Cardiovascular Research Institute
Michael E. DeBakey Institute

2024 Research Symposium

September 19–20, 2024

Cardiovascular Research Institute
College of Medicine
Texas A&M University

The Cardiovascular Research Institute (CVRI) was established in 1998. The CVRI is constituted of three divisions: Cardiac, Lymphatic and Vascular, with more than a hundred current members across seven colleges and schools within Texas A&M University (TAMU) System: College of Medicine, College of Pharmacy, School of Engineering Medicine, College of Veterinary Medicine and Biomedical Science, College of Engineering, College of Agriculture & Life Sciences, and College of Education and Human Development. CVRI scientists have made significant discoveries in the basic physiology of blood vessels, lymphatics, and heart. Other areas of investigation include angiogenesis, lymphangiogenesis, exercise biology, heart failure, atherosclerosis, ischemic heart disease, hypertension, and metabolic diseases. To facilitate research today and for future generations, the CVRI provides an environment for the training of undergraduates, medical students, graduate students, postdoctoral fellows, and residents. The CVRI bestows a platform to foster and share research ideas, and for continuous engagements of activities, such as, seminars, small group meetings, workshop, and symposium, which provide a vibrant environment for trainees and faculty members to build and promote research and education collaborations within TAMU system. Discovery with an emphasis on human health requires basic and clinical research. Our research team consists of basic scientists and physicians/scientists from a wide variety of fields and disciplines. The contributions of our faculty to medical literature can be found on their respective web pages. CVRI investigators' research is funded by the National Institutes of Health, American Heart Association, National Aeronautics and Space Administration, and other agencies.

I would like to express sincere appreciation to the following colleagues for their moral and financial support.

Glenn M. Toney, PhD, FAHA, FAPS
Professor and Head, Department of Medical Physiology, College of Medicine, Texas A&M Health
Glen Laine, PhD
Professor, Director
M. E. DeBakey Research Institute, College of Veterinary Medicine and Biomedical Sciences
Indra K. Reddy, PhD
Interim Chief Operating Officer and Senior Vice President, Texas A&M Health
Allison C. Rice-Ficht, PhD
Regents Professor, Senior Associate Dean for Research, College of Medicine, Texas A&M Health
Dr. John August
Carl B. King Dean, College of Veterinary Medicine & Biomedical Sciences, Texas A&M University

Mariappan Muthuchamy, PhD
CVRI Director

Additional information about the CVRI can be found at https://medicine.tamu.edu/centers/cvri.html

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Lecture and Poster Sessions at College of Medicine
Health Professions Education Building, LL43A–B, LL44
Texas A&M Health Campus, Bryan, TX

September 19–20, 2024

Thursday, September 19, 2024

11:00 am **Registration/Lunch**
Lower-Level Lobby of the Health Professions Education Building

12:00 pm **Introduction and Remarks**

Welcome Address
Mariappan Muthuchamy, PhD
CVRI Director

Introductory Remarks
Allison C. Rice-Ficht, PhD
Regents Professor, Interim Senior Associate Dean for Research
College of Medicine, Texas A&M Health

Mansoor A. Khan, PhD, RPh
Dean, Regents and Distinguished University Professor
College of Pharmacy, Texas A&M Health

Dr. John August
Carl B. King Dean, College of Veterinary Medicine & Biomedical Sciences
Texas A&M University

Division of Cardiac Biology Session
Session Chair: Carl Tong, MD, PhD, FACC

12:30 pm **Keynote Speaker:**
Jennifer L. Strande, MD, PhD, FAHA
Medical Director, Amgen, Thousand Oaks, CA
From Academia to Industry: Navigating the Ampersand between Research & Development

1:15 pm **Annie Newell-Fugate, PhD**
Assistant Professor, Department of Veterinary Physiology and Pharmacology
College of Veterinary Medicine & Biomedical Sciences
Using single nuclei transcriptomics to uncover the effects of exercise on myeloid and lymphoid cells in the epicardial adipose tissue.

