A. Personal Statement.

As a Principal Investigator, I am focused on signaling cross talk between the endothelium, stem cells, and muscle cells during peripheral arterial disease (PAD). I have expertise in skeletal muscle and vascular cell biology, oxidative stress and reactive oxygen species, muscle plasticity, genetics, mitochondrial function, glycolytic flux, and bioenergetics contributions to disease manifestations. My laboratory at East Carolina University, in the Diabetes and Obesity Institute (ECDOI) is focused on translating the exciting idea of muscle’s influence on vascular biology in settings of ischemic disease, including critical limb ischemia (CLI). This work is an integral bridge between skeletal muscle and vascular biology and undertakes cell biology experimentation on the protein interactions regulating endothelial and muscle cell communication and subsequent arteriogenesis, angiogenesis, and capillary network alterations that are dictated by the local microenvironment during ischemic insult.

Recently, we have undertaken a series of studies in collaboration with clinicians (D.J. Yamaguchi, I.Pipinos, B. Annex) to better translate our pre-clinical findings into the clinical disease state. This work is integral to better understanding how muscle function ties to pathologic outcomes both pre-clinically and clinically. This collaborative effort has led to the collection and storage of a large number of tissues from PAD patients in my laboratory and makes us one of very few laboratories in the world with tissues representative of the entire clinical spectrum of PAD. We are uniquely positioned to translate any pre-clinical findings into clinical readouts, given our ongoing and productive clinical collaborations. This work best represented in a recent paper for our collaborative team involving a clinical sample based identification of a unique bioenergetics profile in the skeletal muscles of critical limb ischemia patients:

We have specifically undertaken series of preliminary studies with Dr. Yamaguchi (ECU) to examine the role of BAG3 in clinical manifestations of PAD. In collaboration with physicians at Temple University, we recently identified unique variants in BAG3 (Bcl-2 associated athanogene 3) exclusively in 10% of individuals of African descent with cardiomyopathy. The variants discovered contributed to idiopathic dilated cardiomyopathy outcomes. Our preliminary work has identified a similar incidence rate of the same BAG3 variants (16%) in a small sample size of African American patients here at ECU. Additional work further demonstrated that these patients harbor more severe myopathic outcomes in ischemic limb muscle cells. This proposal will test the therapeutic efficiency of human WT BAG3 in ischemic limb skeletal muscles and will examine the consequences of BAG3 variants specific to the AA population on these processes. Our ability to collect both plasma and limb muscle samples from age matched control patients and PAD patients across the clinical spectrum, combined with our collective experience with primary cell isolation, genetics, molecular biology, and pre-clinical models of PAD uniquely position us to rigorously test our hypotheses. Given this, we feel strongly, based on our clinical and basic science collaborative team that the completion of the studies in this proposal will reveal unique insights into the following: mechanisms of ischemic limb pathology; mechanisms for the inherent differences in clinical presentations of PAD as dictated by health disparities; and development of novel therapies and/or biomarkers for this disease.

B. Positions and Honors.

**Positions**

**1999-2005**  
Ph.D. (August 6, 2005)  Graduate Research Assistant, Integrative Muscle Biology, University of South Carolina: Laboratory of James A. Carson, PhD.

**2005-2008**  
Post-Doctoral Associate (June 22, 2005), Exercise Biochemistry, University of Florida, Laboratory of Scott Powers, EdD, PhD.

**2008-2009**  
Post-Doctoral Fellow (July 1, 2008), Molecular Biology, Duke University Medical Center, Laboratory of Zhen Yan, PhD. *Dr. Yan left Duke Medical in December 2008 for University of Virginia Medical Center.

**2009-2010**  
Post-Doctoral Fellow (Jan. 1, 2009), Cardiology/Molecular Biology/Genetics, Duke University Medical Center, Laboratory of Christopher Kontos, MD.

**2010-2013**  
Senior Research Associate (Sept. 1, 2010), Division of Cardiology, Duke University Medical Center.

**2013-2018**  
Assistant Professor (July 15, 2013), Department of Physiology, Diabetes and Obesity Institute, East Carolina University, Brody School of Medicine.

**2017-Present**  
Adjunct (January 1, 2017), Department of Cardiovascular Sciences, East Carolina Heart Institute, East Carolina University, Brody School of Medicine.

**2018-Present**  
Associate Professor (July 1, 2018, with Tenure), Department of Physiology, Diabetes and Obesity Institute, East Carolina Heart Institute, East Carolina University, Brody School of Medicine.

**Honors and Awards**

**2005**  
University of South Carolina – Department of Exercise Science Doctoral Student Achievement Award. University of South Carolina, Columbia, SC.

