

WAKE FOREST UNIVERSITY SCHOOL OF MEDICINE
Claude D. Pepper Older Americans Independence Center

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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.

Research Career Development Core (RCDC)

Stephen Kritchevsky, PhD 336/713-8548

Denise Houston, PhD 336/713-8588

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 cpautry@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)

Pilot / Exploratory Studies Core (PESC)

Dalane Kitzman, MD 336/716-3274

Thomas Register, PhD 336/716-1557

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.

Clinical Research Core (CRC)

Jack Rejeski, PhD 336/758-5837

Anthony Marsh, PhD 336/758-4643

Jeff Williamson, MD, MHS 336/713/8583

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 HFpEF. This hypothesis is based on multiple lines of evidence indicating that: 1) older HFpEF 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 HFpEF patients following endurance training; 3) skeletal muscle oxidative metabolism is reduced in HFpEF; 4) impaired skeletal muscle oxygen utilization limits exercise performance in HFpEF; and 5) HFpEF patients have fewer type-I oxidative muscle fibers. Based on these data, we began to examine skeletal muscle mitochondrial bioenergetics in patients with HFpEF and as a regulator of exercise intolerance. Our preliminary data indicate that HFpEF 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 HFpEF. Importantly, our data further indicate that weight loss can increase mitochondrial content and improve function in HFpEF patients. Taken together, our findings suggest that HFpEF 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 HFpEF (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 HFpEF control patients comparing them to those with HFpEF.

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.

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.

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

R01HL122393/ 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 α_1 subunit, essential molecule for muscle contraction, was down-regulated at both the RNA and protein levels. The following specific aims will test the hypotheses that: (1) TnT3 regulates voltage-gated Ca²⁺ channel α_1 subunit (Cav1.1) expression in fast adult myofibers, and (2) decreased nuclear FL-TnT3 and increased CT-TnT3 fraction result in decreased Cav1.1 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 Cav1.1 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 \geq 55 yrs; BMI \geq 25 kg/m² and \leq 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 intervention 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.

Rejeski, Ip, Marsh, Miller and Farmer. Measuring Disability in Older Adults: The ICF Framework. Geriatr Gerontol Int 8: 48–54, 2008

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.

C. 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

Christina Furdui, PhD (Biochemistry and Cancer Biology)

Oswaldo 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 postterminal. 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

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 Upadhyya, 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.

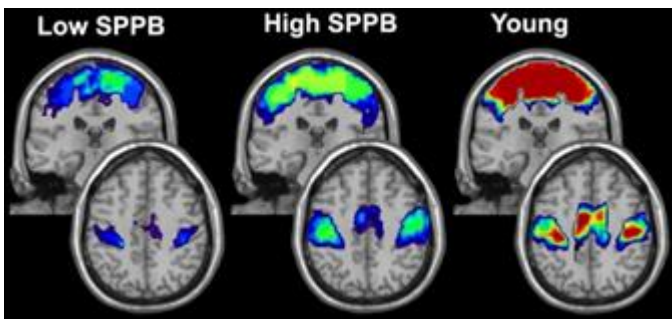
Mediterranean vs. Western Diet Effects on NHP Mitochondrial Bioenergetics & Physical Function- Carol Shively, PhD (Pathology/CompMed), and Anthony Molina, PhD.

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 (PGC1a, SIRT1, SIRT3, and TFAM). To achieve these aims, we will utilize muscle biopsy samples already being collected as part of the EVIDENCE (Exploring Vitamin D's Effects on Neuromuscular Endpoints) trial (R01 AG042411; Houston, PI). The EVIDENCE trial is a 12-month, double-blind randomized placebo controlled trial in 200 older (65-89 yrs) men and women with initial 25(OH)D concentrations of 20-<30 ng/mL to determine the effect of vitamin D3 supplementation (2000 IU/d of vitamin D3 or placebo) on change in neuromuscular functions that are established risk-factors for falls in older adults. A subset of randomly selected participants (n=40; 20 from each group) will undergo a muscle biopsy at baseline and 4 month follow-up to examine changes in underlying physiological mechanisms. For this pilot, we will assess the bioenergetic profile of isolated mitochondria and muscle fibers as well as the expression of mitochondrial proteins and regulators of mitochondria biogenesis in pre- and post-muscle biopsy samples from 20 participants (10 per intervention group). Understanding the association between vitamin D and mitochondrial bioenergetics can improve our understanding of the underlying mechanisms linking vitamin D and muscle function and the potential benefits of remediating low 25(OH)D concentrations in older adults. Moreover, this work will open a new area of research focused on the role of nutritional interventions on mitochondrial bioenergetics.

Study Status: To date, we have completed assessments on 10 pre-intervention, and 4 post-intervention participants enrolled in the EVIDENCE clinical trial. In addition, we have recruited and profiled 4 participants in our pilot sub-study which is focused on older adults with initial 25(OH)D concentrations of 13-<18 ng/mL (cutoffs that are lower than used in the EVIDENCE trial).

Pilot Projects completed in prior years:

Project 1. Development of a Human Retinal Research Bank for Aging Studies (Johnson, Ph.D. and Tytell, Ph.D., 1992-1993). This study supported development of a human retinal research bank for the analysis of changing in the eyes associated with aging. Over 200 eyes have been collected and processed. This retinal bank

was being used for a number of different studies, among others a study examining the effect of heat shock proteins on free radical damage in aging eyes. Two publications resulted from this pilot work.

Project 2. Assay of Chronic Changes in Trabecular Bone to Determine Correlates with Osteoporosis (Webber, Ph.D., 1992-1993) This pilot project was funded to develop a simple, non-invasive technology capable of correlating fractal analyses of radiographs of the spine with quantitative digital radiologic assay of bone density abstracted from related regions in individuals exhibiting varying amounts of osteoporotic deformity. The pilot project proved the feasibility of the technology and results were reported and led to further NIH funding (Variable aperture dental tomosynthetic X ray system, NIH-5R01DE12227-03, PI Webber)

Project 3. Pepper Center Functional Status Index: Development and Validation (Rejeski, Ph.D., 1992-1993). This pilot study funded methodological work to develop a performance-based measure of function. This index was used in the FAST study and has been and is currently being used in several other OAIC and NIH-funded trials (e.g. ADAPT, PARIS I&II, PIE, REACT I&II). The results of this work were published in two articles and the instrument has later been used as a primary outcome in many other publications from OAIC investigators.