1:35 pm **Carl Tong, MD, PhD, FACC[1], Kia Parsi, MD[2]**
[1]Associate Professor, Department of Medical Physiology, College of Medicine
[2]Executive Director, A&M Rural and Community Health Institute
World's first revelations of calcium to cross-bridge coupling within intact beating hearts and TAMU launches novel prospective clinical study on multisensory remote monitoring of rural heart failure patients.

1:55 pm **Break**

2:15 pm **Mahua Choudhury, PhD**
Associate Professor, Pharmaceutical Sciences, College of Pharmacy
Co-Director of Center for Microencapsulation and Drug Delivery
Epigenetic Biomarkers and Regulation in Hypertension during Pregnancy

2:35 pm **Reza Avazmohammadi, PhD**
Assistant Professor
Department of Biomedical Engineering, College of Engineering
Role of biomechanical remodeling of the heart in its transition to heart failure

2:55 pm **Trevor Self**
Graduate Student, Department of Veterinary Physiology and Pharmacology
Hypoxia impairs Kv7 channel function in porcine coronary arterioles

3:05 pm **Rana Raza Mehdi**
Graduate Student, Department of Biomedical Engineering
Deep Learning-Based Estimation of Infarcted Myocardium from Strain Imaging

3:15 pm **Samantha Pozo Navarro**
Graduate Student, Department of Medical Physiology, College of Medicine
Project BP: A Student-led Blood Pressure Screening Initiative

3:30–5:00 pm **Poster Presentation Session I**

5:30 pm Dinner at Hilton Hotel, 801 E. University Drive, College Station

Friday, September 20, 2024

7:30 pm **Breakfast**

Division of Lymphatic Biology Session
Session Chair: Joseph M. Rutkowski, PhD

8:30 am **Keynote Speaker:**
J. Brandon Dixon, PhD
Woodruff Professor, Georgia Institute of Technology, Atlanta, GA
Leveraging biomaterials to enhance lymphatic formation and function

9:15 am **Sanjukta Chakraborty, PhD**
Associate Professor, Department of Medical Physiology, College of Medicine
Lymphatics and Cancer Metastasis: Bridging the Gaps

9:35 am **Walter E. Cromer, PhD**
Instructional Assistant Professor
Department of Medical Physiology, College of Medicine
Alterations of Jak/Stat Balance in the Space Flight Lymph Node

9:55 am **Break**

10:15 am **Feng Zhao, PhD**
Professor, Department of Biomedical Engineering, College of Engineering
Tissue engineering strategies for cardiac and lymphatic tissue regeneration

10:35 am **Brett Mitchell, PhD**
Professor, Department of Medical Physiology, College of Medicine
Lymphatics and Renin-Angiotensin System

10:55 am **Shedreanna Johnson**
Graduate Student, Department of Medical Physiology, College of Medicine
Lymphatic Structure and Function are Associated with Duchenne Muscular Dystrophy Pathogenesis in a Canine Model

11:05 am **Saranya Kannan, PhD**
Postdoctoral Research Associate, Department of Medical Physiology
Therapeutically-induced lymphangiogenesis is ineffective in resolving established kidney disease in mice

11:15 am **Alvis Chiu**
Graduate Student, Department of Biomedical Engineering
Fibroblast-Generated Extracellular Matrix Guides Anastomosis during Wound Healing in an Engineered Lymphatic Skin Flap

11:30–1:30 pm **Poster Presentation Session II and Lunch**

Division of Vascular Biology Session
Session Chair: Travis Hein, PhD

1:30 pm **Keynote Speaker:**
Jefferson C. Frisbee, PhD
Ting-Yim Lee Endowed Chair and Professor
Western University, Ontario, Canada
Metabolic Disease, Cerebral Vasculopathy and Depressive Symptoms: Pulling Signals from the Noise

2:15 pm **John N. Stallone, PhD**
Professor, Department of Veterinary Physiology and Pharmacology, College of Veterinary Medicine & Biomedical Sciences
Sex Differences in Cardiometabolic Effects of the Androgens: Challenging the Dogma

