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<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>
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<tr>
<td>Name</td>
<td>Year</td>
<td>Field</td>
<td>Grant/Funding Details</td>
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<tr>
<td>Stasa Tadic, MD</td>
<td>2007</td>
<td>Geri</td>
<td>Hartford Scholar, K23</td>
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<tr>
<td>Kimberley Faulkner, PhD</td>
<td>2007-08</td>
<td>Epi</td>
<td>NIOSH grants</td>
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<td>Theodre Huppert, PhD</td>
<td>2007-09</td>
<td>Rad Bioeng</td>
<td>R01, R21, DARPA Co-I, SBIR Co-I</td>
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<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>
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<tr>
<td>Elizabeth Hile, PT, PhD</td>
<td>2010-11</td>
<td>PT</td>
<td>Komen Foundation, PCORI Co-PI</td>
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<tr>
<td>Neelesh Nadkarni, MD, PhD</td>
<td>2010-12</td>
<td>Geri</td>
<td>Hartford Scholar, K23</td>
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<tr>
<td>Ervin Sejdic, PhD</td>
<td>2011</td>
<td>Bioeng</td>
<td>R01</td>
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<td>Zachary Marcum, PharmD</td>
<td>2011-14</td>
<td>Geri Pharm</td>
<td>Co-I R01, Magee Foundation, Beckwith Foundation</td>
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<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>
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<tr>
<td>Linwah Yip, MD</td>
<td>2013-14</td>
<td>Surgery</td>
<td>Hartford Scholar, R03</td>
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<tr>
<td>Bethany Barone-Gibbs, PhD</td>
<td>2014</td>
<td>Health</td>
<td>American Heart Association</td>
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<tr>
<td>Shachi Tyagi, MD</td>
<td>2014-17</td>
<td>Geriatrics</td>
<td>Hartford Scholar</td>
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<td>Laurie Sanders, PhD</td>
<td>2014-17</td>
<td>Neurology</td>
<td>CTSI Grant</td>
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</table>

Section IV. Publications

2015


Section V. External Advisory Board Members 2015-2016

Nicolaas Bohnen, MD, PhD, Professor Radiology, Professor Neurology, University of Michigan – 6 Years

Pamela Duncan, PT, PHD, Professor Neurology, Wake Forest University – 11 Years

Luigi Ferrucci, MD, PhD, Scientific Director, NIA/NIH – 11 Years

Joe Verghese, MD, Professor of Medicine, Division of Geriatrics, Albert Einstein College of Medicine – 9 Years (ended 6/2016)

George A Kuchel, MD, CM, FRCP, AGSF, Professor Geriatrics and Gerontology, University of Connecticut- (Newly Appointed)
University of Pittsburgh
Awards and Recognition 2015-2016

Barone-Gibbs, Bethany
- 'Outstanding Junior Scientist' award from the University of Pittsburgh's Aging Institute at the 2015 conference
- Aging Institute Junior Faculty Award (2015)
- American Heart Association Fellowship (March 2016)

Bon, Jessica
- Young Investigator Award: 6/15
- Division of Pulmonary, Allergy & CCM, U. of Pitt.
- Junior Translational Scholar Award: 8/15
- Division of Pulmonary, Allergy & CCM, U. of Pitt.

Forman, Daniel
- Best Doctors in American Award

Glynn, Nancy
- Alumni Service Award, May 2015
- Distinguished Alumni Award – May 2015
- Margaret F. Gloninger Service Award

Greenamyre, J Timothy
- Listed, Best Doctors in America, 2015
- Elected, Association of American Physicians, 2015
- Vice Chair, Gordon Research Conference on Parkinson’s Disease, 2015-17
- Mentor, New Chair Orientation, Center for Scientific Review (CSR), NIH, 2015

Greenspan, Susan
- Vice President, National Osteoporosis Foundation, 2016
- Co-Chair Interdisciplinary Symposium on Osteoporosis, 2016
- Best Doctors in American Award, 2016
- Best Doctors in Pittsburgh Award, 2016
- Member, Clinical Trials Advisory Panel, NIA, 2016

Hanlon, Joseph
- William B. Abrams Award in Geriatric Clinical Pharmacology, American Society of Clinical Pharmacology and Therapeutics, 2016
- Faculty Honoree Convocation Award, UPITTT, 2016
- Sustained Contributions to Research Literature Award, American Society of Health-Systems Pharmacists, 2015

Jain, Samay
- Michael J. Fox Foundation for Parkinson Research (PI) - Rapid Response Innovation Award
• American Parkinson Disease Association, Inc (Consultant) : Mortality in PD: The PEACE Consortium
• UPMC Mitochondria, Aging and Metabolism Pilot Project Program (co-investigator): Assessment of peripheral mtDNA damage and dysfunction as a biomarker of Parkinson’s disease
• Best Abstract, Parkinson Study Group Annual Meeting 2015

Naples, Jennifer
• Best Paper - Epidemiology Paper Session, American Geriatrics Society Annual Meeting 2015, Washington, DC

Newman, Anne
• Understanding human aging: an epidemiologic perspective. Provost’s Inaugural Lecture Katherine Detre Endowed Chair of Population Health Sciences; University of Pittsburgh, Pittsburgh, PA, USA. March 19, 2015
• Member, Council, NIA, 2016

Park, Mijung
• AAPINA- Okura Mental Health Leadership Foundation Fellow
• Retirement Research Foundation Scholarship
• RWJF Workshop on Immigration, Immigrants and Health, stipend support
• Okura Award

Resnick, Neil
• Best Doctors in America, 2016
• Best Doctors in Pittsburgh Award, 2016
• Member National Summit on Health Care, Washington DC, 2016

Rosano, Caterina
• Tenured Professor of Epidemiology
• Elected Member of the American Society for Clinical Investigation (ASCI)
• 2016 Invited Recipient, United Health Council
• 2016 Invited Recipient, Klein-Vogelbach Award for the Research of Human Movement

Sanders, Laurie
• Top Basic Science Poster Award, Annual Meeting OAIC 2016

Sejdic, Ervin
• Presidential Early Career Awards for Scientists and Engineers

Tyagi, Shachi
• R21 scored at 1st percentile
Minority Research at University of Pittsburgh

General Description of Minority Activities

We work with several local programs to recruit and retain applicants from underrepresented groups. These include our own Career Education and Enhancement for Health Care Research Diversity (CEED) Program and the School of Medicine's Diversity Office. The CEED Program was developed in collaboration with the Center for Health Equity Research and Promotion (CHERP) in direct response to the NIH's plan for CTSAs to develop programs that enhance minority recruitment and retention in clinical research. The CEED, one of the ICRE programs, provides training in grant application writing, presentation skills, and other research development skills necessary to junior faculty and postdoctoral fellows. Dr. Rubio, co-leader of the RCDC and DMAIC oversees the CEED program. The goal is to have Scholars in the CEED Program develop competitive career development proposals. The program also has exceptional potential to recruit, develop, and support junior faculty from underrepresented populations and serves as a model for other academic institutions. The CEED has been extended across the pipeline to include medical students and most recently residents and serves as a pipeline for recruiting underrepresented minorities into the Pepper Scholars Program. We have been successful in recruiting and retaining under-represented minorities. Since 2004 we have groomed RCDC trainees including 1 with disability (Cowan), 2 Native Americans (Spencer and Goins), 1 African American (Coley) and 4 Hispanic (Almeida, Ambrosio, Piva, Torres-Oviedo).

Based on efforts by the Schools of the Health Sciences (SHS) and Pitt administration, minority participation in the SHS training programs has increased over 10 years. With assistance from the Office of Health Sciences Diversity, the Center for Race and Social Problems (School of Social Work), and the CHERP, we advertise in major journals and newsletters as well as mailings to residency, fellowship and training directors, locally and nationally. We promote the program at national meetings, by advertisements, by word of mouth, and by targeted efforts at traditionally minority institutions with doctoral programs. We work to retain minority fellows by addressing barriers, providing didactic and research experiences, using our interest group on the mentoring of minorities to improve and enhance mentoring of minorities, promoting the NIH loan repayment programs, and providing protected time. We have extensive networking opportunities available through the SHS for minority students, residents, fellows, and faculty and will encourage all our minority scholars to take advantage of these venues.

Fabrisia Ambrosio, PhD, MPT is an Assistant Professor in the Department of Physical Medicine & Rehabilitation at the University of Pittsburgh. She holds secondary appointments in the Departments of Physical Therapy, Orthopaedic Surgery, and Microbiology & Molecular Genetics.

Dr. Ambrosio's research has the long-term goal of developing Regenerative Rehabilitation approaches to improve the skeletal muscle healing and functional recovery. Her laboratory uses murine and human models to investigate the underlying mechanisms by which targeted and specific mechanotransductive signals can be used to enhance donor and/or host stem cell functionality. Dr. Ambrosio's research has been supported by the NIH, the DOD, the Foundation for Physical Therapy, the Claude D. Pepper Older American's Independence Center, and the University of Pittsburgh Institute on Aging. In 2006, she was awarded a Scholar's position within
the K12 Comprehensive Opportunities in Rehabilitation Research Training program. In 2011, she was awarded a K01 Career Development Award from the National Institute on Aging of the NIH.

**Sara Piva, PhD, PT, OCS, FAAOMPT** is an Associate Professor, Physical Therapy Department, Assistant Professor, Clinical and Translational Science Institute. Dr. Sara Piva’s research focuses on the effectiveness and mechanisms of rehabilitation interventions to improve function in patients with arthritis. She seeks to understand how muscle metabolism and function (muscle phenotype, fatness, strength) change in response to rehabilitation interventions and how these changes impact subject’s functioning. She currently conducts research funded by NIH on the use of neuromuscular electrical stimulation to reverse muscle atrophy in patients with rheumatoid arthritis along with the effects of the intervention on skeletal muscle structure and physiology. She also conducts research funded by the Rehabilitation Institute on the effectiveness of intensive exercises and physical activity promotion on functioning and activity participation in patients after total knee arthroplasty.

She has been awarded a K01 career development grant from NIH-NICHD entitled Neuromuscular electrical stimulation in individuals with rheumatoid arthritis (RA). She has been involved in pepper pilot projects that have examined the effects of balance training on mobility of patients post total knee replacement. She was recently awarded funding from the University of Pittsburgh Rehabilitation Institute to test the effectiveness of a Comprehensive Behavioral Intervention to improve physical function, physical activity, maintain body weight, and decrease blood pressure in patient post total knee replacement. She is currently the Co-leader of a pilot award entitled “Peripheral nerve function changes with exercise intervention after local knee replacement” with Dr. Elsa Strotmeyer.

**Gelsy Torres-Oviedo, PhD,** is an Assistant Professor of Bioengineering. Her mentors include Drs. Mark Redfern and Patrick Sparto. She is focusing on motor adaptation for walking in older adults. She uses a split-belt treadmill to create novel environmental conditions and challenges. A pepper pilot has supported her to examine, “Understanding locomotor plasticity in older adults”. She was awarded a National Science Foundation BRIGE grant to examine motor adaptation of human locomotion and balance control. She was recently awarded a grant from the American Heart Association entitled “Understanding patient-specific deficits causing step asymmetry post-stroke: a step towards personalizing gait rehabilitation”.
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 clinical trial on fall prevention.

Our current theme is to “Identify pathways of physical function loss and gain and develop targeted interventions to improve functional recovery from illness in older adults”.

Our general hypothesis is that aging induces mild but significant biological and metabolic changes that — in combination with patient factors – 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 through the Leadership/Administrative Core (LAC), as well as the activities of our Research Education Center program (REC), 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.

Section II. Research, Resources and Activities

A. Cores

UTMB’s OAIC has 6 cores:

1) Leadership/Administrative Core (LAC)
2) Research Education Core (REC)
3) Pilot/Exploratory Studies Core (PESC)
4) Clinical Research Resource Core (RC1)
5) Metabolism & Biology Resource Core (MBRC2)
6) Biostatistics & Data Management Resource Core (BDMRC3)

LAC: 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 re-allocation 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.

REC: The goal of the REC 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 REC 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 REC scholars with the skills necessary to establish productive scientific careers.

Current REC Scholars:

CHRISTOPHER FRY, PHD
Mentor: Blake Rasmussen, PhD

Research Project Description: The loss of skeletal muscle strength and function (sarcopenia) is accompanied by deleterious changes in muscle quality, with increased accumulation of connective tissue. With advancing age, an overproduction of muscle extracellular matrix (ECM - connective tissue) can negatively impact the plasticity and function of muscle. Concomitant with the decline in lean tissue, a decline in skeletal muscle stem cell, or satellite cell, number and activity occurs. While we have recently demonstrated that the lifelong genetic depletion of satellite cells does not promote the onset of sarcopenia, increased accumulation of muscle connective tissue occurred in older animals. Fibrogenic/adipogenic progenitor (FAP) cells are key contributors to connective tissue biosynthesis, giving rise to pro-fibrotic cells that overproduce ECM. Our hypothesis is that the reduction in satellite cells with age results in dysregulation of FAP activity leading to the accumulation of ECM in aging muscle. Specifically, we hypothesize that reduced paracrine activity of aged satellite cells directs the functional phenotype FAPs to promote a fibrogenic differentiation program.

ADDIE MIDDLETON, PHD, DPT, PT
Mentor: Kenneth J. Ottenbacher, PhD, OTR

Research Project Description: Older adults are at increased risk of functional decline, especially following a hospitalization. One of the primary goals of post-acute care is to improve functional independence. My research focuses on outcomes following post-acute care in older adults. I recently completed a project examining the degree to which patients’ discharge self-care, mobility, and cognitive functional status were associated with the risk of an unplanned rehospitalization over the 30 days following discharge from post-acute care. A nationally representative sample of older adults (100% Medicare data) was used to address the study objective. Findings indicated that even after controlling for sociodemographic and other clinical factors, self-care, mobility, and cognition remained significant predictors of 30-day unplanned rehospitalization. The manuscript reporting study findings has been revised and resubmitted to the Journal of General Internal Medicine. This project set the foundation for the project I am currently working on examining the long-term outcomes associated with rehospitalizations among older adults. The primary objective of the study is to determine the association between 30-day unplanned rehospitalizations after post-acute care and the following six-month outcomes: 1) number of hospital admissions, 2) days in a non-acute rehabilitation setting, and 3) mortality.