**2007**  
American Physiological Society (APS), Environmental & Exercise Physiology Section Postdoctoral Gravitational Physiology Award. Experimental Biology, Washington, DC.

**2008**  

**2009**  
Trainee 2009-2010, 2T32HL069749-06 (PI: Rockman), Postdoc Training in Cardiovascular Clinical Research.

**2010**  
NIH/NHLBI Pathway to Independence Award (K99/R00). "Peripheral endothelial and muscle cell pathology in cardiovascular disease."

**2012**  
Duke LEADER: Leadership Development for Researchers Program, Selected Participant.

**2012**  
Department of Medicine, Duke University Medical Center Internal Core Facility Research Voucher
C. Contributions to Science

1. Oxidative stress is a common component of cardiac and skeletal muscle myopathies. A key portion of my professional training was focused on understanding potential sources of- and adequate therapeutic methodology to suppress the negative effects of oxidant burdens in striated muscle. There is an important parallel with this early career work and our current investigation for cardiomyopathies and myofibrillar myopathies associated with cardiovascular diseases. This work is critical to the understanding the local myopathic environment created by oxidants, including the burdens that may contribute to ischemic contractile dysfunction and muscle necrosis.

   
   
   

2. Peripheral artery disease (PAD) is caused by atherosclerosis of the peripheral arteries, most commonly in the lower extremities, and is nearly as prevalent as coronary artery disease (CAD), with 8-12 million individuals affected in the US. PAD presents as either intermittent claudication (IC, pain with exertion that is relieved with rest) or critical limb ischemia (CLI, pain at rest with or without tissue necrosis or gangrene). In recent years, we have been an integral part of the greater scientific understanding of the link between the muscle cell’s adaptive responses to stress and the perfusion or vascular density of the limb as well as signaling through the traditional vascular receptor tyrosine kinases. The recent works below have significant implications for advancing effective therapeutics aimed specifically at the myopathy of PAD, as well as other ischemic diseases. They also highlight the McClung lab’s commitment to understanding the complex paracrine relationship between muscle and endothelial cells in muscle tissues.

   
   
3. An accurate understanding of the pathogenesis of ischemia and the development of adequate therapies requires accurate pre-clinical modeling of human cardiovascular diseases. In recent years, we have been actively involved in refining atherosclerosis models in mice. This reflects the flexibility of the lab to adapt and implement unique model systems and methodologies to appropriately mimic the ischemic microenvironment that we are actively observing in the tissues we collect from clinical PAD patients.


4. To truly understand cardiovascular disease risks and/or the biological outcomes of varying cardiovascular diseases, it is pivotal to incorporate a detailed understanding of genetic contributors to individualized disease. Independently, and in collaboration with clinicians at the University of Nebraska Medical Center, Temple University Medical Center, Duke University Medical Center, and The University of Virginia School of Medicine, we are actively involved in studying novel human cardiovascular disease related genetic variants. We are also collaboratively involved in studying genetic targets and variants involved in muscle myopathies associated with other diseases, such as cancer (Brcal).


5. Patients with PAD, in addition to vascular defects, have altered muscle metabolism, mitochondrial respiration, altered expression of mitochondrial enzymes, increased oxidative stress, and somatic mutations in mitochondrial genes, although to date these have been largely interpreted as secondary pathologies rather than potential contributors to the etiology of PAD. Muscle mitochondria are critical to energy production and redox homeostasis, and alterations or exacerbations in limb perfusion such as those induced by ischemia could contribute to alterations in mitochondrial content and/or function. To this end, we have worked extensively in the bioenergetics’ area to define the muscle mitochondrial contribution to PAD. This includes a detailed mitochondrial characterization of mitochondria from the limb skeletal muscles of patients across the clinical spectrum of PAD.


Complete List of Published Work in My Bibliography:

D. Research Support.

Active Research Support

R01-HL201725 (PI: Kontos, Co-I: McClung) 9/1/2015—8/31/2019
National Institutes of Health
VEGF Cognate Receptor Signaling in Resident Muscle Progenitor Cells During Ischemia
Division of Cardiology, Duke University Medical Center

R01-HL125695 (PI: McClung) 4/1/2015—3/31/2020
NHLBI, National Institutes of Health
Genetic Determinants of Limb Pathology in Peripheral Artery Disease
Department of Physiology, East Carolina University, Brody School of Medicine, Greenville, NC.

Completed within the past 3 years

R00-HL103797 (PI: McClung) 1/1/2014—12/30/2017
NIH/NHLBI K99/R00 Pathway to Independence Award
Peripheral endothelial and muscle cell pathology in cardiovascular disease
Department of Physiology, East Carolina University, Brody School of Medicine, Greenville, NC.