Project 4. Central Peptidergic Function in the Aging Female: Steroid Therapy (Sundberg, Ph.D., 1992-1993). This study examined the effect of aging and caloric restriction on spinal cord oxytocin levels in rats. Results demonstrated that spinal cord oxytocin levels are generally higher in the male than the female rat and that aging was associated with a significant reduction of oxytocin. This project has led 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 led 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 Kitman). 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. Kitman'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 involvement 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 led 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-

meter test. These data supported the LIFE Trial Application (UO1 AG022376). Paper published in JAGS 52:972-976, 2004.

Project 34. Anti-inflammatory drugs and performance in aged rats (Carter 2001-2003)

This study compared the effects of long-term ACE inhibition on physical performance and body composition in aged rats (24 to 30 months of age). These data show that age related declines in physical performance were moderately attenuated with ACE inhibition. These effects were most likely modulated changing body composition as animals receiving ACE inhibition treatment were lost significant amounts of fat mass, as measured by DXA, relative to the control group. This study resulted in 2 published manuscripts and a R01 AG024526-01.

Project 35. Potential contribution of inflammation and skeletal muscle loss to disability in diastolic heart failure and the potential role of ACE inhibitor therapy (Kitzman, MD, 2001-2004) Results to date suggest that stable, ambulatory elderly patients with diastolic heart failure have greater interstitial fat within the muscle compartment compared to healthy matched controls and this tended to be associated with lower exercise tolerance. In addition, 32 muscle biopsies were performed in 22 subjects (including 1 year follow up). This work was in conjunction with the Research Development Core, and supported the development of thigh muscle biopsy techniques. In addition, the scope has been expanded in order to add biopsies in older patients with systolic heart failure being enrolled in an NHLBI funded trial of exercise training for mortality reduction (HF-ACTION) in a collaborative effort with several other Pepper Centers. Competitive renewal of the parent study began 7/1/05 (RO1 AG 18915), including a Merit Award Extension.

Project 36. Relationships between biomarker of the systemic oxidative stress, 8-iso-PGF-M, systemic inflammatory markers, and muscular function (Ilyasova, PhD, 2002-2004). This is an ancillary study to the NIH-funded TRAIN study (PI: Pahor). The required 60 participants have been recruited and their baseline specimens, urine and plasma, are being collected. Follow-up data and specimens of all 60 participants are finished and laboratory measurements are complete. Data analyses are complete. Data was also used to support a R01 that was funded (R01 AG0265556) for a previous RCDC fellow (Cesari).

Project 37. Power training in older adults: mechanisms underlying change in muscle function (Marsh, PhD, 2002-2004). Data collection, entry and cleaning is complete. Results show power training is a feasible, safe, and efficacious intervention. The power group showed similar improvements in knee extension and leg press strength to the strength group. The power group showed significantly larger improvements in knee extension and leg press power compared to the strength group. The strength and power improvements for the power group were significantly different from control. Thus the effect of the intervention was considerable. An RO1 has been submitted twice and both times not scored. As a result two RO3's have been submitted and both unfunded. Two manuscripts have been published and one accepted.

Project 38. Leg blood flow, sarcopenia and physical function, (Hundley, MD, 2002-2004).

Thirty six individuals were enrolled with 26 completing all aspects of the study. This project resulted in development of a new, noninvasive method to measure blood flow in the aorta and peripheral arteries at rest and after submaximal exercise, as well as assess in a near-simultaneous fashion leg muscle mass and in vitro muscle composition. Methods and data from the project were incorporated into NIH RO1 HL076438-01A1 that was funded 2/1/07-12/31/11, and form the basis for the STTR application that was 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 TNF α). Data analyses are complete and a R21 award was submitted in June 08.

Project 42. Developing CT measures of Adiposity and Body Composition for application in population based and genomic research (Carr, MD, 2004-2005). This pilot project is performing body composition phenotyping of a subset of 400 DHS participants with CT assessments of abdominal adiposity, hepatic steatosis, and psoas muscle attenuation. Assays of inflammatory markers and for adiponectin and leptin have been completed. One manuscript has been published.

Project 43. Optical Imaging of Skeletal Muscle (Hamilton, MD, 2004-2005) A multidisciplinary team from Wake Forest Biomedical Engineering and NanoSonic Inc. has built a device that will allow in vivo assessment of skeletal muscle tissue. The prototype device now being tested utilizes optical fiber inside a standard 22 Ga. hypodermic needle, an infrared wavelength light source, coupled with a detector and a laptop PC. To date, we have been able to identify signatures within the IR spectrum that consistently match to specific fiber types. SBIR proposal "Minimally Invasive in vivo Muscle Biopsy with a Fiber Optic Probe" was submitted to NSF on December 1, 2005 with Nanosonic as our industrial partner as was not funded.

Project 44. Pericardial Fat and Subclinical and Clinical measures of Cardiovascular disease in a multi-ethnic sample of US adults. (2005-2006 PI: J. Ding) Investigators have developed a new method to measure the volume of pericardial fat in large epidemiologic studies. To examine the validity of this new method, they measured pericardial fat in a sample 10 Diabetes Heart Study participants. They also measured pericardial fat in a sample of 160 Multi-Ethnic Study of Atherosclerosis participants from Forsyth County, NC to examine the reproducibility of the new method. Finally, they assessed the association of pericardial fat with calcified coronary plaque. Using the preliminary data from this project, a R01 grant proposal was funded (R01 HL085323) and one paper has been published.

Project 45. Metabolic and Genetic Determinants of Non-Alcoholic Fatty Liver Disease in African-Americans and Hispanic Americans. (2005-2006 PI: L. Wagenknecht) This pilot will examine the epidemiology of fatty liver in a subset of 300 participants in the IRAS Family Study with specific attention given to age-related differences in the risk factor profile for fatty liver, and the relationship of fatty liver to cytokines, muscle mass by DXA, and physical function. This preliminary analysis included 85 non-diabetic Hispanic Americans from 9 pedigrees. An important result was the high prevalence of fatty liver among persons with the Metabolic Syndrome (MetS). Overall, fatty liver (LS ratio < 1.0) was detected in 20% (17/85) of the subjects; 10% (7/70) among those without MetS and 67% (10/15) among those with MetS. An abstract has been published and the IRAS family study was funded for another 5 years.