MONIQUE PAPPADIS, PHD, MED
Mentor: James Goodwin, MD

Research Project Description: Dr. Pappadis’ project involves conducting qualitative analyses of interviews regarding post-stroke experiences of cognitive, communication and emotional deficits among community-dwelling older adults with stroke. This work is to identify specific needs of this population for rehabilitation to improve their recovery post stroke.

https://utmb.influuent.utsystem.edu/en/persons/monique-pappadis

PESC: 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 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 $50,000 per year, and also small exploratory projects with 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.
Currently Funded Pilot Studies:

<table>
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<tr>
<th>Year 16 (09/01/15-08/31/16)</th>
<th>E. Lichar Dillon</th>
<th>Internal Medicine - Endocrinology</th>
<th>Cycled Testosterone Therapy to Improve Physical Function in Frail Nursing Home Residents</th>
<th>$25,000</th>
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<tbody>
<tr>
<td></td>
<td>Steven Fisher, PhD, PT</td>
<td>Physical Therapy</td>
<td>Fall Risk Reduction in the Elderly Through the Physical Therapy Management of Incontinence</td>
<td>$10,000 (2nd year)</td>
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<td></td>
<td>Christopher Fry, PhD (REC Scholar)</td>
<td>Nutrition &amp; Metabolism</td>
<td>Satellite Cell Regulation in Fibrogenic/ Adipogenic Progenitor Cell Activity in the Development of Skeletal Muscle Fibrosis during Aging</td>
<td>$10,000</td>
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<td></td>
<td>Lynne Hughes, PhD, PT</td>
<td>Physical Therapy</td>
<td>Feasibility of a Post-Hospitalization PT Intervention in Patients with Pneumonia</td>
<td>$20,000</td>
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<tr>
<td></td>
<td>Sara Nowakowski, PhD</td>
<td>Obstetrics &amp; Gynecology</td>
<td>Effects of Inactivity and Rehabilitation on Sleep in Bedridden Older Adults</td>
<td>$20,000</td>
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**CRRC1:** The Clinical Research Resource Core (CRRC1) will continue 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 in patient centered outcomes research (PCOR) in recovery from illness, 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 developing an ICU research lab we are able to capture these patients earlier and follow their recovery. The CRRC1 will also continue to prioritize the recruitment and retention of a diverse subject population including women and older adults of racial/ethnic minority origin.
**CRRC1 supported external projects (EP):**
(Regulat. = Regulatory support; R = Recruitment only; T = Testing support)

<table>
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<tr>
<th>PI</th>
<th>Agency</th>
<th>Grant number</th>
<th>Title</th>
<th>Period</th>
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<tbody>
<tr>
<td>Durham (site)</td>
<td>NIAMS</td>
<td>R44AR054993</td>
<td>Non-Invasive Assessment of Skeletal Muscle Loss in Cancer Patients</td>
<td>07/01/07-06/30/15</td>
<td>30^R</td>
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<td>Goodwin</td>
<td>AHRQ</td>
<td>R24 HS022134</td>
<td>Patient Centered Outcomes Research in the Elderly</td>
<td>05/01/13-04/30/18</td>
<td>Regulat. support</td>
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<td>Goodwin</td>
<td>NIA</td>
<td>T32 AG002070</td>
<td>Health of Older Minorities – Training Grant</td>
<td>05/01/04-04/30/16</td>
<td>Regulat. support</td>
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<td>Lyons</td>
<td>AHA</td>
<td>13BGIA17110021</td>
<td>STEP AND GO: A Study of Technology-Based Exercise Promotion</td>
<td>07/01/13-06/30/15</td>
<td>50^R,T</td>
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<td>Ottenbacher</td>
<td>NICH D</td>
<td>K12 HD055929</td>
<td>Rehabilitation Research Career Development Program</td>
<td>09/25/07-08/31/17</td>
<td>Regulat. support</td>
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<td>Ottenbacher</td>
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<td>Interdisciplinary Rehabilitation Research Training Program</td>
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<td>Ottenbacher</td>
<td>NICH D</td>
<td>R01 HD06944301</td>
<td>Hospital Readmission &amp; Inpatient Medical Rehabilitation</td>
<td>07/05/12-04/30/16</td>
<td>Regulat. support</td>
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<td>Paddon-Jones</td>
<td>NINR</td>
<td>R01 NR01297301</td>
<td>Preserving Muscle Mass &amp; Function in Bedridden Older Adults</td>
<td>02/15/12-12/31/16</td>
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<td>Paddon-Jones</td>
<td>DRI</td>
<td>1146a</td>
<td>Whey, Protein, Aging &amp; Physical Inactivity</td>
<td>01/01/13-12/31/16</td>
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<td>Paddon-Jones</td>
<td>DRI</td>
<td>1146b</td>
<td>Distributed Protein Intake, Whey Protein &amp; Aging</td>
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<td>Rasmussen</td>
<td>NIAMS</td>
<td>R01 AR049877</td>
<td>Nutritional &amp; Contractile Regulation of Muscle Growth</td>
<td>09/15/08-08/31/14</td>
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<td>Rasmussen</td>
<td>Solae</td>
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<td>A Randomized, Controlled Double Blind Acute Study: Effects of Protein Blends on Muscle Protein Synthesis &amp; Breakdown in Aging</td>
<td>10/01/12-09/01/14</td>
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<td>Effect of Specific Amino Acids on Human Muscle Protein Synthesis</td>
<td>11/14/15-12/31/15</td>
<td>40 Reg, R, T</td>
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<td>Rasmussen</td>
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<td>Nutrient Sensing and Signaling in Aging Muscle</td>
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<td>Reistetter</td>
<td>AHRQ</td>
<td>R24 HS022134</td>
<td>Comparative Effectiveness of Patient-Centered Outcomes Following IRF and SNF Stroke Rehabilitation</td>
<td>05/01/13-04/30/18</td>
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<td>Riall</td>
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<td>Grant #</td>
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<td>End Date</td>
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<td>Support in Cancer</td>
<td>Sharma UT System</td>
<td>08/31/15</td>
<td>Integrated Computer Based Clinical Decision Support System to Improve Care Transition of Patients Hospitalized for Congestive Heart Failure and COPD</td>
<td>10/01/10 - 09/30/15</td>
<td>Regulat. support</td>
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<td>Sharma UT System</td>
<td>06/01/12 - 05/31/15</td>
<td>Systems Engineering to Provide Integrated Care for Patients</td>
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<td>Sharma Sunovision</td>
<td>07/01/15 - 04/30/16</td>
<td>Economic and Humanistic Impact of Low Peak Inspiratory Flow Rate (PIFR) in COPD Patients: An Observational Analysis</td>
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<td>40 Reg, R, T</td>
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<tr>
<td>Sheffield-Moore Nutrition &amp; Anabolic Interventions in Cancer Cachexia</td>
<td>Sheffield-Moore NCI</td>
<td>04/18/08 - 01/31/15</td>
<td>Nutrition &amp; Anabolic Interventions in Cancer Cachexia</td>
<td>04/18/08 - 01/31/15</td>
<td>60 R, T</td>
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<td>Sheffield-Moore Viagra Administration and Muscle Growth &amp; Fatigue in Older Humans</td>
<td>Sheffield-Moore Moody Fdn</td>
<td>04/02/12 - 04/01/15</td>
<td>Viagra Administration and Muscle Growth &amp; Fatigue in Older Humans</td>
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<td>72 R, T</td>
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<td>Sidossis Effect of Brown Adipose Tissue Activation on Insulin Sensitivity in Humans</td>
<td>Sidossis ADA I-14-TS-35</td>
<td>01/01/14 - 12/31/16</td>
<td>Effect of Brown Adipose Tissue Activation on Insulin Sensitivity in Humans</td>
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<td>60 R, T</td>
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<td>Tan Developing Decision Support on Mammography in Women with Limited Life Expectancy</td>
<td>Tan AHRQ R24 HS022134</td>
<td>05/01/13 - 04/30/18</td>
<td>Developing Decision Support on Mammography in Women with Limited Life Expectancy</td>
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<td>Urban Testosterone &amp; Leucine Supplementation as Gender Specific Countermeasures Against Musculoskeletal Loss</td>
<td>Urban NASA NNX10AP86G</td>
<td>07/30/10 - 07/29/14</td>
<td>Testosterone &amp; Leucine Supplementation as Gender Specific Countermeasures Against Musculoskeletal Loss</td>
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<td>Urban Continuous versus Cycling Long-Term Testosterone</td>
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<td>Urban Whey Peptide Following Resistance Exercise &amp; Anabolic Signaling &amp; Muscle</td>
<td>Urban Meg Milk</td>
<td>08/06/13 - 12/05/15</td>
<td>Whey Peptide Following Resistance Exercise &amp; Anabolic Signaling &amp; Muscle</td>
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<td>Urban ASPirin in Reducing the Effects on the Elderly</td>
<td>Urban NIA U01 AG029824</td>
<td>10/10/11 - 01/31/17</td>
<td>ASPirin in Reducing the Effects on the Elderly</td>
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<td>Urban A Randomized Trial of a Multifactorial Fall Injury Prevention Strategy (STRIDE)</td>
<td>Urban NIA U01 AG048270</td>
<td>05/15/14 - 02/28/19</td>
<td>A Randomized Trial of a Multifactorial Fall Injury Prevention Strategy (STRIDE)</td>
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<td>Urban Whey Protein &amp; Exercise to Accelerate Recovery after Acute Hospitalization</td>
<td>Urban DRI 1229</td>
<td>01/01/14 - 12/31/16</td>
<td>Whey Protein &amp; Exercise to Accelerate Recovery after Acute Hospitalization</td>
<td></td>
<td>100 R, T</td>
</tr>
</tbody>
</table>
MBRC2: 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 molecular, morphological, or 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

Services/support provided by the MBRC2:
- Biorepository
- Stable isotope methodologies for metabolic studies
- Mass spectrometry analyses
- Metabolic modeling
- Total urinary nitrogen analyses
- Cell signaling
- Gene expression
- Muscle morphology (microscopy)
- Cell culture (muscle)
- Transgenic mouse models

### OAIC Pilot Projects, Developmental Projects, and Trainee Projects supported by the MBRC2

<table>
<thead>
<tr>
<th>PI</th>
<th>Title</th>
<th>Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celeste Finnerty, PhD</td>
<td>Predictors of Recovery from Burns in the Elderly</td>
<td>Repository</td>
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<tr>
<td>PI</td>
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<td>Grant number</td>
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<tr>
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</tr>
<tr>
<td>Nisha Garg, PhD</td>
<td>Repository</td>
<td>R01 AG033761</td>
</tr>
<tr>
<td>Roberto Garofalo, MD</td>
<td>NIA</td>
<td>R01 AG038556</td>
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<tr>
<td>Christopher Fry, PhD</td>
<td>NIAMS</td>
<td>R44AR054993</td>
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<td>Demidmaa Tuvdendorj, MD, PhD</td>
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<td>R01 NR012973</td>
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<tr>
<td>Volpi</td>
<td>MegMilk</td>
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</table>
BDMRC3: As a new core, the major activities of the BDM Core have involved organization of members’ activities within the structure of the larger Center activities. To this end, the major activities of the Core largely involved providing statistical and data management support to existing project and pilot projects that have come online within the past year.

In particular, each project funded by the Pilot/Exploratory Studies Core was assigned a BDM Core member to advise project investigators in their design and analysis plans. For each funded study, it was required that the assigned BDM Core member work with the investigator until the study was considered satisfactory before funding would be awarded.

**External projects supported by the BDMRC3**

<table>
<thead>
<tr>
<th>PI</th>
<th>Agency</th>
<th>Grant number</th>
<th>Title</th>
<th>Period</th>
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<tr>
<td>Goodwin</td>
<td>CPRIT</td>
<td>RP101207</td>
<td>Comparative Effectiveness Research on Cancer in Texas</td>
<td>08/01/10-07/31/16</td>
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<tr>
<td>Goodwin</td>
<td>AHRQ</td>
<td>R24 HS022134</td>
<td>Patient Centered Outcomes Research in the Elderly</td>
<td>05/01/13-04/30/18</td>
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<tr>
<td>Kuo</td>
<td>AHRQ</td>
<td>R01 HS02064201</td>
<td>Assessing the Role of Nurse Practitioner in Primary Care of Older Adults</td>
<td>07/05/12-04/30/15</td>
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<tr>
<td>Lyons</td>
<td>AHA</td>
<td>13BGIA17110021</td>
<td>STEP AND GO: A Study of Technology-based Exercise Promotion</td>
<td>07/01/13-06/30/15</td>
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<tr>
<td>Markides</td>
<td>NIA</td>
<td>R01 AG10939</td>
<td>Longitudinal Study of Mexican American Elderly Health</td>
<td>04/01/15-03/31/19</td>
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<tr>
<td>Ottenbacher</td>
<td>NIDRR</td>
<td>H133P110012</td>
<td>Interdisciplinary Rehabilitation Research Training Program</td>
<td>10/01/11-09/30/16</td>
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<td>Ottenbacher</td>
<td>NICHD</td>
<td>R24 HD065702</td>
<td>National Center for Medical Rehabilitation Research Center for Rehabilitation Research Using Large Datasets</td>
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<td>Ottenbacher</td>
<td>NICHD</td>
<td>R01 HD06944301</td>
<td>Hospital Readmission and Inpatient Medical Rehabilitation</td>
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<td>Reistetter</td>
<td>NICHD</td>
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<td>Regional Variability in Inpatient Rehabilitation among Medicare Beneficiaries</td>
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<td>Riall</td>
<td>CPRIT</td>
<td>RP101207</td>
<td>Quality of Post-Treatment Surveillance of Older Cancer Patients in Texas</td>
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<td>Sheffield-Moore</td>
<td>NCI</td>
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<td>Nutrition &amp; Anabolic Interventions in Cancer Cachexia</td>
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<td>Growth &amp; Fatigue in Older Humans</td>
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<td>Volpi</td>
<td>Meg</td>
<td>Whey Peptide Following Resistance</td>
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<td>Milk</td>
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<td>Volpi</td>
<td>DRI</td>
<td>Whey Protein &amp; Exercise to</td>
<td>01/01/14</td>
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<td>Accelerate Recovery After Acute</td>
<td>12/31/16</td>
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<td>Hospitalization in Previously</td>
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<td>Independent Older Adults</td>
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<td>Volpi</td>
<td>NIA</td>
<td>Nutrition &amp; Exercise to Improve</td>
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<td>R01 AG030070</td>
<td>Protein Metabolism &amp; Prevent</td>
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<td>Sarcopenia in Aging</td>
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<td>Wong</td>
<td>NIA</td>
<td>The Mexican Health and Aging</td>
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<td>R01 AG018016</td>
<td>Study II (MHAS)</td>
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</table>

B. Research (See CRRC1, MBRC2, & BDMRC3 in Core section)
C. Pilots (See PESC in Core section)

Section III. Career Development: Provide names and funding subsequent to Pepper pilot funding.