2:35 pm **Glenn M. Toney, PhD, FAHA, FAPS**
Professor and Head
Department of Medical Physiology, College of Medicine
Neurogenic Contributions to Hypertension: How neural circuit-specific persistent plasticity can sustain high blood pressure

2:55 pm **Break**

3:15 pm **Shameena Bake, PhD**
Research Assistant Professor
Department of Neuroscience and Experimental Therapeutics, College of Medicine
Prenatal alcohol exposure and adult ischemic stroke outcomes

3:35 pm **Kayla Bayless, PhD**
Associate Professor
Department of Medical Physiology, College of Medicine
Distinguishing the molecular signatures of tip-like cells during angiogenic sprout initiation

3:45 pm **Dylan Pham, PhD**
Postdoctoral Research Associate
Department of Medical Physiology, College of Medicine
Temporal Impact of Diabetes on Ocular Vascular Function and Neural Retina Morphology in INS2(AKITA) Mice

3:55 pm **Ankit Kumar**
Graduate Student, Department of Biomedical Engineering
Hemadyne: Ultrafast pump recreates clinical hemodynamics and endothelial responses in preclinical human biology-modeling microsystems

4:05 pm **Sarah Bondos, PhD**
Associate Professor, Department of Medical Physiology, College of Medicine
Stabilizing angiogenic growth factors

4:25 pm **Awards and Conclusion**

Awards presented by CVRI Scientific Committee Co-Chairs:
Sanjukta Chakraborty, PhD[1], Feng Zhao, PhD[2]
[1]Associate Professor, Department of Medical Physiology, College of Medicine
[2]Professor, Department of Biomedical Engineering, College of Engineering

4:45 pm **Concluding Remarks**
David C. Zawieja, PhD
Regents Professor, Department of Medical Physiology, College of Medicine

5:00–6:00 pm **Social**

Executive Committee

David C. Zawieja, PhD
Executive Director
Department of Medical Physiology, Texas A&M Health

Mariappan Muthuchamy, PhD
Director
Department of Medical Physiology, Texas A&M Health

Travis Hein, PhD
Director of the Division of Vascular Biology
Department of Medical Physiology, Texas A&M Health

Joseph Rutkowski, PhD
Director of the Division of Lymphatic Biology
Department of Medical Physiology, Texas A&M Health

Carl Tong, MD, PhD, FACC
Director of the Division of Cardiac Biology
Department of Medical Physiology, Texas A&M Health

Farida Sohrabji, PhD
ad hoc CVRI EC member
Department of Neuroscience & Experimental Therapeutics, Texas A&M Health

Glen Laine, PhD
ad hoc CVRI EC member
M. E. DeBakey Institute, College of Veterinary Medicine and Biomedical Sciences

Scientific Program Committee

Sanjukta Chakraborty, PhD (Chair)
Department of Medical Physiology, College of Medicine, Texas A&M Health

John C. Criscione, PhD
Department of Biomedical Engineering, College of Engineering Texas A&M University

Cristine L. Heaps, PhD
Department of Veterinary Physiology and Pharmacology,
College of Veterinary Medicine and Biomedical Sciences, Texas A&M University

Travis Hein, PhD
Department of Medical Physiology, College of Medicine, Texas A&M Health

Mariappan Muthuchamy, PhD
Department of Medical Physiology, College of Medicine, Texas A&M Health

Joseph M. Rutkowski, PhD
Department of Medical Physiology, College of Medicine, Texas A&M Health

Randolph H. Stewart, PhD
Department of Veterinary Physiology & Pharmacology,
College of Veterinary Medicine and Biomedical Sciences, Texas A&M University

Carl W. Tong, MD, PhD, FACC
Department of Medical Physiology, College of Medicine, Texas A&M Health

Andreea Trache, PhD
Department of Medical Physiology, College of Medicine, Texas A&M Health

David C. Zawieja, PhD
Department of Medical Physiology, College of Medicine, Texas A&M Health

Feng Zhao, PhD (Co-Chair)
Department of Biomedical Engineering, College of Engineering, Texas A&M University