Project 46. Impact of an Exercise Program on Physical Function, Body Composition, and Quality of Life in Aging Recipients of Renal Allografts. (2005-2007 PI: E. Hartmann) The aim of this pilot is to yield preliminary data to design a large scale intervention and prevention trial. This study has two components: an observational cohort consisting of 26 dialysis patients aged 60 years or greater awaiting transplantation, and a substudy of up to 20 transplanted patients randomized to either usual care or fitness training. This pilot is unique in that it focuses on the older renal transplant recipient controlling for prior physical state in a way that

other studies have not. Data from this pilot lead to The American Society of Nephrology and the Association of Subspecialty Professors Grant (7/1/2006-6/30/2008).

Project 47. Effects of Sarcopenic Obesity on Recovery from a Trip. (2006-2007 PI: M. Madigan) This pilot will use an existing experimental model of trip recovery 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 hypothesize's that it is the magnitude and duration of acute systemic inflammation seen with Acute Respiratory Failure (ARF) that specifically contributes to the delay in mobility recovery for aged ARF patients. For the ARF patient, we suspect that Early ICU Mobility serves to reduce the magnitude or duration of the acute inflammation, in elderly patients, more so than in young patients. This pilot will analyze serum cytokines to determine whether a relationship exists between inflammatory cytokines on ICU days 0-7 and subsequent mobility limitations at hospital discharge. These data will seek to explore the *role of Early Mobility as a moderator of cytokine-mediated muscle dysfunction*. 78 of the planned 100 people have been enrolled into the study. Three manuscripts have been published and a NIH R01 NR011186 grant was funded in 2009. Five separate presentations at international meetings (1 podium, 1 abstract, and 3 invited talks at symposia), a NCBH-sponsored 1/2 day conference for Physical Therapists, two intramural grants funded (Cross Campus and Pepper Center), and an Innovation Profile, *Four-Step Protocol Determines Therapy for Patients With Acute Respiratory Failure, Leading to Improved Mobility, Shorter Stays*, appeared in the March 2009 issue of the AHRQ Health Care Innovations Exchange Web site (www.innovations.ahrq.gov).

Project 51. Molecular Characterization of Adipose Density by Non-Invasive Imaging in Humans and Non-Human Primates (2009-2011 PI: H. Shi) The aim of this study is to determine whether higher adipose density measured by CT imaging in nonhuman primates exposed to a high-fat diet is positively correlated with greater adipose inflammation and macrophage infiltration. This study is a joint effort between the PI (Hang Shi) and Dr. Thomas Register at primate Center. After discussing the collaboration with Dr. Register to split the workload of this project, the PI will use FACS analysis of adipose macrophage content and JNK activity/phosphorylation as two outcomes to determine the status of adipose inflammation. We recently succeeded in developing the methodology for FACS analysis of adipose macrophage content, a technology that can be broadly used in evaluating macrophage and other immune cell infiltration into adipose tissue in various model systems including mouse, primate and human. We will now use this newly-developed analysis to examine the macrophage content in human adipose tissue. Study is completed and 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 pathway⁴. Taken together these findings suggest that the activation of ERK /MAPK pathway by visfatin in chondrocytes could contribute to loss of IGF-1 function and provide the possible mechanism for IGF-1 resistance in OA.

Project 53.

Vitamin D status, VDR polymorphisms, and physical function in older adults (2007-2011 PI: D. Houston)

The first aim to examine the association between vitamin D status, using circulating levels of 25(OH) D and PTH, and muscle strength and physical performance in the LIFE-P Study is underway. Approximately 50% of the LIFE-P cohort had 25(OH) D levels indicative of insufficiency (<50 nmol/L). Participants with insufficient 25(OH) D levels had significantly lower SPPB scores and slower 400-m walk speeds at baseline compared to those with sufficient levels. Participants who had insufficient 25(OH)D levels at baseline but sufficient levels at follow-up had significant improvements in SPPB scores after adjustment for demographics, intervention group, season, BMI, and physical activity (Mean change (SD): 0.57 (0.22), p=0.01). The results were presented (2008- American Geriatrics Society and Gerontological Society of America; 2009-Experimental Biology) and the manuscript is in press (J Gerontol A Biol Sci Med Sci. 2011; 66(4):430-6).

Project 54.

ACE gene polymorphisms and resistance training in COPD. (2007-2010 PI: M. Berry)

This project, included in our competitive renewal for year 1 funding, also applied for and received funding through the WFU Translational Science Institute, resulting in significant 'leveraging' of OAIC funding. We have finished recruitment and the exercise intervention portions of our study. We enrolled 34 participants (goal of 32) and 26 participants completed all screening visits, the 12-week exercise intervention, and all follow-up visits. Data analysis is ongoing, and the project has arranged for Dr. Nicklas' lab to measure serum CRP, IL6, and TNF- α .

Project 55.

Wake Seniors - Establishing a partnership with Senior Living Communities (2008-2010 PI: J.

Williamson) This is an OAIC/TSI co-funded project that is a collaborative translational research project between Wake Forest University, Wake Forest University Baptist Medical Center, and Senior Living Communities. The long range objective is to implement and evaluate a variety of interventions that are designed to prevent, rehabilitate, or slow the loss of functional decline. Over the past year we have: (1) built a

web-based data entry system for our research with SLC; (2) set-up computers in 6 facilities and now have the web-based entry system fully operational at these sites; and (3) tested and entered demographic, health, and disability related data on 189 participants at these 6 sites.

Project 56.

NORMALS – A Study to Develop a Database of Determinants of Physical Function in Healthy Older Persons Free of Co-Morbidities (2008-2009 PI: D. Kitzman) This is a competitively funded OAIC supplement study. The primary aim is to establish a shared, central database from a group of healthy, older male and female volunteers free of chronic medical diseases that includes detailed standardized assessments of physical performance and body composition. A majority of the data have been entered, cleaned, and made available to the Pepper Center database, thus fulfilling in part the primary aim of this grant. The muscle biopsy cores are being analyzed in Dr. Kraus' lab at Duke University and the fresh single muscle fiber analyses were performed in Dr. Osvaldo Delbono's lab here at Wake Forest Medical Center. The automated instrument allowed us to measure fiber specific force, contraction velocity and power in the same fiber in approximately 60 fibers. The data from the Healthy NORMALS Study were also included as preliminary data for "I'm Fit" project application which was funded. (PI: Dr. Nicklas). Data clean-up has been completed, analyses are underway, and preliminary results will be presented at the National Pepper Investigators meeting in April 2011. Already, several requests for use of data have been received and approved, including from junior faculty and for pilot studies and RCDC scholars.