Past five years:

José Manuel Barral, MD, PhD (Pilot awardee 2010-2011)
- Awarded 13GRNT17290006 from AHA (07/01/2013-06/30/2015) entitled, “UNC-45 Facilitated Myosin Folding and its Regulation by Hsp90”

William Durham, PhD (Pilot awardee 2010-2011)
- Awarded R23 AR054993 from NIAMS (07/01/2012-06/30/2015) entitled, “Noninvasive Assessment of Skeletal Muscle Loss in Cancer Patients – Phase 2” [Site PI]

Michael Kinsky, MD (Pilot awardee 2010-2011)
- Awarded W81XWH1210598 from DOD (09/30/2012-09/29/2016) entitled, “Smart Oxygen Monitors to Diagnose and Treat Cardiopulmonary Injuries”

Oberhauser, Andres F. (Pilot awardee 2010-2014)
- Awarded R01 GM118534 from NIDDK (05/01/2016 - 04/30/2020) entitled, “The UNC-45 as a Modulator of Myosin Biogenesis and Function”

Labros Sidossis, PhD (Pilot awardee 2011-2013)
- Awarded 67666 from ADA (01/01/2014-12/31/2016) entitled, “Effect of Brown Adipose Tissue Activation on Insulin Sensitivity in Humans”
- Awarded GM056687 from NIH (09/01/2014-08/31/2018) entitled, “Mechanisms of Fenofibrate Alone or Combined with Propranolol in Burned Patients”

Lyons, Elizabeth J. (Pilot awardee 2013-2014)
- Awarded MRSG-14-165-01-CPPB from ACS (01/01/2015-12/31/20219) entitled, “Self-Monitoring Activity: A Randomized Trial of Game-Oriented Applications”
- Awarded 13BGIA17110021 from AHA (07/01/2013-06/30/2015) entitled, “Step and Go: A Study of Technology-Based Exercise Promotion”

Przkora, Rene (Pilot awardee 2013-2014)
- Awarded 2014 Mentored Research Award from the International Anesthesia Research Society (07/01/2014 – 06/30/2016) entitled, “Preconditioning of Older Patients undergoing Hip Joint Replacement Surgery”

Section IV. Publications: Provide only those that are a direct result of Pepper Center resources and list publications published in the 2015-2016 years only.


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

**Neil Alexander, MD** Years of Service: 9  
University of Michigan  
Professor, Division of Geriatric and Palliative Medicine, Department of Internal Medicine  
Research Professor, Institute of Gerontology  
Director, Mobility Research Center  
Director, VA Ann Arbor Health Care System GRECC  

**Stephen Kritchevsky, PhD** Years of Service: 5  
Wake Forest School of Medicine  
Deputy Director, Translational Science Institute  
Director, Sticht Center on Aging  
Professor, Gerontology and Geriatric Medicine  

**Nicolas Musi, MD** Years of Service: 1  
University of Texas Health Science Center – San Antonio  
Professor of Medicine  
Director, Barshop Institute for Longevity and Aging Studies  
Director, Center for Healthy Aging  
Director, San Antonio Geriatric Research, Education, and Clinical Center (GRECC)  
Barshop Institute for Longevity and Aging Studies  
South Texas Veterans Health Care System
Recognition and Awards

UTMB OAIC

2015 Robert W. Kleemeier Award – Gerontological Society of America
Awarded to Kyriakos Markides, PhD (UTMB OAIC PESC Co-Leader)

2016 ACRM Gold Key Award – American Congress of Rehabilitation Medicine
Awarded to Kenneth J. Ottenbacher, PhD, OTR (UTMB OAIC REC Leader)

2015 Richard D. McKenna Memorial Lecture – Canadian Association for Gastroenterology
Title: Fifty Years of Gastroenterology, A Personal Reflection (Banff, Canada – Feb. 28, 2015)
Given by Don W. Powell, MD (UTMB OAIC Internal Advisor)

2016 Texas Regional Chapter of the American College of Sports Medicine Honor Award –
Awarded to Elena Volpi, MD, PhD (UTMB OAIC Director and Clinical Research-RC1 Leader)

2015-2017 Chair of the NIH Aging Systems and Geriatrics Study Section
Appointee: Elena Volpi, MD, PhD (UTMB OAIC Director and Clinical Research-RC1 Leader)

Fellow of the American College of Sports Medicine
Awarded to Douglas Paddon-Jones, PhD (UTMB Clinical Research-RC1 Co-Leader)

2015 Texas Super Doctor
Awarded to Gulshan Sharma, MD, MPH (UTMB Clinical Research-RC1 Co-Leader)

2015 Best Doctors in America
Awarded to Gulshan Sharma, MD, MPH (UTMB Clinical Research-RC1 Co-Leader)
Minority Research

UTMB OAIC

Trainees:

David Flores, PhD
Research Scientist, Department of Preventive Medicine and Community Health
Funded by diversity supplement to the Hispanic Established Populations for Epidemiologic Studies of the Elderly (H-EPESE)
Mentor: K. Markides

Marc A. Garcia, PhD
Postdoctoral Trainee, Sealy Center on Aging
Mentors: R. Wong & K. Markides

Justin C. Howard
MSTAR Student
UTMB Medical School Student
Mentors: E. Volpi & R. Deer

Monique Pappadis, PhD
Pepper (RL5) Scholar
Assistant Professor, Division of Rehabilitation Sciences
Mentors: K. Ottenbacher & J. Goodwin

Joseph Saenz, PhD
Doctoral student
Graduated in May 2016, PhD Program in Population Health Sciences
Title of dissertation: Facets of Socioeconomic Position and the Onset and Progression of Functional Limitation in Mexico
Lead advisor: R. Wong

Monica Watford, MS, OTR
Doctoral student
Will graduate in August, PhD Program in Rehabilitation Sciences
Title of dissertation: Examining Trends and Evaluating Outcomes within the Context of Caretaker Support in Older Minorities with Traumatic Brain Injury
Lead advisor: K. Ottenbacher

Research:

New R01 grant:
  Title: Long-term Health Outcomes in Mexican American Older Adults
  PI: K. Ottenbacher
  Source: National Institute on Minority Health and Health Disparities, National Institutes of Health, DHHS
Amount: $1,550,000 (Grant# R01 MD-010355)
Period: 2015-2019

Rebeca Wong, PhD conducts research that compares minority with majority populations using data from the U.S. Health and Retirement Study:

- With Marc Garcia, PhD and Brian Downer, PhD, we are estimating the life expectancy free of physical disability and cognitive impairment by US older adults, by race/ethnic groups. The work compares Hispanics with non-Hispanic Whites and Blacks.

- With Brian Downer, PhD and Carlos Diaz-Venegas, PhD, we are examining the prevalence and socioeconomic determinants of cognitive impairment and dementia by US older adults, by race/ethnic groups. The work compares Hispanics with non-Hispanic Whites and Blacks.

- With Miriam Mutambudzi, PhD and Cesar Gonzalez-Gonzalez, PhD, we are conducting an analysis of the impact of diabetes on work and retirement patterns of older adults in the US, also comparing Hispanics with non-Hispanic groups.

Kyriakos Markides, PhD is conducting work with David Flores, PhD focusing on health and health care issues in older Mexican Americans in comparison to other groups.
SA Pepper OAIC Annual Directory Outline

Section I. Description of Center
The central premise of the San Antonio Claude D. Pepper Older Americans Independence Center (SA OAIC) is that basic aging research has advanced to the point where scientifically validated, aging-modulating approaches are ready to be tested and translated into human therapies. Our Center was conceived as an Intervention Program that will advance discoveries obtained in rodents into the preclinical arena using a non-human primate model, the common marmoset, and from the pre-clinical arena into humans through clinical studies. To fulfill this goal, our Center provides investigators with the scientific infrastructure and services that are requisite to translate innovative interventions that target the aging process and age-related diseases into humans. Initially, our major focus is pharmacological interventions; however, regenerative and gene transfer interventions also will be tested as they become available.

The Specific Objectives of the SA OAIC are:

1. To provide, through Resource Core (RC-1—Pre-clinical Research Core), functional assessment (health span) services, and determine the effect of interventions on lifespan. This Core also supports pharmacokinetic, pharmacodynamics, safety, and tolerability assessment of aging-modulating interventions.
2. To provide human clinical research and pharmacology services to studies of interventions aimed at preventing physiological decline and age-related diseases through Resource Core (RC-2 – Clinical Research Core). Services provided by this core include study design, subject recruitment, subject retention, and procedures to assess physical performance, cognition, glucose metabolism, vascular function, atherosclerosis, exercise tolerance, gait, balance, imaging, and specimen (blood, muscle, fat) processing. This core also performs pharmacokinetic studies in humans.
3. To provide, through the Biostatistics Core (RC3), expertise in data entry systems, data quality control, data security, and state-of-the-art quantitative and qualitative analytic and medical informatics strategies.
4. To provide assistance to faculty for developing research programs in gerontology and geriatrics, the Research Career Development Core (RCDC) provides protected research time, research training, and mentorship to SA OAIC Scholars. All scholars will have research projects, mentoring teams and specific short and long-term career goals.
5. The Pilot and Exploratory Studies Core (PESC) funds pilot projects to gather preliminary data that may guide the design of future studies.

Section II. Research, Resources and Activities

A. Cores

LEADERSHIP AND ADMINISTRATIVE CORE (LAC)
Core Leader: Nicolas Musi, MD
Co-Leader: Randy Strong, PhD

This core oversees the overall coordination, monitoring, compliance, evaluation, and reporting functions of the SA OAIC. It promotes institutional interactions and external relationships. The LAC supports the Executive Committee, the Institutional Advisory Committee, and the External Advisory Board.
The LAC co-sponsors a weekly seminar series with our on-campus partners, an annual retreat, visiting professor series, topical workgroups, grant planning meetings, and national conferences.

RESEARCH CAREER DEVELOPMENT CORE (RCDC)
Core Leader: Michael Lichtenstein, MD
Co-Leader: Peter Hornsby, PhD

This core promotes the career development of early-stage investigators. Accessing the research education, training and career development resources of UTHSCSA’s Institute for Integration of Medicine and Science (IIMS) and the robust and unique aging research resources and research education programs in South Texas, our Mentored Research Career Development Scholars are trained in the mechanisms that govern the aging process, and in the design of pre-clinical and clinical interventions for diseases and conditions that affect older adults. All SA OAIC Scholars will have research projects, mentoring teams, and specific short- and long-term career goals. The RCDC also will sponsor various training and mentoring research experiences.

The UTHSCSA and its partners offer a rich pool of available trainees and mentors, additional sources of career funding, laboratories, and multiple opportunities for didactic coursework. SA OAIC scholars also are eligible for pilot support from the PESC.

PILOT AND EXPLORATORY STUDIES CORE (PESC)
Core Leader: Robert Clark, MD
Co-Leader: Alfred L. Fisher, MD, PhD

This core seeks to draw investigators into aging research relevant to the theme of the SA OAIC and to promote early stage research that will set the stage for the development of both larger definitive studies and successful grant applications to continue the research project. To advance these goals the core leadership seeks the creation of novel aging research, and manages the application, review, selection, monitoring, and subsequent tracking of pilot proposals.

RC1: PRE-CLINICAL RESEARCH AND ANALYTICAL PHARMACOLOGY CORE (PRAP)
Core Leader: Suzette Tardif, PhD
Co-Leader: Randy Strong, PhD

This core supports pre-clinical (animal) projects that explore the basic biology of aging and evaluate interventions that target the aging process to enhance healthy aging, as well as to prevent and better treat aging-related diseases. To this end, the Core conducts research in a nonhuman primate model (marmoset) to investigate the mechanism of action, pharmacokinetics, toxicity, and efficacy of drugs that might prolong healthspan, facilitating translation of potential aging-modulating drugs to the clinical setting.

RC-2: CLINICAL RESEARCH CORE (CRC)
Core Leader: Dean Kellogg, MD, PhD
Co-Leader: Sara Espinoza, MD, MPH
This core assists basic and clinical investigators in developing rigorous and appropriately powered clinical studies and trial concepts that will lead to innovative approaches to improve healthspan and lifespan, and facilitates implementation and execution of translational human studies and clinical trials by investigators.

The Core provides expertise and coordinated access to resources and technology in both our Pepper Center and facilities throughout our institution to maximize the depth of phenotypic characterization relevant to aging in trial outcomes. Training in clinical research for early-stage faculty and those new to clinical research is also available. This Core is also available to provide research project consultation and planning, assistance with safety and regulatory compliance processes, facilitates research subject recruitment and retention, and coordinates relationships with relevant SA OAIC Cores and other Core facilities of our institution.

RC-3: BIOSTATISTICS AND DATA MANAGEMENT CORE (BDMC)
Core Leader: Jonathan Gelfond, MD, PhD
Co-Leaders: Alfredo Tirado-Ramos, PhD; Alex Bokov, PhD

This core provides expertise in study design and development of database applications. Services include comprehensive biostatistical support, data quality control, and data security. This Core also provides assistance related to grant proposals (e.g. study design, statistical methods, power and sample size calculations) and manuscript preparation, and will play an active role in the KL2 program, tailored to the focus of the SA OAIC BDMC provides biostatistical and data management support to all SA OAIC Developmental Projects, Pilot Studies, and research projects from KL2 Scholars, and will support the other center cores in reporting and regulatory functions through the IDEAS data management system used for quality improvement processes across the SA OAIC. Services are also available to external projects.