Poster Judges

Sakhila K. Banu, PhD
Department of Veterinary Integrative Biosciences, Texas A&M University

Brandon Dixon, PhD
G. W. Woodruff School of Mechanical Engineering, Georgia Institute of Technology

Shannon Glaser, PhD
Department of Medical Physiology, College of Medicine, Texas A&M Health

Zhenyu Li, PhD
Department of Pharmaceutical Sciences, Irma Lerma Rangel College of Pharmacy, Texas A&M University, Kingsville, TX

Brett Mitchell, PhD
Department of Medical Physiology, College of Medicine, Texas A&M Health

Annie Newell-Fugate, PhD
Department of Veterinary Physiology and Pharmacology, Texas A&M University

Mendell Rimer, PhD
Department of Neuroscience & Experimental Therapeutics, Texas A&M Health

Joseph M. Rutkowski, PhD
Department of Medical Physiology, College of Medicine, Texas A&M Health

John N. Stallone, PhD
Department of Veterinary Physiology and Pharmacology, Texas A&M University

Carl W. Tong, MD, PhD, FACC
Department of Medical Physiology, College of Medicine, Texas A&M Health

Nasir Uddin, PhD
Department of Medical Physiology, College of Medicine, Texas A&M Health

Guoyao Wu, PhD
Department of Animal Sciences, Texas A&M University

Xin Wu, PhD
Department of Neuroscience & Experimental Therapeutics, Texas A&M Health

Feng Zhao, PhD
Department of Biomedical Engineering, Texas A&M University

Organizing Committee

Vince Cupit
Administrative Coordinator I
Department of Medical Physiology, College of Medicine, Texas A&M Health

Tina Mendoza
Business Administrator II
Department of Medical Physiology, College of Medicine, Texas A&M Health

Mariappan Muthuchamy, PhD
CVRI Director
Department of Medical Physiology, College of Medicine, Texas A&M Health

Oksana Nekrashevych, MPH
Project Coordinator II
Department of Medical Physiology, College of Medicine, Texas A&M Health

Amelia Rodriguez
Business Coordinator II
Department of Medical Physiology, College of Medicine, Texas A&M Health

Oral Presentation Abstracts

(in alphabetical order by presenter)

Role of biomechanical remodeling of the heart in its transition to heart failure

Reza Avazmohammadi, PhD
Assistant Professor
Department of Biomedical Engineering, College of Engineering

The mortality of patients with cardiovascular diseases succumbing to systolic and diastolic heart failure (HF) is on the rise, with a notable increase from 2010 to 2021. A significant portion of HF patients have an underlying structural heart disease (SHD) with a chronic or acute impairment in the biomechanical function of the myocardium. However, our understanding of how biomechanical remodeling in the myocardium contributes to the development of HF remains limited. In this talk, I highlight the mechanistic role of biomechanical remodeling of the myocardium in the transition of pulmonary hypertension (PH) and myocardial infarction (MI) to HF in the right and left heart, respectively.

PH results in increased right ventricle (RV) afterload, leading to RV dysfunction and, ultimately, RV failure. We performed a rodent study compromising mild to severe PH animal models. Our multiscale biomechanical analysis indicated that excessive stiffening of the RV myocardium accelerates RV-pulmonary artery decoupling, a key hallmark of right heart failure. Interestingly, although hypertrophy and fibrosis occurred in both mild and severe PH, certain fiber-level remodeling events, including increased tautness of collagen fibers and significant reorientations of myofibers, contributed to excessive biomechanical maladaptation of the RV in the severe case. Similarly, in our rodent study of MI, the maladaptive biomechanical remodeling of the left ventricular (LV) myocardium post-MI accelerated the transition to HF. Although the LV myocardium circumferential stiffness remained unchanged with time, longitudinal stiffness tended to increase post-MI, thus altering the overall anisotropy of LV myocardium tissues. An increased longitudinal bias post-MI strongly correlated with LV decompensation post-MI.

Overall, the strong correlation between myocardial biomechanics and cardiac function suggests that studying alterations in biomechanical markers could provide insights into the mechanisms through which SHDs transition to HF. The quantification of these markers through cardiac imaging offers to improve early prognostication of HF.