Project 57.

Age, Body Composition, Functional Status and Immune Function in African Green Monkeys (2010-2011 PI: J. Stehle)

A recent WFU OAIC pilot project (PI: C. Shively, see below) demonstrated that aged monkeys walk slower and have other functional differences compared to younger counterparts. The objective of this proposal is to determine potential mechanisms in which chronic systemic inflammation influences age related declines in physical ability in young adult and aged African Green Monkeys. The project is evaluating interactions between dendritic cells (DCs) and T helper cells which may skew differentiation towards the inflammatory Th17 pathway. DC cytokine profiles in older subjects will be compared to those produced by younger subjects; and types of helper T cells present within the adipose tissue will be assessed in relation to age and body composition. Relationships between these immunological parameters, serum levels of inflammatory markers, and physical function as a surrogate for disability risk in the non-human primate population will provide mechanistic insights into the role of immune system dysfunction in physical decline.

Project 58.

Computed Tomography (CT) Imaging of Lingual Muscle/Fat Composition in Community-Dwelling Older Adult Aspirators and Non-Aspirators (2009-2011 PI: S. Butler)

Oropharyngeal aspiration plays an important role in the development of pneumonia in the elderly. The primary aim 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.

Skeletal Muscle Chaperone Proteins and Metabolic Function in Aging (2009-2011 PI: K. Kavanagh)

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. Geranylgeranylacetone, 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 affects the expression and function of vitamin K-dependent proteins implicated in joint health and leads to more severe knee OA.

Project 66.

Brain Transmitters as Markers of Autonomic Profiling in the Elderly (2010-2011 PI: D. Diz)

Brain imaging may provide a useful, non-invasive means to evaluate autonomic functioning in the elderly. The objective of this project is to determine the reactions of healthy, sedentary men and women, 20 to 75 yrs of age, to carefully selected environmental tests, in conjunction with resting continuous blood pressures for spectral and sequence analysis of sympathetic and parasympathetic balance, and to establish interrelationships between these findings and central transmitter/metabolite profiles using vivo ¹H Magnetic Resonance Spectroscopy (MRS). The tests are intended to simulate a number of ordinary life stresses e.g., lifting and straining (isometric exercise), sudden increases in intrathoracic pressure (Valsalva), and cold exposure (hand immersion). Stress responses will be monitored primarily by non-invasive methods such as impedance cardiography and continuous blood pressure monitoring. The overall goal is to establish one or more neurotransmitters or metabolites in dorsal medullary nuclei as indicators of centrally mediated disturbances in autonomic function, obviating the need for more extensive and invasive testing.

Projects completed in current cycle:

Project 67.

Preservation of Muscle Performance and Metabolism in Aging through HSP Induction (2012) (PI: Kylie Kavanagh, PhD)

Sarcopenia and insulin resistance are common co-morbidities seen in aging, and they set the clinical stage for diabetes and fall risk which are both conditions of great public health significance. In addition, aging is associated with significant loss of innervation in mixed fiber type skeletal muscle, and reductions in the protective chaperone proteins, heat shock protein (HSP)-70 and HSP90. This pilot is assessing the potential for induced increases in HSP70 and 90 to attenuate age-associated sarcopenia. The central hypothesis is that the protection of muscle mass and function through HSP induction will preserve glycemic control that typically deteriorates with aging.

Project 68.

Upper Limb Kinematics and Muscular Compensation during Activities of Daily Living in Older Adults with Rotator Cuff Impairment (2012) (PI: K. Saul, PhD)

Approximately 20-50% of older adults (≥ 65 yrs) live with a rotator cuff tear, which is associated with decreased shoulder strength, restricted range of motion, and limited upper limb function. These deficits compromise the performance of activities of daily living (ADLs), and ultimately can lead to loss of independence. Individuals with a torn rotator cuff use compensatory movements to complete upper limb tasks, with deviations from the desired movement and a reliance on unimpaired muscles for movement production. The muscles most responsible for the ability to perform important ADL tasks with and without compensation have not been identified. The objective of this study is to investigate the effect of rotator cuff tear on joint movement and muscular compensations in important upper limb ADL tasks, using subject assessment and musculoskeletal modeling. The primary hypothesis is that older adults with a rotator cuff tear will use a restricted range of motion and have altered muscle coordination when performing upper limb ADLs, and that compensatory movement will reduce the strength required to accomplish the ADL tasks.

Project 69.

Bioenergetics, Mitochondrial Quality Control, and Physical Ability in Older Adults- Anthony Molina, PhD (RCDC scholar) The primary accomplishment of this project was the generation of protocols that allow us to assess the bioenergetic profile of mitochondria isolated from skeletal muscle biopsies. The details of this methodology have been described in detail in a recent publication (JOVE 2015). Baseline data from this study have led to one published manuscript, two that are in review, and one in preparation. These detail the relationships of mitochondrial bioenergetics with physical function, obesity, adiposity, and inflammation in older adults. Methodologies developed as well as data generated have been used to support a number of external grant applications with investigators across multiple departments (including cardiology, molecular medicine, exercise physiology) and with other members of the Aging Center. These have resulted in 3 funded RO1's thus far. The IM FIT parent study, and funds from this pilot, also allowed us to develop blood based

bioenergetic profiling techniques. Development of this assay has led to two provisional patent applications with support from Wake Forest Innovations. Moreover, the Molina lab has proposed to utilize these techniques in three external grant applications currently under review with the NIA and the American Heart Association.

Project 70.

The Effect of Age on Recovery from Acute Lung Injury-Induced Skeletal Muscle Wasting in Mice-Dr. Daniel Clark Files. MD (RCDC scholar) This pilot grant has been instrumental in providing funds to complete critical experiments that led to publications and has been the foundation for a transition of my research into aging. Another publication was accepted which contains some data funded through this project. Another manuscript is in preparation regarding the role of MuRF1 in aging mice with acute lung injury.

Project 71.