B. Research

SA OAIC resources contributed to a successful R01 proposal and two publications.

Adam Salmon, PhD, an Assistant Professor of Research in UTHSCSA’s Department of Molecular Medicine and the Barshop Institute, received a $2.7 million R01 award from the National Institute on Aging to study the role of mTOR inhibition in longevity and aging in a nonhuman primate. During this five-year study, Dr. Salmon’s lab will test whether mTOR inhibition through chronic administration of rapamycin delays aging in a non-human primate, the common marmoset, as an important step towards translational approaches to delay age-related disease in humans. While inhibition of the mTOR signaling pathway has been shown to extend both lifespan and healthspan in mice, the implications of these findings for improving normal, healthy aging in humans is largely unknown. Dr. Salmon’s study is a promising step towards bridging this knowledge gap.

In one published study, SA OAIC investigators found that long-term treatment of marmoset monkeys with orally-administered encapsulated rapamycin resulted in no overall effects on body weight and only a small decrease in fat mass over the first few months of treatment. Moreover, the study demonstrated that marmosets offer an interesting alternative animal model for future intervention testing and translational modeling. See Ross C, Salmon A, Strong R, Fernandez E, Javors M, Richardson A, Tardif


C. Pilots

2015 Pilots:

“Evaluating pharmacokinetics and tolerability of metformin and acarbose in the marmoset”, Elizabeth Fernandez, PhD, Investigator

“Methylene blue enhancement of fMRI brain activity, memory, and cognition in healthy aging and MCI”, Peter Fox, MD and Pavel Rodriguez, MD, PhD, Co-Investigators

“Metformin for preventing frailty in high-risk older adults”, Sara Espinoza, MD, MPH, Principal Investigator

“Exploration of GDF11 as a rejuvenation factor in a non-human primate”, Senlin Li, PhD, Principal Investigator

“RAPA & Acarbose / Effect of mTOR Inhibition and other Metabolism Modulating Intervention on the Elderly: Immune, Cognitive, and Functional Consequences”, Dean Kellogg, MD, PhD and Ellen Kraig, PhD, Co-Investigators

These projects are ongoing as of the date of this report.

2016 Pilots:

Pending administrative approvals, the following projects have been selected for funding in response to our 2016 PESC RFA:

“A novel gene therapy to retard motor neuron degenerative disease and sarcopenia”, Qitao Ran, PhD and Corinna Ross, PhD, Co-Investigators

“Feasibility of using the iron-chelator deferiprone in Mild Cognitive Impairment (MCI)”, Donald Royall, MD and Dean Kellogg, MD, PhD, Co-Investigators

“NAD Modulation to Improve Cognition in Mild Cognitive Impairment (MCI)”, Becky Powers, MD and Miranda Orr, PhD, Co-Investigators
“Effect of Stress-Busting Program on Caregivers’ Quality of Life, Immunology/Stress Biomarkers and Cellular Aging”, Lyda Arevalo-Flechas, PhD and Chih-Ko Yeh, DDS, Co-Investigators

An RFA to recruit the next cohort of pilot projects will be released in Fall 2016.

Section III. Career Development: Provide names and funding subsequent to Pepper pilot funding.

The first three SA OAIC career development scholars have just begun Year 2 of their two-year scholar positions. Our current scholars are:

**Sukeshi Patel, MD**  
**Research Project:** A study to evaluate proteostasis modulation with histone deacetylase (HDAC) inhibitors as potential aging modulating agents in cancer patients.

Dr. Patel’s research focus is on the effects of proteostasis modulation with histone deacetylase (HDAC) inhibitors as aging modulation agents in cancer patients. Her research takes advantage of an active ongoing phase II study of Vorinistat, a pan-DHAC inhibitor and hydroxychloroquine in colorectal cancer patients. In animal models, Vorinistat plus hydroxychloroquine enhance apoptotic activity. In her time as a KL2 scholar, Dr. Patel has been collecting and banking specimens from research subjects. She has developed a budget and will be evaluating the drug effects on pro-inflammatory factors produced by senescent cells (e.g., IL-1, IL-6, TNFα).

**Kelly Reveles, PharmD, PhD**  
**Research Project:** Comparison of gut microbiota composition and inflammation in elderly proton pump inhibitor-users and non-users.

In this prospective study, Dr. Reveles will determine the changes in the microbiome of older adults before and after exposure to PPI, investigating alterations in (a) fecal microbiota, (b) systemic inflammatory markers, and (c) IGF-1 levels. Dr. Reveles has obtained IRB approval for her protocol, finalized a budget for recruitment of research volunteers, and specimen processing. She is working in conjunction with our Clinical and Translational Science Award (CTSA) to utilize the out-patient clinical research center to evaluate subjects and obtain specimens.

**Corinna Ross, PhD**  
**Research Project:** The effects of chronic rapamycin treatment on motor and cognitive function in a nonhuman primate model of aging, common marmosets.

In the fall, Dr. Ross moved her marmosets from the Southwest National Primate Center to the UTHSCSA Barrier facility at the STCBM. There they will first be subject to collection of baseline physiological and behavioral data prior to beginning rapamycin dosing. This stage is ongoing. Animals will be trained in this time to accept the rapa dose orally, move into testing cages, target an object and weigh. Baseline physiological data to be collected will include metabolic assessments (fasting glucose, fasting insulin, response to glucose challenge, respirometry, and blood pressure). Baseline behavioral data will focus upon initial training ability and response to handling and restraint. Animals will be divided into two cohorts (rapa and control). After this initial phase of the experiments, Dr. Ross will begin collecting data on these animals to assess the effects of rapa on health status.
An RFA to recruit the next class of scholars will be released in Fall 2016.

**Section IV. Publications:** Provide only those that are a direct result of Pepper Center resources and list publications published in the 2015-2016 years only.

Ross, Corinna; Salmon, Adam; Strong, Randy; Fernandez, Elizabeth; Javors, Marty; Richardson, Arlan; Tardif, Suzette Metabolic consequences of long-term rapamycin exposure on common marmoset monkeys (Callithrix jacchus). Aging. 2015 Nov; 7 (11):964-73

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>Years of service</th>
</tr>
</thead>
<tbody>
<tr>
<td>James L. Kirkland, MD</td>
<td>Mayo Clinic</td>
<td>1 year of service</td>
</tr>
<tr>
<td>Stephen Kritchevsky, PhD (Chair)</td>
<td>Wake Forest School of Medicine</td>
<td>1 year of service</td>
</tr>
<tr>
<td>Stephanie Studenski, MD, MPH</td>
<td>National Institute on Aging</td>
<td>1 year of service</td>
</tr>
<tr>
<td>Douglas Seals, PhD</td>
<td>University of Colorado, Boulder</td>
<td>1 year of service</td>
</tr>
</tbody>
</table>
University of Texas Health Sciences Center, San Antonio Pepper Center
2015-2016
Recognition and Awards

Robert Clark, MD – Core Leader, Pilot and Exploratory Studies Core, San Antonio Pepper Center – Elected President of the Society for Leukocyte Biology, a position that he will hold throughout 2016 and 2017
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-three faculty members from thirteen departments (Internal Medicine, Biomedical Engineering, Cardiology, Human Genomics, Infectious Disease, Molecular Medicine, Neurology, Pathology, Public Health Sciences, Physiology/Pharmacology, Urogynecology & Pelvic Reconstructive Surgery Surgical Sciences and Health & Exercise Sciences at Wake Forest University).

Over the past twenty-four 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 main operational objective is 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, 18 clinical studies (all which are funded by the NIH), 2 research development projects, and 6 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 supported studies.
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, 46 junior faculty members have been supported.

The current junior faculty members are:

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

Kathryn Callahan, MD  
 kcallahan@wakehealth.edu  
Assistant Professor, Gerontology and Geriatric Medicine

Candace Parker-Autry, MD  
cpaautry@wakehealth.edu  
Assistant Professor, Urogynecology & Pelvic Reconstructive Surgery

Rebecca Henderson, MD  
rhenderson@wakehealth.edu  
Assistant Professor, Gerontology and Geriatric Medicine, (Emerging Scholar)

Sunghye Kim, MD, MMSc  
skim@wakehealth.edu  
Assistant Professor, General Internal 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 23 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 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 14 independently funded studies, 3 RCDC junior faculty project, and 2 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:** Understanding the Physiology of Bioenergetics and Aging Trial (UPBEAT)  
**Leaders:** Anthony Molina, PhD, Jamehl Demons, MD, Mary Lyles, MD, Dalane Kitzman, MD  
**Assistant Professor, Gerontology & Geriatric Medicine**  
**American Heart Association 15MCPRP25680019 / 2015-2017**
This study will test the hypothesis that skeletal muscle bioenergetic decline, due to mitochondrial dysfunction, is a major contributor to exercise intolerance in patients with HFP EF. This hypothesis is based on multiple lines of evidence indicating that: 1) older HFP EF patients have reduced peak exercise arteriovenous-oxygen difference that contributes to reduced peak VO2; 2) improved peak exercise arteriovenous-oxygen difference accounts for nearly all peak VO2 improvement in HFP EF patients following endurance training; 3) skeletal muscle oxidative metabolism is reduced in HFP EF; 4) impaired skeletal muscle oxygen utilization limits exercise performance in HFP EF; and 5) HFP EF patients have fewer type-I oxidative muscle fibers. Based on these data, we began to examine skeletal muscle mitochondrial bioenergetics in patients with HFP EF and as a regulator of exercise intolerance. Our preliminary data indicate that HFP EF patients exhibit reduced mitochondrial content, biogenesis, and expression of Mitofusin 2, a critical regulator of mitochondrial fusion. These skeletal muscle mitochondrial deficits are related to both peak VO2 and 6 min walk distance. Interestingly, similar mitochondrial alterations are reported with obesity and insulin resistance, common risk factors for HFP EF. Importantly, our data further indicate that weight loss can increase mitochondrial content and improve function in HFP EF patients. Taken together, our findings suggest that HFP EF bioenergetic decline is due to impaired mitochondrial biogenesis and dynamics, the balance of fusion and fission that mediates mitochondrial structure and the disposal of dysfunctional organelles by autophagy. This system, referred to as Mitochondrial Quality Control (mitoQC).

We propose two Specific Aims designed to address our primary hypothesis: 1) To comprehensively examine the bioenergetic differences between skeletal muscle samples from patients with HFP EF (performed under the SECRET 2 protocol-IRB# 32364) and healthy age/weight/gender-matched controls (this protocol). 2) To examine associations of mitoQC measures with peak VO2, 6 min walk distance, muscle strength and quality, and body composition, in HFP EF control patients comparing them to those with HFP EF.

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.
IBC is collecting blood and muscle samples for storage into the biospecimen repository.

Study Status: Recruitment is underway.

Project 2.
Project Title: ENabling Reduction of low-Grade Inflammation in Seniors (ENRGISE)
Leaders: Stephen Kritchevsky, PhD, Jamehl Demons, MD,
Professors, Gerontology & Geriatric Medicine
U01AG050499 / 2015-2018
Growing evidence shows that low-grade chronic inflammation, characterized by elevations in plasma C-reactive protein, tumor necrosis factor alpha, and particularly Interleukin-6 (IL-6), is an independent risk factor of disability, impaired mobility, and lower walking speed. Low-grade chronic inflammation is a modifiable risk factor. However, it is unknown whether interventions that reduce the levels of inflammatory markers per se improve mobility, or avert decline in mobility in older persons.
To address this gap in evidence we conduct the randomized clinical trial ENRGISE (ENabling Reduction of low-Grade Inflammation in SEniors) to test the ability of anti-inflammatory interventions for preventing major mobility disability by improving or preserving walking ability. We have maximized the public health impact by selecting interventions that are safe, tolerable, acceptable, and affordable for vulnerable older persons. Specifically, in this trial we test the efficacy vs. placebo of the angiotensin receptor blocker losartan and omega-3 polyunsaturated fatty acids in the form of fish oil, alone and in combination. Both angiotensin receptor blockers and omega-3 polyunsaturated fatty acids have shown to reduce IL-6 in clinical trials and preliminary data suggest that they may improve physical function.

We recruit older persons who are at risk for, or with, mobility impairment, as measured by slow gait speed and self-reported mobility difficulty, and who have elevated levels of IL-6, the marker most consistently associated with mobility limitations. Preliminary data regarding feasibility need to be gathered before such a trial can be
effectively designed and implemented. We conduct The ENRGISE Pilot Study to assess the effects of the interventions on several inflammatory markers, walking speed, physical function and strength. This allows us to refine the design, recruitment yields, target population, adherence, retention, tolerability, sample-size, and cost for the main ENRGISE trial.

CRC trained the staff and oversees the physical performance testing and core battery
BIC is part of the Data Management Center for the study
IBC is collecting blood for storage into the studies biospecimen repository.
**Study Status:** Recruitment is underway.

**Project 3.**
**Project Title:** Weight Loss for Seniors
**Leaders:** Kristen Beavers, PhD Daniel P. Beavers, PhD, Rebecca Henderson, MD, and Stephen B. Kritchevsky, PhD
**Assistant Professor, Health and Exercise Science, WFU**
**Jason Pharmaceuticals, Inc and the WFSM Older Americans Independence Center / 2015-2018**
The primary goal of this study is to determine whether adherence to a high protein (≥1.0 g/kg/d) weight loss program results in improved physical function by favorably affecting body composition compared to weight stability in obese, older adults. This will be accomplished by conducting a 24-week trial in 124 obese (BMI 30- 40 kg/m2), older (65-79 years) men and women, at risk for mobility disability, randomized to either: (1) high protein intake (≥1.0 g/kg/d; n=62) during weight loss, or (2) weight-stable control (n=62).

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.
IBC is collecting blood for storage into the biospecimen repository.
**Study Status:** Recruitment and intervention is underway.

**Project 4.**
**Project Title:** Intervening on sedentary behavior to prevent weight regain in older adults (SitLess)
**Leaders:** Barbara Nicklas, PhD and Jack Rejeski, PhD
**Professors, Gerontology & Geriatric Medicine; Health and Exercise Science, WFU**
**R56AG051624 2015-2016**
The proposed research will test an innovative, scalable, and acceptable behavioral intervention that targets this known risk factor for weight gain. We found that this intervention is feasible and well-tolerated by older adults; if proven to be effective against weight regain, it would add important scientific input for advancing treatment guidelines. We hypothesize that, in older adults, intervening on SB will be more effective for preventing weight regain than the conventional approach of intervening on exercise behavior. Our pilot data provide evidence that a novel, highly acceptable, behavioral intervention (SitLess) that focuses on increased awareness of SB employing accelerometry-based self-monitoring, that is reinforced with other self-regulatory strategies, improves weight loss during the intensive phase of treatment and prevents weight regain during a short (5-month) follow-up phase. The main goal of the proposed study is to definitively test the efficacy of this intervention for longer-term maintenance of lost weight. This will be accomplished with a 24-month trial in 225 obese (BMI=30-40 kg/m2) older (65-79 yrs) adults randomized to one of three interventions, all with a caloric restriction intervention for weight loss (WL) plus: 1) moderate-intensity aerobic exercise (WL+EX); 2) intervening on SB (WL+SitLess); or 3) (WL+EX+SitLess). Participants will undergo a 12-month WL intervention involving a 6-month intensive phase with decreasing contact from months 7 to 12, and a minimal contact, self-managed, 12-month follow-up phase to address these aims and hypotheses: Aim 1: To determine whether addition of an intervention that targets sedentary behavior to a standard WL intervention that only targets EX results in a larger 24-month reduction in body weight in older, obese adults. Primary hypothesis: WL+EX+SitLess will have lower 24-month body weight than either WL+EX or WL+SitLess. Secondary hypothesis: WL+SitLess will have lower 24-month body weight than WL+EX. Aim 2: To compare the effects
of the interventions on volume and pattern of sedentary behavior and physical activity and determine if these factors predict weight regain during the 12-month follow-up phase. Hypothesis: WL+EX+SitLess will have higher total physical activity energy expenditure, less sedentary behavior, more breaks in sedentary behavior, and more minutes of light and moderate-vigorous activity averaged across follow-up than either WL+EX or WL+SitLess. Hypothesis: Irrespective of treatment arm, greater activity energy expenditure and less minutes of sedentary behavior after the 12-month WL phase will be predictive of less weight regain during the 12-month follow-up.

Aim 3: To evaluate 24-month treatment effects on clinical outcomes (body composition, functional fitness, cardiometabolic risk, fatigue, appetite and diet intake) and social cognitive measures; and to explore whether 6-month change in social cognitive measures mediate change in body weight at 12- and 24-months.

Hypothesis: WL+EX+SitLess will improve the tertiary outcomes more than either WL+EX or WL+SitLess.

CRC will train the staff and oversee the physical performance testing and core battery.
BIC will support the collection and data entry of the core battery data into the common database.
BRC will support the acquisition of DEXA scans.
IBC will collect blood for storage into the biospecimen repository.

Study Status: This is a planning grant and the R01 should be funded shortly.

Project 5.
Project Title: Renal Function and Chronic Kidney Disease in Aging (BICARBONATE Study)
Leader: Snezana Petrovic, MD, PhD
Assistant Professor, Department of Physiology and Pharmacology
R21 AG051866 / 2016-2017

We proposed the current study and protocol based on the evidence summarized above and our preliminary studies, which suggest that: (1) In the Health Aging and Body Composition cohort (age 70-79) lower dietary acid load associates with stable kidney function over a 7-year follow-up, independent of age, race, gender, BMI, diabetes, hypertension or smoking status; (2) metabolomics analysis in participants of the African American Diabetes Heart Study suggested that it is feasible to segregate a urine metabolomics profile in the early stages of CKD (stages 2 and 3), and that lower consumption of base-forming fruits and vegetables and higher rates of acid excretion may be associated with CKD and its progression.

We therefore hypothesized that decreasing metabolic acid production by titrating dietary acid load may ameliorate the generally expected, age-related decline in kidney function, decrease loss of lean body mass, preserve physical function, and ameliorate disability. The objectives of this exploratory R21 project are to establish the feasibility of the proposed approach in the elderly and the project is designed to follow three Specific Aims: Aim 1. Recruit and randomize 80 elderly participants to an oral bicarbonate intervention aimed at titrating net dietary acid load or placebo. The purpose of this aim is to determine the feasibility of achieving ~ 50% reduction in net acid excretion (NAE/Cr meq/g) by the kidney at 6 months in elderly participants following oral bicarbonate supplementation, compared to the placebo group. Aim 2. Ascertain recruitment yields, adherence to the assessment schedule, compliance with and sustainability of the intervention over 6 months; and collect data on variability and longitudinal correlation structure of the parameters related to potential endpoints of a future full-scale clinical trial (kidney function, lean body mass, and functional outcomes). Aim 3. Explore the feasibility of using metabolomics to detect effects of decreased net acid load on kidney function as a potentially more sensitive method of monitoring kidney function than current clinical markers. Importantly, metabolomics will provide clues about the metabolic pathways activated/deactivated during the intervention, and help determine the mechanism of the beneficial effect of decreased acid load on the kidney. This proof-of-principle proposal is a first step towards development of a new intervention to improve prevention and treatment of mobility disability. This is a randomized, double-blind; placebo-controlled trial designed as exploratory R21 project aimed to establish the feasibility of the oral bicarbonate supplementation in the elderly.

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:** Study recruitment is underway.

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**Project 6.**
**Project Title:** The Effects of Aquatic Prehabilitation in Knee OA Patients on Knee Arthroplasty Outcomes (Aquatic Prehab)
**Leader:** Sunghye Kim, MD, Leanne Groban, MD, Jeff Williamson, MD, Stephen Messier, PhD, Jason Lang, MD, and John Shields, MD
**NIA R03 AG050919/ GEMSSTAR Award / 2015-2017**

We hypothesize that preoperative aquatic exercise will improve mobility, body composition and inflammatory profile in older patients with advanced OA. These improved preoperative mobility, body composition, and inflammatory status will in turn, lead to better postoperative outcomes and recovery. In designing a prehabilitation protocol, it was suggested the protocol should be tailored to participant’s ability for maximum effect. We will use an individualized aquatic exercise per each participant’s ability and tolerance to increase the benefit of exercise and adherence to the exercise protocol: participants with better exercise capacity will be challenged with higher intensity exercise while participants with lower exercise capacity will start with low intensity exercise. In summary, we will screen subjects on their mobility using an innovative tool, MAT-sf and enroll subjects who are most likely to benefit from preoperative aquatic exercise. We will use individualized aquatic exercise as a prehabilitation tool, which is the most comfortable way to exercise in patients with osteoarthritis but has never been tried as a prehabilitation tool. If our study shows promising results, it would open a door for a new intervention in this population. The proposed prospective randomized pilot study will recruit participants aged 50 years and older who are scheduled for primary total knee replacement surgery (TKA).

CRC trained the staff and oversees the physical performance testing and core battery.

IBC is collecting blood for storage into the biospecimen repository.

**Study Status:** Study recruitment is underway.

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**Project 7.**
**Project Title:** Promoting Healthy Living: Innovation in Primary Care
**Leader:** Kathryn Callahan, MD
**Associate Professor, Gerontology & Geriatric Medicine**
**CTSI Pilot / 2016-2017**

This study aims to:
To assess the feasibility and acceptability of implementing a screening protocol for impaired mobility as a “vital sign” for older adults seen in differing primary care settings. We will use the REAIM framework to implement a clinician’s mobility “tool kit” intervention that involves: (a) mobility assessment with a 4-meter gait speed, (b) the Mobility Assessment Tool, short form (MAT-sf), a 3-minute patient self-report tool developed within our own Pepper Center, and (c) motivational counseling with a mobility counseling tool to foster readiness for increasing PA. We will partner with practices to implement practice-specific protocols for the mobility tool kit intervention. Feasibility will be evaluated by implementation metrics such as the program’s reach of the target population, its adoption at different sites, fidelity to the protocol, consistency of delivery, impact of the intervention on cost and time, and training and technical support needs. Acceptability will be assessed for partner stakeholders (providers and staff) and participants by asking the perceived value, ease, and satisfaction with the mobility tool kit.

To develop and implement a motivational counseling tool that will frame the results from the mobility assessment screen with regard to each patient’s own valued activities of daily living and an individualized risk of losing mobility, drawn from the evidence base. The purpose of this mobility counseling for PA readiness is to (a) accentuate the risk of not taking action, and (b) motivate patients to participate in PA to reduce that risk. The impact and value of the counseling tool as compared with usual care will be assessed by older adults’ self-
reported change in their perceived risk of losing valued activities and by attendance at practice-based informational sessions regarding how to engage in PA.

CRC will train the clinic staff on these measures.
BIC is supporting the collection and data entry of the core battery data into the common database.

Project 8.
Project Title: Epigenetics of Weight-Loss and Glycemic Improvement
Leader: Jingzhong Ding, MD, PhD
Associate Professor, Gerontology & Geriatric Medicine
R01 DK103531/2016-2021
Our overarching goal is to advance our understanding of the regulation of the CMTN and its contribution to susceptibility to T2DM, by determining weight loss-induced transcriptional changes and epigenetic regulators (DNA methylation) of this network that are related to glucose metabolism. We anticipate that the molecular features of the CMTN mediate weight loss-induced glycemic changes and expect that the knowledge gained may provide novel modifiable targets for further evaluation in animals and humans. The objectives of this project is to translate these intriguing observations into meaningful improvements in human health, much more information is needed about regulation of the CMTN, and the associated cellular, physiologic and clinical changes that occur when this network is altered. Therefore, our overarching goal is to advance our understanding of the regulation of the CMTN and its contribution to susceptibility to T2DM, by determining weight loss-induced transcriptional changes and epigenetic regulators (DNA methylation) of this network that are related to glucose metabolism. We anticipate that the molecular features of the CMTN mediate weight loss-induced glycemic changes and expect that the knowledge gained may provide novel modifiable targets for further evaluation in animals and humans.
To achieve our goal, we will pursue the following specific aims: Aim 1. To test whether weight loss intervention rebalances methylomic/transcriptomic profiles in monocytes and adipocytes from obese persons. Aim 2. To determine whether weight loss-induced methylation and transcriptional changes in human monocytes and adipocytes correlate with whole body glycemic improvements. Exploratory Aim. To explore whether the observed molecular changes in human monocytes alter glucose metabolism in human adipocytes, skeletal myocytes, and hepatocytes using in vitro models.

CRC will train the staff and oversee the physical performance testing and core battery.
BIC will support the collection and data entry of the core battery data into the common database.
BRC will support the acquisition of DEXA scans.
IBC will collect blood for storage into the biospecimen repository.

Study Status: Finalizing protocol and data collection forms. Recruitment will start this fall.

Project 9.
Project Title: Social Stress, Diet, and Primate Monocyte Programming in Cardiovascular Risk
Leader: Tom Register, PhD
Professor, Department of Pathology
R01 HL122393/2015-2020
This project seeks to determine the effects of psychosocial stress on monocytes (cells that are important in inflammation and cardiovascular disease), and to evaluate whether a healthier diet can improve the hypothesized adverse effects of psychosocial stress on monocyte characteristics. We will conduct genomic and epigenomic studies of peripheral blood monocytes and examine their relationships to cardiovascular disease outcomes in female nonhuman primates. If successful, the proposed study could provide a widely applicable and cost-effective intervention on psychological stress, reducing the burden of cardiovascular disease in millions of Americans.

IBC is supporting the work on monocytes.
Project 10.
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 performs 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: Recruitment and intervention are ongoing.

Project 11.
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

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 performs 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 12.
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, β-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 13.
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 α1 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 Ca2+ channel α1 subunit (Cav1.1) expression in fast adult myofibers, and (2) decreased nuclear FL-TnT3 and increased CT-TnT3 fraction result in decreased CaCnα1 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 μ-calpain prevents age-dependent increase in TnT3 fragmentation and reduced CaCnα1 expression and sarcoplasmic reticulum Ca2+ release. The proposed studies will define a novel role for TnT3 as a regulator of Cav1.1 expression 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 14.
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 ≥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 performs 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 15.
Project Title: Cooperative Lifestyle Intervention Program (CLIP) II
Leaders: Jack Rejeski, PhD and Anthony Marsh, PhD, Professors, Health and Exercise Sciences, WFU
R01 HL076441 / 2012-2017
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 16.
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 trained the staff and oversees 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 is complete and intervention is ongoing.

Project 17.
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 trained the staff and oversees the physical performance testing and core battery and assisting with recruitment.

Study Status: Recruitment and intervention continues.

Project 18.
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:**
- **Systolic Blood Pressure Intervention Trial (SPRINT HEART)**
  Dalane Kitzman, MD, Professor, Department of Internal Medicine Section on Cardiology, NIH R01 HL107257/ 2010-2015

- **Early Supported Discharge for Improving Functional Outcomes After Stroke**
  Pamela Duncan, PhD, PT, Professor, Department of Neurology, PCS-11403-14531 / 2015-2020

- **Cardiac Imaging of Thoracic Fat and Aortic Stiffness in older High Risk Patients**
  Tina Brinkley, PhD Dept of Internal Medicine, Section on Gerontology and Geriatric Medicine
  K01 AG033652/ 2010-2015

- **Lifestyle Interventions and Independence for Elders (LIFE)**
  Stephen Kritchevsky, PhD, Professor, Dept of Internal Medicine, Section on Gerontology and Geriatric Medicine
  U01 AG022376 /2010-2016

- **Minimizing Physical Function Decline in Older Adults Receiving Chemotherapy (PA AML)**
  Heidi Klepin, MD, Assistant Professor, Hematology/ Oncology K23 AG038361/ 2011-2013

- **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

- **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

- **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

- **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
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

Physical Activity and Total Health (PATH)
Leader: Capri Foy, PhD, Assistant Professor, Division of Public Health Sciences
R21 AG027413/ 2008-2011 (no-cost extension)

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

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

Vascular Stiffness and Pulmonary Congestion (PREDICT)
Gregory Hundley, MD, Assistant Professor, Dept of Internal Medicine Cardiology and Radiology
NIH R01 HL076468 / 2007-2012

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

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)

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

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

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

Cooperative Lifestyle Intervention Program (CLIP)
Jack Rejeski, PhD, Professor, Department of Health and Exercise Sciences, Wake Forest University
NIH M01-RR07122 / 2005-2010

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
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

Rehabilitation and Exercise Training After Hospitalization: Assessing Benefit in Acute Heart Failure Pilot Study (REHAB-HF Pilot)
Dalane Kitzman, MD, Professor, Cardiology

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

Diet, Exercise and Metabolism in Older Women (DEMO)
Leader: Barbara Nicklas, PhD, Professor, Dept of Internal Medicine, Section on Gerontology and Geriatric Medicine NIH 1R01 AG20583 / 2002-2007

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-1U01HL6374701A2 / 2002-2009

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 will be 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). Methylomic (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. Methylomic 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.