Pericyte Subtype Balance Determines the Success of Muscle Repair with Aging – Osvaldo Delbono, MD, PhD This pilot helped us to investigate the role of pericytes in the neuromuscular junction stability with aging. We collected monkey muscle to further characterize its pericyte subpopulations and examine their involvement in the NMJ composition with aging.

Project 72.

Impact of medical weight loss on physical function in severely obese older adults – Jamy Ard, MD Participants completed the 24 week intervention and follow up. Of the 28 randomized participants, only 1 person dropped from study participation and follow up measurements. Program engagement was consistent throughout the 24 weeks of intervention for both study groups. We are currently conducting final analyses and this will provide overall direction of further research focus.

Project 73.

Health Outcomes after Participating in Exercise (HOPE): A Pilot Study – Denise Houston, PhD, RD A random sample of participants (n=60) from 5 completed/ongoing exercise and weight loss studies (INFINITE, I'M FIT, SECRET, CLIP, IDEA) were recalled and interviewed (in clinic or by phone) from Oct 2013 thru May 2014. The response rate was excellent of 88% (42 participants completed a clinic visit; 10 completed a phone interview; 1 was deceased; 5 refused; and 2 unable to contact). Analyses of the complete data set is ongoing and manuscript in preparation. The mean follow-up time between the end of the original intervention trials and the HOPE follow-up visit was approximately 3.5 yrs. Among those attending a HOPE clinic visit (n=42), those in the exercise only group had lost 2% of their body weight while those in the exercise plus weight loss group had gained 6% of their body weight since the end of the original intervention, suggesting that most of the weight loss during the intervention was regained. For change in body composition since the end of the original intervention, there was a 5% increase in fat mass and 7% decrease in lean mass in the exercise only group; while in the exercise plus weight loss group there was a 25% increase in fat mass and 2% decrease in lean mass. SPPB summary score, repeated chair stand time, 4 m walk speed, and 400 m walk speed were similar in both groups at the HOPE follow-up visit suggesting that weight regain did not adversely affect physical function. An R01 AG051352 entitled “Long-term function and health effects of intentional weight loss in obese elders” was submitted to NIH/NIA 12/8/14 (reviewed 2/5/15; 35th percentile); Co-PIs, Houston & Nicklas; Co-Is: Kritchevsky, Miller, Kitzman, Rejeski, Messier. We plan to revise and resubmit for July 2015 deadline.

Project 74.

Prospective Randomized Intervention to Improve Exercise Intolerance (PRIORITIES) – Dalane Kitzman, MD

All patients have completed the study. Primary outcomes have been analyzed which showed a modest improvement in physical function. Results presented at the Nitrates conference at the Reynolda conference. Manuscript in preparation. The secondary outcome (perfusion) is undergoing image analyses.

Project 75.**Effect of dietary nitrate + protein supplementation on body composition and muscle function in older adults undergoing a resistance training program- Gary Miller, PhD**

Data from this project is being used for 2 graduate thesis project and 1 undergraduate thesis project. Data analysis has just begun and once complete we hope that this will allow investigators to submit for a large external grant looking at the important issue of improving responses of resistance exercise training in older adults.

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

Project Dates by Years	Grant Number	Grant Name	Award PI	Funding Source
2016-2018	R21 AG051077	Bioenergetics and Rehabilitation in Older Adult Patients with Acute Health Failure	Molina	NIA
2016-2021	R01 DK103531	Epigenetics of Weight-Loss and Glycemin Improvement	Ding	NIDDK
2016-2017	R21 AG051866	Renal Function and Chronic Kidney Disease in Aging	Petrovic	NIA
2016-2021	R01AG051624	Intervening on sedentary behavior to prevent weight regain in older adults	Nicklas	NIA
2016-2021	R01 DK103531	Tropin T and Excitation- Contraction Coupling in Aging Skeletal Muscle	Ding	NIDDK
2015-2018	U01AG050499	ENabling Reduction of low-Grade Inflammation in Seniors	Kritchevsky	
2015-2017	R03 AG050919	The Effects of Aquatic Prehabilitation in Knee OA Patients on Knee Anthroplasty Outcomes	Kim	NIA / GEMSSTAR
2015-2017	15MCPRP25680019	Understanding the Physiology of Bioenergetics and Aging Trial	Molina	AMA
2015-2018	Jason Pharmaceuticals	Weight Loss for Seniors Study	Beavers	Jason Pharma
2015-2020	PCS-11403-145	Early Supoprted Discharge for Improving Functional Outcomes After stroke	Duncan	PCORI
2015-2020	R01AG018915	Study of the Effects Caloric Restriction and Exercise Training in patients with heart failure and a normal ejection fraction (SECRET 2)	Kitzman	NIA

2014-2019	R01 AG 045551	A Trial Of Rehabilitation Therapy In Older Acute HeartFailure (REHAB HF)	Kitzman	NIA
2014-2018	2R01AG018915	Exercise Intolerance in Older HFPEF Patients	Kitzman	NIA
2013-2018	R01 AG013934	Tropin T and Excitation-Contraction Coupling in Aging Skeletal Muscle	Delbono	NIA
2013-2018	R01 AG042411	Exploring Vitamin D's Effects on Neuromuscular Endpoints Study (EVIDENCE)	Houston	NIA/
2013-2018	K01 AG043547	Cognitive/Brain Effects of Adding Weight Loss to Exercise in Obese Older Adults (INFINITE MIND)	Hugenschmidt	NIA
2012-2016	K01 AR063167	Identifying Vitamin K Dependent Pathways in Osteoarthritis Progression	Shea	
2012-2017	2T32AG033534	Training Program in Gerontological and Geriatric Medicine	Kritchevsky	NIA
2012-2017	2R01 HL076441	Cooperative Lifestyle Intervention Program (CLIP -II)	Rejeski	NHLBI
2012-2014	R21 AR062284	Vitamin K, Knee Osteoarthritis, and Physical Function in Older Adults	Kritchevsky	NIAMS
		Rehabilitation and Exercise Training after Hospitalization: Assessing benefit in Acute Heart Failure Pilot Study (Rehab HF)	Kitzman	
2011-2016	R01HL109429	Prosocial Behavior and Volunteerism to Promote Physical Activity in Older Adults (PACE)	Foy	NHLBI
2011-2016	s/univ of Pitt	Exceptional Survival; Trajectories to Functional Aging	Kritchevsky	NIA
2011-2016	R01 AR059105	Strength Training & Arthritis Trial (START)	Messier	NIAMS
2011-2016	HHSN 271-00004C	Women's Health Initiative Memory Study New contract	Shumaker	NIA
2011-2015	sub/U of S.CA	Environmental Determinants of Cognitive Aging in the Women's Health Initiative Memory Study	Espeland	NIA
2011-2015	R01 DK092237	Action for Health in Diabetes Brain Magnetic Resonance Imaging Ancillary Study	Espeland	NIDDK
2011-2015	R01HL107257	Systolic Blood Pressure Intervention Trial (SPRINT-HEART)	Kitzman	NHLBI
2011-2015	HHSN 2682011	ACCORDION MIND - main study	Williamson	NHLBI
2011-2014	R03 AR061050	Invivo role of S100A4 in OA pathophysiology	Yammani	NIAMS
2011-2013	R21 ES01720	Pesticide Exposure and Age-Related Changes in Cognitive Function	Nguyen	NIEHS
2011-2013	Arthritis Foundation #5387	Vitamin K Nutritional Status and Osteoarthritis Progress	Shea	Arthritis FNDN
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	HHSN2682011000 07C	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 AG033652	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	HHSN2682011000 04C	WHI Southeast Regional Center	Shumaker	NHLBI

2010-2015	K01 HP0050	Geriatric Academic Career Award	Watkins	DHHS/HRSA
2010-2014	R01 HL092301	Whole Genome Association Analysis of the Diabetes Heart Study	Bowden	NHLBI
2010-2014	R01 MH083664	An RCT of CBT-Telephone for Late-Life Generalized Anxiety Disorder	Brenes	NIMH
2010-2014	R01 HL098445	Longitudinal Changes in Pericardial Adiposity and Subclinical Atherosclerosis	Carr	NHLBI
2010-2014	R01 DK085175	GUARDIAN	Wagenknecht	NIDDK
2010-2014	U01 HL096814	Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study (NCS)	Wagenknecht	NHLBI
2010-2012		ASPREE clinic site	Demons	NIA
2010-2012	N/A	Picker Institute/Gold Foundation	Watkins	Picker Institute
2010-2012	HSN 271-00023C	ACCORDION MIND - MRI	Williamson	NHLBI
2009-2018	RFP HC0904	SPRINT Coordinating Center S.E. Network	Goff	NHLBI/NIA/NINDS
2009-2017	RFP HC0904	SPRINT MIND Memory in Decreased Hypertension	Williamson	NHLBI
2009-2015	U01 AG022376	Physical Exercise to Prevent Disability Study (LIFE) WFU Field Center	Kritchevsky	NIA
2009-2015	U01 AG022376	LIFE Data Management, Analysis and Quality Control Center	Miller	NIA
2009-2015	R01 CA133483	Radiation -induced brain injury and cognitive dysfunction in aging rats	Riddle	NCI
2009-2015	U01 AG022376	LIFE Cognition Study	Williamson	NIA
2009-2014	R01 AG015820	Age-dependent regulation of excitation-contraction coupling	Delbono	NIA
2009-2014	T32 HL091824	Multi disciplinary Training in Cardiovascular Imaging	Hundley	NHLBI
2009-2014	K01 AG33641	Chaperone Proteins in a Primate Model of Age-Related Metabolic Disease	Kavanagh	NIA
2009-2014	R37 AG018915	Exercise intolerance in elderly diastolic heart failure	Kitzman	NIA
2009-2014	R01 AG033087	Intentional Weight Reduction and Physical and Cognitive Function - Look AHEAD ancillary study	Kritchevsky	NIA
2009-2014	R01 AG032098	Genetic Determinants of Visceral Adiposity	Liu	NIA
2009-2014	R01 HL101250	Epigenome-Wide Association Study of DNA Methylation and Artherosclerosis	Liu	NHLBI
2009-2014	U01 MH086127	Prolonging Remission in Depressive Elderly (PRIDE)	McCall	NIMH
2009-2014	R011NR011186	Standardized Rehabilitation Therapy for ICU Patients with Acute Respiratory Failure TARGETT	Morris	NHLBI
2009-2014	R01 HL093713	Effect of Fat Loss on Functional and Cardiovascular Benefits of Aerobic Exercise	Nicklas	NHLBI
2009-2014	R01 AG020583	Loss of Fat Tissue and Functional Response to Exercise in Older, Obese Adults	Nicklas	NIA
2009-2013	N01 HC95095	The CARDIA Computed Tomography Reading Center	Carr	NHLBI
2009-2013	R21 AG033385	FBT-PET Study of Aging Skeletal Muscle	Delbono	NIA
2009-2013	R01 AG033727	Estrogen, Angiotensin, and Diastolic Function	Groban	NIA
2009-2013	R01 AG020572	Neural Signaling and Age-Related Cognitive Impairment	Nicolle	NIA
2009-2013	R01 DK084172	The AMP-Activated Protein Kinase (AMPK) Antagonizes Inflammation Through SIRT1	Shi	NIDDK
2009-2012	N01 HC95159	MESA SHARe	Burke	NHLBI
2009-2012	R03 TW008091	Role of Calcium Channels in Aging Skeletal Muscle	Delbono	NIA
2009-2012	N/A	A.D. Aware: Mentally Stimulating Activities for Treatment of Apathy in Early Stage Alzheimer's	Sink	Alzheimer's Association