**Study Status:** Leveraging an ongoing 5-month weight loss invention trial, we purified monocytes from blood and adipocytes from abdominal subcutaneous fat with subsequent analyses and quantified the transcriptome in monocytes of 16 sedentary obese men and women, age 65-80 years, pre- and post- intervention. The intervention significantly down-regulated SQLE (p: 0.04) while its association with other members of the cyan modules did not reach statistical significance (p: 0.06-0.83), although the effect directions were all consistent with the observed obesity associations in MESA. Furthermore, changes in the HOMA measure of insulin resistance were inversely associated with changes in ABCA1 and MYLIP (p: 0.05) while the association of HOMA changes with other members of the cyan modules did not reach statistical significance (p: 0.08-0.95), although the effect directions were all consistent with the observed Type II diabetes associations in MESA. A manuscript that summarizes the findings is under revision at Diabetes.

**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 (flurobenzyltrozamicol)-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.
The Sympathetic Nervous System Regulates the Stability of the Neuromuscular Junction with Aging

Christina Furdui, PhD (Biochemistry and Cancer Biology)
Osvaldo Delbono, PhD (Internal Medicine – Gerontology & Geriatrics Medicine)

Over time, declining muscle force and power lead to mobility disability and impaired quality of life. In aging rodents and adults, skeletal muscle undergoes a process of denervation and reinnervation, and denervation is strongly implicated in the onset and progressive decline of skeletal muscle mass, composition, and function, termed sarcopenia. Whether muscle denervation starts at the myofiber or the central or peripheral nervous system is controversial. Answering this question is crucial for developing targeted interventions to prevent or reverse age-related decline in skeletal muscle innervation and consequent loss of mass and force. The neuromuscular junction (NMJ) is a tripartite synapse composed of the presynaptic motor neuron axon, postsynaptic myofiber specialization, and nonmyelinating perisynaptic or terminal Schwann cells (tSCs). With age, the NMJ becomes unstable in a process characterized by fragmentation, shrinkage, and simplification of the postsynaptic side. Detailed studies indicate that the tripartite model includes elements that are crucial for normal skeletal muscle structure and function. Why, then, does the normally stable NMJ eventually destabilize? In

Pilots

Pilots Just Initiated

Using baseline brain imaging to predict success in weight loss interventions in older adults
Paul Laurienti, MD, PhD (Radiology and Translational Science)

Ensuring successful weight loss and then subsequent weight maintenance in obese older adults is an ongoing problem. The majority of existing research has focused on lifestyle behavior change interventions; specifically, changes in diet and/or levels of physical activity. However, little attention has been paid to neurobiological factors that may contribute to the success of these interventions. The identification of anatomical or functional brain networks that are predictive of successful weight loss could lead to personalized interventions designed to increase success at the individual level. Our recent research has clearly demonstrated that brain circuits are associated with food craving and self-regulation of eating behaviors [1–3]. We identified the Hot-state Brain Network of Appetite (HBN-A) that is highly connected following fasting and exhibits reduced connectivity following a liquid meal replacement [4]. The reduction of connectivity in the HBN-A was associated with lower craving and hunger. A more recent study further implicated this network in eating behavior and weight loss by showing that communication efficiency of the HBN-A was a significant predictor of weight loss after a 6-month diet and exercise intervention [5]. We propose to use machine-learning applied to baseline brain imaging data to discriminate success with weight loss. The main outcome of interest is the amount of weight lost during the first 6-month intensive phase of treatment with the goal of being able to discriminate between participants who fall into the upper and lower half of this distribution. An exploratory analysis will determine if machine learning can also predict physical function. We will use data from two existing Pepper Center projects that examined weight loss in older adults. The first study (CLIP-II) evaluated mobility disability following a community-based intervention that included weight loss, weight loss + aerobic exercise, and weight loss + resistance training. Brain imaging data was collected on a subset of participants before the intervention and at 6 months. We have begun examining baseline brain imaging data and have promising preliminary analyses using a support vector machine to predict weight loss based on brain anatomy. We anticipate that when combined with functional brain networks, the performance of the classification algorithm will improve substantially. The second study (INFINITE) examined aerobic fitness in older adults following exercise combined with moderate or intensive caloric restriction. Brain imaging data collected on a subset of participants by Dr. Christina Hugenschmidt will be used to determine if the machine learning algorithm developed on the CLIP-II data can be cross-validated in an independent data set. The preliminary data generated by this proposal will position us to submit an R01 designed to predict weight loss success, a priori, in older adults participating in weight loss programs and to eventually develop pharmacologic and/or mindfulness-based behavioral interventions to treat this at-risk group. Of relevance to this project is the fact that in December of 2015, NIDDK conducted a workshop to stimulate interest in investigating phenotypes for weight loss. Dr. Rejeski, a co-investigator on this project, was an invited speaker at that workshop. It is anticipated that an RFA on this topic will be released within the coming year.

The Sympathetic Nervous System Regulates the Stability of the Neuromuscular Junction with Aging

Paul Laurienti, MD, PhD (Radiology and Translational Science)

The skeletal muscle structure and function. Why, then, does the normally stable NMJ eventually destabilize? In
humans, autonomic innervation and function become impaired with age. Sympathetic axons innervate skeletal muscle fibers, and some investigators have suggested that they innervate the myofiber at the NMJ, but their role in maintaining NMJ integrity over time is unknown. Here, we propose a new, quadripartite model—composed of the motor neuron axon, postsynaptic myofiber specialization, tSCs, and sympathetic neuron axon—by which myofiber sympathetic innervation directly innervate the myofiber at the NMJ, regulate motor innervation and autophagy, and stabilizes the NMJ. We hypothesize that (1) the sympathetic nervous system (SNS) innervates the skeletal muscle at the mouse NMJ, while age-dependent sympathetic denervation leads to NMJ instability, disorganization, and motor denervation; and (2) maintenance of sympathetic innervation significantly prevents motor denervation, NMJ functional decline, and sarcopenia with aging. The following specific aims are designed to test these hypotheses. Aim 1. To preliminarily test whether chronic sympathetic denervation with aging causes NMJ disorganization, motor denervation, NMJ transmission failure, and sarcopenia. Aim 2. To preliminarily test whether muscle sympathetic denervation mediates decreased Atg7, autophagy flux, and acetylcholine receptor (AChR), and this can be prevented by induced Atg7 expression. The long-term goal of this project is to define the cross-talk between the sympathetic and motor nervous systems at the skeletal muscle; the link between two hallmarks of aging skeletal muscle-NMJ alterations and sarcopenia; and the role that regulation of autophagy by sympathetic innervation plays in aging at the NMJ.

The current pilot projects are:

**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.

**Study Status:** Recruitment is underway.

**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.

**Study Status:** Recruitment is underway.

**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.
Study Status: We have revised the aims to include PBMCs only. We are scheduling the large blood draw from which we derive the PBMC’s to coincide with other assessments in the parent project that will be useful for comparisons (Aims 1, 2, and 3). We have nearly completed the physical function assessments (Aims 2 and 3). We already submitted one NIH grant application (February 2016) and another is planned for June 5, 2016 (Aim 4).

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.

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, the team is analyzing data from this pilot. It is being leveraged with data collected using other pilot funds. We are actively working with the study statistician, Iris Leng and meeting monthly with other investigators involved with the parent study to work on manuscript preparation and R01 submission in early Fall 2016.

**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 (PGClα, 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 chondrocytes 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-

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 subudy 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.** (2005-2007 PI: M. Madigan) This pilot will use an existing experimental model of trip recovery will be used to 1) evaluate the effect of obesity on the ability to recover from trip (Specific Aim 1), and 2) 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 hypothesis’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 a 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 pathway. 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 Sc. 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.
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)
Oral pharyngeal aspiration plays an important role in the development of pneumonia in the elderly. The primary aim 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.
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. Geranylgeranylace tone, 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.
Aging and Physical Function in Primates (2009-2011 PI: C. Shively)
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.**  
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 Nitrites conference at the Reynolds 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.

Project 76.
Weight loss strategy designed to protect bones, muscle and kidney function in elderly subjects – Snezana Petrovic, PhD
Statistical analysis was done in May 2015 and the pilot was completed soon after. Results led to the funding of an R21 to further test bicarbonate supplementation as a means to alleviate loss of lean mass during intentional weight loss.

Project 77.
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. Molina was recently funded 3 external grants with the NIA and the American Heart Association.

Project 78.
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 79.
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 80.
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 81.
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. This has been resubmitted.

Project 81.
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.

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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<td>2016-2018</td>
<td>R21 AG051077</td>
<td>Bioenergetics and Rehabilitation in Older Adult Patients with Acute Health Failure</td>
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<td>2016-2021</td>
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<td>Epigenetics of Weight-Loss and Glycemin Improvement</td>
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<td>2016-2017</td>
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<td>Renal Function and Chronic Kidney Disease in Aging</td>
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<td>2016-2021</td>
<td>R01 AG051624</td>
<td>Intervening on sedentary behavior to prevent weight regain in older adults</td>
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<td>NIA</td>
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<td>2016-2021</td>
<td>R01 DK103531</td>
<td>Tropin T and Excitation-Contraction Coupling in Aging Skeletal Muscle</td>
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<td>2015-2018</td>
<td>U01 AG050499</td>
<td>EEnabling Reduction of low-Grade Inflammation in Seniors</td>
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<td>2015-2017</td>
<td>R03 AG050919</td>
<td>The Effects of Aquatic Prehabilitation in Knee OA Patients on Knee Arthroplasty Outcomes</td>
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<td>Understanding the Physiology of Bioenergetics and Aging Trial</td>
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<td>Weight Loss for Seniors Study</td>
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<td>2015-2020</td>
<td>PCS-11403-145</td>
<td>Early Supoprted Discharge for Improving Functional Outcomes After stroke</td>
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<td>R01 AG018915</td>
<td>Study of the Effects Caloric Restriction and Exercise Training in patients with heart failure and a normal ejection fraction (SECRET 2)</td>
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<td>K01 AG043547</td>
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<td>Vitamin K, Knee Osteoarthritis, and Physical Function in Older Adults</td>
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<td>Rehabilitation and Exercise Training after Hospitalization: Assessing benefit in Acute Heart Failure Pilot Study (Rehab HF)</td>
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<td>Pesticide Exposure and Age-Related Changes in Cognitive Function</td>
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| 2011-2013 | Arthritis Foundation #5387 | Vitamin K Nutritional Status and Osteoarthritis Progress               | Shea             | Arthritis FDN
<p>| 2011-2013 | N/a          | Epigenetic Regulation of Macrophage Polarization by Saturated Fat          | Shi              | AHA      |
| 2011-2012 | U01 HL080295 | CHS Events follow-up Study                                                  | Burke            | NHLBI    |
| 2011-2012 | K23 AG038361 | Minimizing Physical Function Decline in Older Adults Receiving Chemotherapy | Klepin           | NIA      |
| 2011-2012 | N/A          | Minimizing Physical Function Decline in Older Adults Receiving Chemotherapy | Klepin           | AFAR     |
| 2010-2016 | HHSN268201100007C | New ARIC Study contract - Field Centers                              | Wagenknecht      | NHLBI    |
| 2010-2016 | U01AG029824  | Aspirin in Reducing Events in the Elderly (ASPREE)                          | Williamson       | NIA      |
| 2010-2015 | R01 DK066358 | Genetics of African American Type 2 Diabetes                                | Bowden           | NIDDK    |
| 2010-2015 | K01 AG033562 | Cardiac Imaging of Thoracic Fat and Aortic Stiffness in older High Risk Patients | Brinkley         | NIA      |
| 2010-2015 | K01 HP20490  | Geriatric Academic Career Award                                             | Callahan         | DHHS/HRSA |
| 2010-2015 | HHSN268201100004C | WHI Southeast Regional Center                                   | Shumaker         | NHLBI    |</p>
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<td>LIFE Data Management, Analysis and Quality Control Center</td>
<td>Miller</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>2009-2014</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>
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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>
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<td>2009-2014</td>
<td>R01 AG032098</td>
<td>Genetic Determinants of Visceral Adiposity</td>
<td>Liu</td>
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<td>2009-2014</td>
<td>R01 HL01250</td>
<td>Epigenome-Wide Association Study of DNA Methylation and Atherosclerosis</td>
<td>Liu</td>
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<td>2009-2014</td>
<td>U01 MH086127</td>
<td>Prolonging Remission in Depressive Elderly (PRIDE)</td>
<td>McCall</td>
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<td>2009-2014</td>
<td>R011NR011186</td>
<td>Standardized Rehabilitation Therapy for ICU Patients with Acute Respiratory Failure TARGETT</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>
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<td>R01 AG020583</td>
<td>Loss of Fat Tissue and Functional Response to Exercise in Older, Obese Adults</td>
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<td>2009-2013</td>
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<td>R01 DK084172</td>
<td>The AMP-Activated Protein Kinase (AMPK) Antagonizes Inflammation Through SIRT1</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>
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<td>Occupational Injuries Among Immigrant Poultry Workers: Development and Progression</td>
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<td>Phase III Study of Donepezil in the Irradiated Brain</td>
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<td>R01 HL087103</td>
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<td>Multi-Center Trial to Evaluate Home-Based Assessment Methods</td>
<td>Sink</td>
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Wake Forest Pepper Center 2015-2016 Publications

2016 Under Review


2016 In Press


2016 Journal Publications


2015 Journal Publications


26. Kitzman, D. W., Upadhyya, B., and Reeves, G. Hospitalizations and Prognosis in Elderly Patients With Heart Failure and Preserved Ejection Fraction: Time to Treat the Whole Patient. JACC.Heart Fail.2015:(3)442-444. PMC4780746.