2009-2012	N/A	Comprehensive Program to Strengthen Physicians' Training	Williamson	Donald W. Reynolds Foundation
2008-2013	R01 NS058700	Genetic Epidemiology of Cerebrovascular Disease and Cognition in Diabetes	Bowden	NINDS
2008-2012	R01 DK075681	FHS Genetic Epidemiology of Metabolic Diseases of Obesity	Carr	NHLBI
2008-2012	K01AG030506	Vitamin D Status, Related Gene Polymorphisms and Physic	Houston	NIA
2008-2012	R41/R42 AG030248	Comprehensive MR Imaging of Elderly Vascular Function	Hundley	NIA
2008-2012	R01OH009251	Occupational Injuries Among Immigrant Poultry Workers: Development and Progression	Quandt	NIOSH
2008-2012	2007-0123	Hartford Foundation Center of Excellence	Williamson	Hartford FDN
2007-2012	N01 HC95170	JHS Magnetic Resonance Imaging (MRI) Reading Center, Substudy w/Jackson State University	Carr	NHLBI
2007-2012	R01 HL085571	Predictors of Coronary Artery Calcification in an African American Cohort Subcontract w/University of Michigan, WFUHS Site PI	Carr	NHLBI
2007-2012	R01 DA023573	Neural Analysis of Cocaine Effects on Cognition	Deadwyler	NIDA
2007-2012	R01 AG013934	Single skeletal muscle fiber impairment with aging	Delbono	NIA
2007-2012	R01 AR049003	Integrin Function in Cartilage	Loeser	NIAMS
2007-2012	R01 NR009675	Phase III Study of Donepezil in the Irradiated Brain	Rapp	NINR
2007-2012	R01 HL087103	Depression and Coronary Artery Atherosclerosis in Premenopausal Primates	Shively	NHLBI
2007-2012	U01 AG010483	Multi-Center Trial to Evaluate Home-Based Assesment Methods	Sink	NIA

Wake Forest Pepper Center 2015-2016 Publications

2016 Under Review

1. Bharadwaj, M. S., Tyrrell, D. J., Leng, I., Demons, J. L., Lyles, M. F., Carr, J. J., Nicklas, B. J., and Molina, A. J. *Skeletal muscle mitochondrial bioenergetics and body composition in older adults*. Obesity.2016. *Under Review*.
2. Choi, S. J., Marsh, A. P., Zhang, T., Wang, Z. M., Messi, M. L., Gregory, H., Stone, J., Lyles, M. F., Nicklas, B. J., and Delbono, O. *Intramyocellular lipid and impaired myocyte contraction in lean and obese older adults*. J Gerontol Med Sci.2016. *Under Review*.

2016 In Press

1. Miller, G. D., Nicklas, B. J., and Fernandez, A. *One-Year follow up of Physical Function After Extensive Weight Loss From Laparoscopic Roux-en-Y Gastric Bypass Surgery*. Soc Obes Rel Dis. *In Press*.
2. Pajewski, N. M., Williamson, J. D., Applegate, W. B., Berlowitz, D. R., Bolin, L. P., Chertow, G. M., Krousel-Wood, M. A., Lopez-Barrera, N., Powell, J. R., Roumie, C. L., Still, C., Sink, K. M., Tang, R., Wright, C. B., and Supiano, M. A. *Characterizing Frailty Status in the Systolic Blood Pressure Intervention Trial*. J Gerontol A Biol.Sci Med Sci.2016:(71)649-655. *In Press*.
3. Rejeski, W. J., Marsh, A. P., Brubaker, P. H., Buman, M., Fielding, R. A., Hire, D., Manini, T., Rego, A., and Miller, M. E. *Analysis and Interpretation of Accelerometry Data in Older Adults: The LIFE Study*. J Gerontol A Biol.Sci Med Sci.2016:(71)521-528. *In Press*.
4. Jefferson, M. E., Nicklas, B. J., Chmelo, E. A., Crotts, C. I., Shaltout, H. A., Diz, D. I., Marsh, A. P., and Brinkley, T. E. *Effects of Resistance Training With and Without Caloric Restriction on Arterial Stiffness in Overweight and Obese Older Adults*. Am J Hypertens.2016:(29)494-500. *In Press*.
5. Kim, S., Marsh, A. P., Rustowicz, L., Roach, C., Leng, X. I., Kritchevsky, S. B., Rejeski, W. J., and Groban, L. *Self-reported Mobility in Older Patients Predicts Early Postoperative Outcomes after Elective Noncardiac Surgery*. Anesthesiology.2016:(124)815-825. *In Press*.
6. Henderson, R. M., Lovato, L., Miller, M. E., Fielding, R. A., Church, T. S., Newman, A. B., Buford, T. W., Pahor, M., McDermott, M. M., Stafford, R. S., Lee, D. S., and Kritchevsky, S. B. *Effect of Statin Use on Mobility Disability and its Prevention in At-risk Older Adults: The LIFE Study*. J Gerontol A Biol.Sci Med Sci.2016. *In Press*.
7. Choi, S. J., Files, D. C., Zhang, T., Wang, Z. M., Messi, M. L., Gregory, H., Stone, J., Lyles, M. F., Dhar, S., Marsh, A. P., Nicklas, B. J., and Delbono, O. *Intramyocellular Lipid and Impaired Myofiber Contraction in Normal Weight and Obese Older Adults*. J Gerontol A Biol.Sci Med Sci.2016:(71)557-564. *In Press*.
8. Dotson, V. M., Hsu, F. C., Langaee, T. Y., McDonough, C. W., King, A. C., Cohen, R. A., Newman, A. B., Kritchevsky, S. B., Myers, V., Manini, T. M., and Pahor, M. *Genetic Moderators of the Impact of Physical Activity on Depressive Symptoms*. J Frailty.Aging.2016:(5)6-14. *In Press*.
9. Eggebeen, J., Kim-Shapiro, D. B., Haykowsky, M., Morgan, T. M., Basu, S., Brubaker, P., Rejeski, J., and Kitzman, D. W. *One Week of Daily Dosing With Beetroot Juice Improves Submaximal Endurance and Blood Pressure in Older Patients With Heart Failure and Preserved Ejection Fraction*. JACC.Heart Fail.2016. *In Press*.
10. Buford, T. W., Miller, M. E., Church, T. S., Gill, T. M., Henderson, R., Hsu, F. C., McDermott, M. M., Nadkarni, N., Pahor, M., Stafford, R. S., and Carter, C. S. *Antihypertensive Use and the Effect of a Physical*

Activity Intervention in the Prevention of Major Mobility Disability Among Older Adults: The LIFE Study. J Gerontol A Biol.Sci Med Sci.2016. *In Press.*

2016 Journal Publications

1. Gill, T. M., Pahor, M., Guralnik, J. M., McDermott, M. M., King, A. C., Buford, T. W., Strotmeyer, E. S., Nelson, M. E., Sink, K. M., Demons, J. L., Kashaf, S. S., Walkup, M. P., and Miller, M. E. *Effect of structured physical activity on prevention of serious fall injuries in adults aged 70-89: randomized clinical trial (LIFE Study).* BMJ.2016:(352)i245-. PMC4772786.
2. Irby, M. B., Bond, D. S., Lipton, R. B., Nicklas, B., Houle, T. T., and Penzien, D. B. *Aerobic Exercise for Reducing Migraine Burden: Mechanisms, Markers, and Models of Change Processes.* Headache.2016:(56)357-369. PMC4813301.
3. Kitzman, D. W., Brubaker, P., Morgan, T., Haykowsky, M., Hundley, G., Kraus, W. E., Eggebeen, J., and Nicklas, B. J. *Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial.* JAMA.2016:(315)36-46. PMC4787295.
4. Shao, Q., Cheng, H. J., Callahan, M. F., Kitzman, D. W., Li, W. M., and Cheng, C. P. *Overexpression myocardial inducible nitric oxide synthase exacerbates cardiac dysfunction and beta-adrenergic desensitization in experimental hypothyroidism.* Int.J Cardiol.2016:(204)229-241. PMC4698083.
5. Vidt, M. E., Santago, A. C., Marsh, A. P., Hegedus, E. J., Tuohy, C. J., Poehling, G. G., Freehill, M. T., Miller, M. E., and Saul, K. R. *The effects of a rotator cuff tear on activities of daily living in older adults: A kinematic analysis.* J Biomech.2016:(49)611-617. PMC4779416.
6. Vidt, M. E., Santago, A. C., Tuohy, C. J., Poehling, G. G., Freehill, M. T., Kraft, R. A., Marsh, A. P., Hegedus, E. J., Miller, M. E., and Saul, K. R. *Assessments of Fatty Infiltration and Muscle Atrophy From a Single Magnetic Resonance Image Slice Are Not Predictive of 3-Dimensional Measurements.* Arthroscopy.2016:(32)128-139. PMC4706774.

2015 Journal Publications

1. Andersen, M. M., Kritchevsky, S. B., Morgan, T. M., Hire, D. G., Vasu, S., Brinkley, T. E., Kitzman, D. W., Hamilton, C. A., Soots, S., and Hundley, W. G. *Increased cardiovascular stiffness and impaired age-related functional status.* J Gerontol A Biol.Sci Med Sci.2015:(70)545-553. PMC4400394.
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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.*

WAKE FOREST UNIVERSITY SCHOOL OF MEDICINE

Claude D. Pepper Older Americans Independence Center

2015-2016 Recognition and Awards

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

Medicineors

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

2014-2018 National Advisory Council on Aging (NACA)

Denise Houston, PhD

(2012 – present) Editorial Board, Journal of Gerontology Medical Sciences

(2008 – present) Editorial Board, Journal of Nutrition in Gerontology and Geriatrics

(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

Editorial Boards of the following: The Open Psychiatry Journal, International Journal of Women's
Health, Cardiovascular Psychiatry & Neurology, World Journal of Diabetes

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

**WAKE FOREST UNIVERSITY SCHOOL OF MEDICINE PEPPER CENTER
MINORITY RESEARCH
2015-2016**

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 (ISSTD) 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

Brain Anatomy in Latino Farmworkers Exposed to Pesticides and Nicotine. Laurienti PJ, Burdette JH, Talton J, Pope CN, Summers P, Walker FO, Quandt SA, Lyday RG, Chen H, Howard TD, Arcury TA. *J Occup Environ Med.* 2016 May;58(5):436-43. doi: 10.1097/JOM.0000000000000712. PMID: 27158949

Effects of Lifetime Occupational Pesticide Exposure on Postural Control Among Farmworkers and Non-Farmworkers. Sunwook K, Nussbaum MA, Quandt SA, Laurienti PJ, Arcury TA. *J Occup Environ Med.* 2016 Feb;58(2):133-9. doi: 10.1097/JOM.0000000000000655. PMID: 26849257

Alcohol Consumption and Risk for Dependence Among Male Latino Migrant Farmworkers Compared to Latino Nonfarmworkers in North Carolina. Arcury TA, Talton JW, Summers P, Chen H, Laurienti PJ, Quandt SA. *Alcohol Clin Exp Res.* 2016 Feb;40(2):377-84. doi: 10.1111/acer.12969. PMID: 26842256

Urinary Cotinine Levels Among Latino Tobacco Farmworkers in North Carolina Compared to Latinos Not Employed in Agriculture. Arcury TA, Laurienti PJ, Talton JW, Chen H, Howard TD, Summers P, Quandt SA. *Nicotine Tob Res.* 2016 Jun;18(6):1517-25. doi: 10.1093/ntr/ntv187. Epub 2015 Sep 16. PMID: 26377519

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 Health 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 trial (NHLBI), a randomized trial evaluation long-acting niacin for secondary CVD prevention.

Dr. Peter Morris, Associate Professor, Pulmonary, Critical Care, Allergy, and Immunologic Medicine. Dr. Morris is collecting gender, race, and ethnicity data on the 126 of 326 subjects enrolled within the R01NR011186-01 Standardized Rehabilitation for ICU Patients with Acute Respiratory Failure. This study will provide the information for US hospitals to prioritize and budget for the rehabilitation needs of patients with ARF by demonstrating that Standardized Rehabilitation Therapy, initiated in the ICU,

reduces hospital stays with immediate and sustained improvement in function and quality of life for patients with ARF.

Publications Pertaining to Minority Research:

Quarta, C. C., Buxbaum, J. N., Shah, A. M., Falk, R. H., Claggett, B., Kitzman, D. W., Mosley, T. H., Butler, K. R., Boerwinkle, E., and Solomon, S. D. The amyloidogenic V122I transthyretin variant in elderly black Americans. *N.Engl.J Med.*2015;(372)21-29. PMC4382209.

McNeil C, Sexually Transmitted Diseases. In Insel and Roth eds. *Core Concepts in Health*. 15th ed. McGraw-Hill, 2016. In press.

Barr BC, Nall J, McNeil CJ, Bachmann LH. Implementation of Oral and Rectal Gonococcal and Chlamydial Nucleic Acid Amplification-Based Testing as a Component of Local Health Department Activities. Manuscript submitted. *Journal of Sexually Transmitted Diseases*, February 2016.

McNeil CJ, Kong KS, Anglemyer A, Levy V and Maldonado Y. Results of the Women's Self-Performed Anal Pap (SWAP) Trial in HIV-Infected Women Manuscript accepted. *Journal of Sexually Transmitted Diseases*, March 2016.