48. Shaffer, J. A. and Maurer, M. S. *Multiple Chronic Conditions and Heart Failure: Overlooking the Obvious?* JACC.Heart Fail.2015:(3)551-553.


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

Bret Goodpaster
Florida Hospital, Sanford|Burnham Medical Research Institute
3 year of service

Anne B. Newman
University of Pittsburgh
10 years of service

Stephanie Studenski
National Institute on Aging
3 year of service

Jay Magaziner
University of Maryland, Baltimore
3 year of service

Nir Barzilai
Albert Einstein College of Medicine
5 years of service

- Please note our board has been updated with the new cycle of our Pepper Center grant.
Stephen Kritchevsky, PhD
Editorial Board, Journal of Gerontology Medical Sciences
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

Kristen Beavers, PhD
American Heart Association’s Behavioral Sciences Clinical Committee Member

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 Exhibit
Editorial Board - Journal of Cardiopulmonary Rehabilitation and Prevention
2016 Montoye Scholar Award from the Southeast Chapter of the American College of Sports Medicine

Osvaldo Delbono, PhD
Regular Member, Cellular Mechanisms of Aging and Development (CMAD) Study Section (2015)
Editorial Board of Physiological Mini Reviews (published by the Argentinian Society of Physiology) (2009-present)

Kevin High, MD
Laureate Award, NC ACP Chapter
Reidar Wallin Teaching Award – WFU Molecular Medicine and Translational Science Graduate Program

Denise Houston, PhD
(2012 – present) Editorial Board, Journal of Gerontology Medical Sciences
(May 2016) Distinguished Alumni Award and Delta Omega Alumnus Award, Department of Nutrition, University of North Carolina at Chapel Hill

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)

Kylie Kavanagh, PhD
Wake Forest Baptist Medical Center Early Career Investigator Award for Basic Sciences
Dalane W. Kitzman, M.D.
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

Anthony Marsh, PhD
Editorial board, Journal of Aging and Physical Activity
Editorial board, Journals of Gerontology: Medical Sciences
2015, Fellow of the Gerontological Society of America

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
July, 2015 NIA AD Clinical Trials Special Emphasis Panel
2012-present Member, Guide-IT DSMB, NHLBI appointed
2014-present Member, TCMBB DSMB, NIA appointed
2016-present Member, PROVEN DSMB, NIA appointed
2016-present Statistical Editorial Board Member, Journal of the American Geriatrics Society

Barbara Nicklas, PhD
Standing member NIA Aging Systems and Geriatrics study section (2012)
2014 WFSM Established Investigator in Clinical Sciences Award

Carol A. Shively, PhD

Sally A. Shumaker, PhD
2015 Mentoring Award, Wake Forest School of Medicine
2016 American Association for Cancer Research Team Science Award

Raghunatha Yammani, PhD
Advisory Editor, Arthritis & Rheumatology
Top-performing Reviewer, Journal of Arthritis and Rheumatology

Tan Zhang, PhD
Editorial Board of Gerontology & Geriatrics: Research
General Brief Description of Minority Activities:

The Maya Angelou Research Center for Health Equality (MA-RCHE) 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-RCHE 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.

The following is a report on the faculty career development of Dr. Candice J McNeil through the Research Supplements to Promote Diversity in Health-Related Research Program (PA-12-149) administrative supplement to grant 1 R24 AG044325; “Developing Research at the Interface of HIV and Aging”. Since her award date, Dr. McNeil has completed several of planned career development activities and is working towards completing the project aims in her proposed study Acquisition, Detection, and Progression of HPV Infection in Women Aging with HIV.

In collaboration with her mentors Dr. Kevin High, Dr. Laura Bachmann and Dr. Scott Rhodes, Dr. McNeil designed a structured didactic and mentoring program concurrent with a rigorous research program. She participated in advanced learning/training experiences, didactic sessions to build knowledge/competence in aging research, and mentoring with aging experts. Aging Research Training via NIA Butler-Williams Summer Institute of Aging Research Program; and focused health equity training through the Maya Angelou Center for Health Equity Center of Excellence Health Equity Research Opportunity Fellowship. Dr. McNeil has also gained technical expertise in high resolution anoscopy (HRA) and the management of anal dysplasia through training with the HRA team. Additionally, she presented an abstract/poster at the International Society for Sexually Transmitted Diseases Research (ISSTDR) 2015, participated in regionally invited lectures in NC and FL, and nationally as an expert panelist at the Infectious Diseases Society of America 2015.
Research and Career Development Proposed for the OAIC Investigator Amber K Brooks has a minority supplement funded through the Pepper OAIC. The Principal Investigator is Dr. Stephen Kritchevsky, PhD, and Co-investigator is Dr. Amber K Brooks.

Paul Laurienti is Co-PI on NIH R01 (ES008739) entitled “CBPR ON PESTICIDE EXPOSURE & NEUROLOGICAL OUTCOMES FOR LATINOS: PACE4”. This project is focused on the effects of pesticides and other occupational exposures in Latino farmworkers. We published the following manuscripts related to various aspects of health in Latino farmworkers:


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, 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 Anna Carolina Zaira Rodrigues, 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 collaborating 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 trail (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:


Section I. Description of Center

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<th>Phone</th>
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<tr>
<td>Thomas M. Gill, MD, Director</td>
<td>203-688-9423</td>
<td>203-688-4209</td>
<td><a href="mailto:thomas.gill@yale.edu">thomas.gill@yale.edu</a></td>
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<tr>
<td>Terri R Fried, MD, Co-Director</td>
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<td>203-688-4209</td>
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<td>Joanne M. McGl, Administrator</td>
<td>203-737-1800</td>
<td>203-785-4823</td>
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<td>Denise Acampora, Co-Administrator</td>
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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:

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<td>General Internal Medicine</td>
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<td>Statistical Genomics and Proteomics</td>
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<td>Vascular Biology and Transplantation</td>
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</table>
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

Vincent 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 of 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, Irving Sherwood Wright Professor of Geriatrics and Professor of
   Sociology in Medicine, 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, 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)
B2. OAIC Research Career Development Awardees (area of interest) (2002-2016)

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)

cc. Heidi Zapata, MD, PhD (age and HIV infection)

dd. Lauren Ferrante, MD (critical illness, disability, and vulnerability)

e. Andrew Cohen, MD (guardianship and medical decision making for the unbefriended elderly)

ff. Xi Chen, PhD (social pensions, health, and informal elderly care)
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 (Cardiology) and Professor of Investigative Medicine and of Public Health (Health Policy), 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 (Geriatrics), 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
Senior Research Scientist (Geriatrics), Yale University

Depression in Elderly Medical Homecare Patients
Martha Bruce, PhD, MPH
Professor of Psychiatry and of Community and Family Medicine and of The Dartmouth Institute, Geisel School of Medicine, Dartmouth 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 of 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
Senior Research Scientist (Obstetrics, Gynecology and Reproductive Health), Yale University
Impact of Treatment and Adherence and Adequacy of Follow-up Health Care on Outcome of Congestive Heart Failure
Viola Vaccarino, MD, PhD
Wilton Looney Chair of Cardiovascular Research and 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, LCSW-C
Clinical Social Worker/Therapist Private Practice

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 and Chair 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 (Geriatrics) - Weill Cornell Medical College

Visual Attention Training for Older Drivers
Emily Richardson, PhD
Assistant Research Professor of Psychology - U. of Colorado

**Year 07 (1998-1999)**
A Diagnostic Criteria for Traumatic Grief in Late Life
Holly Prigerson, PhD
Irving Sherwood Wright Professor of Geriatrics and Professor of Sociology in Medicine, Weill Cornell Medical College

Werner Gene: Cellular Processes Leading to Premature Aging and Reduced Life Span
Anna Marie Szekely, MD
Associate Research Scientist Genetics, 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.
Professor of Epidemiology (Social and Behavioral Sciences) and Psychology, School of Public Health, 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.
Irving Sherwood Wright Professor of Geriatrics and Professor of Sociology in Medicine, 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

**Year 11 (2002-2003)**

Involuntary Job Loss as a Precipitating Event for Functional Decline and Depressive Symptoms among Predisposed Workers
William T Gallo, PhD
Professor 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 School of Medicine

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
Shields Warren Mallinckrodt 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
Associate 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)

Year 23 (2015-2016)

Obesity and Delirium: Are Adipokines the Biomarkers that Establish the Cognitive-Metabolic Connection in Critically Ill Older Adults?
Amy Ahasic, MD, MPH
Assistant Professor of Medicine (Pulmonary), Yale University

The Role of Dermal Adipocytes in Dysfunction of Aged Skin
Valerie Horsley, PhD
Maxine F. Singer Associate Professor of Molecular, Cellular, and Developmental Biology and Associate Professor of Dermatology, Yale University
Year 24 (2016-2017)

Breaking the AGEs Toward Recombinant Enzyme Therapies
Jason Crawford, PhD
Associate Professor Chemistry and of Microbial Pathogenesis, Yale University

A Multifactorial Model of Psychiatric Outcomes in Older Persons
Becca Levy, PhD
Professor of Epidemiology (Social and Behavioral Sciences) and Psychology, School of Public Health, Yale University

Rapid Pilot award to support “The Effects of Stress on recovery from Heart Failure”.
Kumar Dhamarajan MD, MBA
Assistant Professor of Medicine (Cardiology), 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>
</tr>
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<tbody>
<tr>
<td>Sharon Inouye, MD, MPH</td>
<td>“Prevention of Delirium in Hospitalized Elderly Patients” - 1992-93</td>
</tr>
<tr>
<td>Milton and Shirley F. Levy Family Chair and Professor of Medicine at Harvard Medical School</td>
<td>“Identifying Precipitating Factors for Delirium in Hospitalized Elderly Patients” - 1993-94</td>
</tr>
<tr>
<td>Director, The Aging Brain Center, Institute for Aging Research, Hebrew Senior Life, Boston, MA</td>
<td></td>
</tr>
<tr>
<td>Thomas A. Glass, Ph.D.</td>
<td>“Psychosocial Intervention in Elderly Stroke Patients: Screening and Assessment” – 1992-93</td>
</tr>
<tr>
<td>Professor of Epidemiology, John Hopkins University, Bloomberg School of Public Health</td>
<td>“Psychosocial Intervention in Elderly Stroke Patients: Intervention” – 1993-94</td>
</tr>
<tr>
<td>Senior Associate Member, Johns 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>
</tr>
<tr>
<td>Harold H. Hines, Jr. Professor of Medicine (Cardiology) and of Investigative Medicine and of Public Health, Yale University</td>
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<tr>
<td>Professor in the Institute of Social and Policy Studies, Yale University</td>
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<tr>
<td>Director, Yale-New Haven Hospital Center for Outcomes Research and Evaluation</td>
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<tr>
<td>Director, Yale Robert Wood Johnson Clinical Scholars Program</td>
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<tr>
<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>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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<tr>
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<td>Core Leader, UCLA OAIC Research Operations Core</td>
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<tr>
<td>Dorothy Baker, PhD, RN-C</td>
<td>Senior Research Scientist (Geriatrics), Yale University</td>
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<td>Name</td>
<td>Title and Institution</td>
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<tr>
<td>Martha L. Bruce, Ph.D., MPH</td>
<td>Professor of Psychiatry and of Community and Family Medicine and of The Dartmouth Institute, Geisel School of Medicine, Dartmouth College</td>
</tr>
<tr>
<td>Dana Leifer, MD</td>
<td>Associate Professor of Neurology, Weill Cornell Medical College</td>
</tr>
<tr>
<td>Benjamin Druss, MD, MPH</td>
<td>Professor of Health Policy and Management, 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>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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<tr>
<td>Thomas M. Gill, MD</td>
<td>Humana Foundation Professor of Medicine (Geriatrics)</td>
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<tr>
<td>Name</td>
<td>Position/Title</td>
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<tr>
<td>Professor of Epidemiology (Chronic Diseases)</td>
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<tr>
<td>Professor of Investigative Medicine</td>
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<tr>
<td>Director, Yale Training Program in Geriatric Clinical Epidemiology and Aging Related Research</td>
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<tr>
<td>Director, Yale Program on Aging</td>
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<td>Director, Yale Pepper Center</td>
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<tr>
<td>Director, Yale Center for Disability and Disabling Disorders;</td>
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<tr>
<td>Mark Horowitz, Ph.D.</td>
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<tr>
<td>Professor of Orthopaedics and Rehabilitation, Yale University</td>
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<tr>
<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>
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<tr>
<td>Norma Weinberg Spungen and Joan Lebson Bildner Professor of Psychiatry and of Psychology, Yale University</td>
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<tr>
<td>Director, Women's Health Research at Yale</td>
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<tr>
<td>Steven Palter, MD</td>
<td></td>
</tr>
<tr>
<td>Medical and Scientific Director, Gold Coast IVF, Syosset, NY</td>
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<tr>
<td>Nina Stachenfeld, Ph.D.</td>
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<tr>
<td>Senior Research Scientist in Obstetrics, Gynecology and Reproductive Science, Yale University</td>
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<td>Name</td>
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<tr>
<td>Viola Vaccarino, MD, Ph.D.</td>
<td>Wilton Looney Chair of Cardiovascular Research</td>
</tr>
<tr>
<td></td>
<td>Professor of Medicine and Chair of Epidemiology, Emory University</td>
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<tr>
<td></td>
<td>Director, Emory Program in Cardiovascular Outcomes Research and Epidemiology</td>
</tr>
<tr>
<td>Sidney Bogardus, Jr., MD</td>
<td>Associate Clinical Professor of Medicine (Digestive Diseases), Yale University</td>
</tr>
<tr>
<td></td>
<td>“Treatment Goals for Persons with Multifactorial Geriatric Health Conditions” RCDC Awardee, 2002-2003</td>
</tr>
<tr>
<td>Loretta DiPietro, Ph.D., MPH</td>
<td>Professor and Chair of the Department of Exercise Science, George Washington University</td>
</tr>
<tr>
<td></td>
<td>Director, Physical Activity in Public Health – MPH Program, George Washington University</td>
</tr>
<tr>
<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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<tr>
<td>Karl Insogna, MD</td>
<td>Professor of Medicine (Endocrinology), Yale University</td>
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<td></td>
<td>Director, Yale Bone Center</td>
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<td>Name</td>
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<tr>
<td>Sandra Moody-Ayers, MD</td>
<td>Associate Clinical Professor of Medicine (Geriatrics) University of California, San Francisco</td>
</tr>
<tr>
<td>Carol van Doorn, Ph.D. LCSW-C</td>
<td>Clinical Social Worker/Therapist, Private Practice, Fredrick, MD</td>
</tr>
<tr>
<td>Mark Whisman, Ph.D.</td>
<td>Professor of Psychology and Neurosciences, University of Colorado, Boulder</td>
</tr>
<tr>
<td>Kenneth Wikler, Ph.D.</td>
<td>Executive Director, Bell Falla &amp; Associates, Bala Cynwyd, PA.</td>
</tr>
<tr>
<td>Anne Williamson, Ph.D.</td>
<td>Associate Professor (Adjunct) of Neurosurgery, Yale University</td>
</tr>
<tr>
<td>Nashaat Boutros, MD</td>
<td>Professor and Chair, Department of Psychiatry, University of Missouri – Kansas City School of Medicine Medical Director, Center for Behavioral Medicine, University of Missouri, Kansas City.</td>
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<tr>
<td>Stewart Frankel, Ph.D.</td>
<td>Associate Professor and Chair of Biology, University of Hartford, CT</td>
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<tr>
<td>M. Carrington Reid, Ph.D., MD,</td>
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<td>Name</td>
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<tr>
<td>Irving Sherwood Wright</td>
<td>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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<tr>
<td>Holly G. Prigerson, Ph.D., MS</td>
<td>Irving Sherwood Wright Professor of Geriatrics and Professor of Sociology in Medicine, Weill Cornell Medical College</td>
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<tr>
<td>Anna Marie Szekely, M.D.</td>
<td>Associate Research Scientist in Genetics and in Neurology, Yale University</td>
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<tr>
<td>Liana Fraenkel, MD, MPH</td>
<td>Professor of Medicine (Rheumatology), Yale University</td>
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<tr>
<td>Barbara I. Gulanski, MD, MPH</td>
<td>Associate Professor Medicine (Endocrinology), Yale University</td>
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<tr>
<td>Jeosok J. Kim, Ph.D.</td>
<td>Professor of Psychology and Neurobiology and Behavior, University of Washington</td>
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<tr>
<td>Henrik G. Dohlman, PhD</td>
<td>Professor and Vice-Chair of Biochemistry and Biophysics and Professor of Pharmacology, University of North Carolina School of Medicine</td>
</tr>
<tr>
<td>Barbara Pober, MD, MPH</td>
<td>Professor of Medical Sciences, Quinnipiac University, School of Medicine</td>
</tr>
<tr>
<td>Becca Levy, Ph.D.</td>
<td>Professor of Epidemiology (Social and Behavioral Sciences) and of Psychology, Yale University</td>
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<tr>
<td>Urszula Masiukiewicz, M.D.</td>
<td>Assistant Clinical Professor of Medicine (Endocrinology), Yale University</td>
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<tr>
<td>Vincent Quagliarello, M.D</td>
<td>Professor of Medicine (Infectious Diseases), Yale University</td>
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<tr>
<td>William T Gallo, PhD</td>
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<td>Name</td>
<td>Title and University</td>
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<tr>
<td>Nikki J Holbrook, PhD</td>
<td>Professor of Public Health, City University of New York</td>
</tr>
<tr>
<td>Retired, Adjunct Professor of Medicine and Pathology, Yale University</td>
<td>“Alterations in Oxidative Stress Response with Human Aging” 2002 - 2003</td>
</tr>
<tr>
<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></td>
<td>Co-Director, Robert Wood Johnson Clinical Scholars Program at Yale University</td>
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<tr>
<td>Margaret Pisani, MD, MPH</td>
<td>Associate Professor of Medicine (Pulmonary), Yale University</td>
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<tr>
<td></td>
<td>Director, Pulmonary and Critical Care Medicine Fellowship</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>
</tr>
<tr>
<td>Karyn Frick, PhD</td>
<td>Professor of Psychology, University of Wisconsin, Milwaukee</td>
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<tr>
<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>
</tr>
<tr>
<td>Dawn Bravata, MD</td>
<td>Associate Professor of Medicine, School of Medicine, Indiana University</td>
</tr>
<tr>
<td>Caroline Zeiss, PhD, BVSc, DACVP</td>
<td>Professor of Comparative Medicine, Associate Professor of Ophthalmology and Visual Sciences, Yale University, Director, Mouse Research Pathology Service, Yale University</td>
</tr>
<tr>
<td>Joseph Agostini, MD</td>
<td>National Medical Director, Medicare, Aetna, Inc. Hartford, CT</td>
</tr>
<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>Daniel Goldstein, MBBS</td>
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<tr>
<td>Professor of Medicine (Cardiology) and</td>
<td>Professor of Medicine (Cardiology) and of Immunobiology, Yale University</td>
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<tr>
<td>Josephine Hoh, PhD</td>
<td>Associate Professor of Epidemiology (Environmental Health) and of</td>
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<td></td>
<td>Ophthalmology and Visual Science, Yale University</td>
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<tr>
<td>Insoo Kang, MD</td>
<td>Associate Professor of Medicine (Rheumatology), Yale University</td>
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<tr>
<td>Julie Ann Sosa, MD, MA, FACS</td>
<td>Professor of Surgery (Endocrine) and of Medicine, Duke University</td>
</tr>
<tr>
<td>Lisa Cataldi-Barry, PhD, MPH</td>
<td>Assistant Professor of Psychiatry, University of Connecticut, Center</td>
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<td>on Aging</td>
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<tr>
<td>Carlos Vaz Fragoso, MD</td>
<td>Associate Professor of Medicine (Geriatrics), Yale University</td>
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<tr>
<td>Sarwat Chaudhry, MD</td>
<td>Associate Professor of Medicine (General) and in the Institute of</td>
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<td>Social and Policy Studies, Yale University</td>
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<tr>
<td>Manisha Juthani-Mehta</td>
<td>Associate Professor of Medicine (Infectious Diseases), Yale University</td>
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<td>Program Director, Infectious Diseases Fellowship Program</td>
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<tr>
<td>Arthur Simen, MD, PhD</td>
<td>Director, Pfizer Inc., Research and Development, Cambridge, Massachusetts</td>
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<td></td>
<td>Assistant Professor (Adjunct) of Psychiatry, Yale University</td>
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<tr>
<td>Patty Lee, MD</td>
<td>Associate Professor of Medicine (Pulmonary), Yale University</td>
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<tr>
<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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<tr>
<td>Ruslan Medzhitov, PhD</td>
<td>David W Wallace Professor of Immunobiology, Yale University</td>
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<td></td>
<td>Member, National Academy of Sciences</td>
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<td>Member, Institute of Medicine</td>
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<tr>
<td>Stephanie Halene, MD</td>
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<tr>
<td>Kathleen Connell, MD</td>
<td>Assistant Professor of Medicine (Hematology), Yale University</td>
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<tr>
<td>Ifat Levy, PhD</td>
<td>Associate Professor of Obstetrics and Gynecology (Urogynecology), University of Colorado</td>
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<tr>
<td>Xiaoyong Yang, PhD</td>
<td>Associate Professor of Comparative Medicine and of Neurobiology, Yale University</td>
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<td>Sandy S. Chang, MD, MHS</td>
<td>Assistant Professor of Medicine (Geriatrics), Case Western Reserve University</td>
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<tr>
<td>Robert Pietrzak, PhD, MPH</td>
<td>Associate Professor of Psychiatry, Yale University</td>
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<tr>
<td>Frank Slack, PhD</td>
<td>Shields Warren Mallinckrodt Professor of Pathology and Medicine, Harvard University</td>
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<tr>
<td>Praveen Mannam, MBBS, MS</td>
<td>Director, Institute for RNA Medicine, Harvard University</td>
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<tr>
<td>Elisabeth Erekson, MD, MPH</td>
<td>Assistant Professor of Obstetrics and Gynecology</td>
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<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>
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<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>Assistant Professor of Medicine (Pulmonary), Yale University</td>
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<tr>
<td>Daniel Weinberger, PhD</td>
<td>Assistant Professor of Epidemiology (Microbial Diseases), Yale University</td>
</tr>
<tr>
<td>Sandy Chang, PhD, MD</td>
<td>Associate Professor of Laboratory Medicine and of Pathology, Yale University</td>
</tr>
<tr>
<td>Matthew Rodenheffer, PhD</td>
<td>Associate Professor of Comparative Medicine and of Molecular, Cellular, and Developmental Biology</td>
</tr>
<tr>
<td>Ruth Montgomery, PhD</td>
<td>Associate Professor of Medicine (Rheumatology), Yale University</td>
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<tr>
<td>Ruth Montgomery, PhD</td>
<td>Associate Dean for Scientific Affairs, Yale School of Medicine</td>
</tr>
<tr>
<td>Amy Ahasic, MD, MPH</td>
<td>Assistant Professor of Medicine (Pulmonary), Yale University</td>
</tr>
<tr>
<td>Valerie Horsley, PhD</td>
<td>Maxine F. Singer Associate Professor of Molecular, Cellular, and Developmental Biology and Associate Professor of Dermatology, Yale University</td>
</tr>
<tr>
<td>Heidi Zapata, MD, PhD</td>
<td>Instructor in Medicine (Infectious Diseases), Yale University</td>
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<tr>
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<tr>
<td>Lauren Ferrante, MD</td>
<td>Instructor in Medicine (Pulmonary), Yale University</td>
</tr>
<tr>
<td>Jason Crawford, PhD</td>
<td>Associate Professor (Chemistry and Microbial Pathogenesis), Yale University</td>
</tr>
<tr>
<td>Andrew Cohen, MD</td>
<td>Instructor in Medicine (Geriatrics), Yale University</td>
</tr>
<tr>
<td>Xi Chen, PhD</td>
<td>Assistant Professor of Public Health (Health Policy) and in the Institute for Social and Policy Studies, Yale University</td>
</tr>
<tr>
<td>Kumar Dhamarajan MD, MBA</td>
<td>Assistant Professor of Medicine (Cardiology), Yale University</td>
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</tbody>
</table>
Section IV. YALE PEPPER CENTER PUBLICATIONS 2015-2016

2015


2016


### 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>3 years</td>
</tr>
<tr>
<td>Kevin P. High, M.D.</td>
<td>Wake Forest Baptist Medical Center</td>
<td>3 years</td>
</tr>
<tr>
<td>Edward R. Marcantonio, M.D.</td>
<td>Harvard Medical School</td>
<td>3 years</td>
</tr>
</tbody>
</table>
RECENT SCIENTIFIC RECOGNITION AND AWARDS
YALE UNIVERSITY
OAIC FACULTY

**Thomas M. Gill, MD**

Merit Award, National Institutes of Health, 2005-2016
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–
Brock Institute and Glennan Center for Geriatrics and Gerontology Visiting Professor Scholar, Eastern Virginia Medical School, 2015.
Visiting Professor, National Institute on Aging Intramural Research Program, 2015.
Visiting Professor, UTMB Sealy Center on Aging, 21th Annual Lefeber Winter Series on Aging, 2016.

**Terri Fried, MD**

Mason F. Lord Lecture and Visiting Professor, Johns Hopkins School of Medicine, 2016

**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

**Leo M. Cooney, Jr., MD**

David J Leffell Prize for Clinical Excellence, Yale School of Medicine, 2014

**Kumar Dharmarajan, MD, MBA**

Beeson Career Development Award in Aging Research, 2014
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
Hartford Center of Excellence Award 2013-2015
GEMSSTAR Award, National Institute on Aging, 2015-2017
T. Franklin Williams Scholar (ATS/AAIM-ASP Career Development Award in Geriatrics) 2015-2017
New Investigator Award, Merck/American Geriatrics Society, 2016
Iva Dostanic Physician Scientist Trainee Award, Yale Medical School, 2016

Ling Han, MD, PhD
Official Delegate to Chinese Congress and Exposition on Gerontology and Health Industry, Suzhou, China, The Gerontological Society of America, 2014

Melissa Knauert, MD
Clinical and Community-Based Research Scholar Award, Yale Center of Clinical Investigation, 2015-2017

Becca Levy, PhD
Senior Scholar Award for Research Related to Disadvantaged Older Adults, Gerontological Society of America and Senior Services of America, 2014

Kasia Lipska, MD, MHS
Beeson Career Development Awards in Aging Research, 2014

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
Ruslan Medzhitov, PhD
Elected to Institute of Medicine, 2014

Terrence Murphy, PhD
Merck/American Geriatrics Society, New Investigator Award, 2014

Alexander Panda, MD, MPH
Beeson Career Development Awards in Aging Research 2012-2017

Carolyn Presley, MD
Robert Wood Johnson Clinical Scholar, 2015-2017
Young Investigator Award, Conquer Cancer Foundation, American Society of Clinical Oncology, 2016

Mary E Tinetti, MD
Best Doctors in America, 2010-2014

Lisa Walke, MD
New York Magazine, Best Doctors, 2014
Fellow, American Geriatrics Society, 2014

Daniel Weinberger PhD
Clinical and Community-Based Research Scholar Award, Yale Center of Clinical Investigation, 2015-2017

Xiaoyong Yang, PhD
Research Scholar Award, American Cancer Society, 2015
New Scholar Award, Ellison Medical Foundation, 2011-2015
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. Kasia Lipska, MD: Hospital Admissions for Diabetes Complications-- Understanding Recent Trends and Etiology
   **Aim:**
   **Hypothesis:**
   There will be an increase in potentially preventable admissions for diabetes nationally, with persistent racial disparities (higher rates among blacks than whites) and regional differences.
   **Progress**
   This aim has been completed and was published in *JAMA Internal Medicine.*
   In this study, we found that hospital admission rates for hypoglycemia now exceed those for hyperglycemia among older Medicare beneficiaries. Although admissions for hypoglycemia have declined modestly since 2007, rates among Black Medicare beneficiaries and those older than 75 years age remain high. The implications of this work are that hypoglycemia now poses a significant health threat to older Americans and there is an urgent need to reduce this burden.