Prenatal alcohol exposure and adult ischemic stroke outcomes

Shameena Bake, Marisa Pinson, Rajesh Miranda and Farida Sohrabji
Department of Neuroscience and Experimental Therapeutics,
College of Medicine

Cardiovascular disease is recognized to have a developmental origin in adverse early life environments. One such source of adversity, prenatal alcohol exposure (PAE) can result in physical and neurobehavioral impairments, collectively termed 'Fetal Alcohol Spectrum Disorders " (FASD). FASD adults are at risk for metabolic, cardiovascular and neurocognitive disabilities. However, very little is known about the contribution of PAE to adult-onset cardiovascular disease, specifically cerebrovascular stroke. Stroke results in immediate sensory and motor disability and, in the chronic phase, results in cognitive impairment and dementia. Our research evaluated whether PAE increases the severity of both the acute and chronic outcomes strokes in adult and aging rats. Pregnant Sprague Dawley rats (bred in-house) were exposed to 10% ethanol or air, for 1 hour from gestational day 8 through 18 using the rodent alcohol inhalation system. Adult (5 month-old) and middle-aged (12 month) offspring were subjected middle cerebral artery occlusion (MCAo). Acute stroke-induced disabilities were assessed at 2d post stroke by neurological scores and vibrissae evoked fore-limb placement task and the extent of infarction. Long-term outcomes were evaluated at 6 months post stroke using the Barnes maze and fear conditioning test. Overall, our data showed poor outcomes in PAE treated groups in several of these measures, which were modified by sex and age at which the stroke occurred. While the underlying mechanisms are not fully understood, our data suggests that stroke alters the levels of known neuroprotectants in PAE groups. Moreover, measures of gut permeability such as LPS and intestinal fatty acid binding protein (iFABP), as well as RNA-seq analysis suggest that PAE affects the enteric portal system. Post-stroke neurological function was correlated with an adipose gene network associated with B-lymphocyte differentiation and nuclear factor κB (NF-κB) signaling and with a liver pro-inflammatory gene network. These studies are the first to demonstrate the specific impact of PAE on stroke, an adult onset disease. Supported by NIH-AA026756.

Adult offspring (5-month-old) were subjected to endothelin-1-induced middle cerebral artery occlusion (MCAo), acute outcomes were evaluated after 2 days and long-term outcomes after 90 days. Acute stroke-induced disabilities were assessed by neurological scores and vibrissae evoked fore-limb placement task and the extent of infarction. We also measured circulating T-cells, neuroprotectants (IGF-1, estrogen), and inflammatory cytokines in brain tissue. Long-term outcomes were evaluated using the fear conditioning test and NORT. Our analysis showed PAE increased infarct volume but significantly increased neurological deficits in both sexes. MCAo in middle-aged PAE rats caused significant behavioral deficits: higher neurological scores and greater cross-midline impairment in PAE-females. However, brain infarction was greater in both male and female PAE rats compared to control stroke rats. The ratio of circulating CD4:CD8 T-cells was reduced in PAE animals than in the control group. Moreover, the ratio of inflammatory mediators such as IL-6, IL-17a, and RANTES was significantly elevated in the ischemic hemisphere compared to the non-ischemic hemisphere only in PAE animals. Fear conditioning/ acquisition, a test to assess associative learning, showed the percentage of freezing over the tone-shock pairing trials was similar in both control and PAE males. Meanwhile, in females, the control animals exhibited more freezing than the PAE animals. The present findings support the hypothesis that PAE contributes to adverse effects on both acute and long-term stroke outcomes as indicated by altered circulating T-cells, immediate poor neurological function, and impaired associative learning during long-term recovery.

Stabilizing angiogenic growth factors

Sarah Bondos, PhD
Associate Professor, Department of Medical Physiology, College of Medicine

Preeclampsia (PE) is the leading cause of maternal and fetal mortality, requiring the development of early, precise biomarkers for effective diagnosis. Current biomarkers often target late gestation or lack the sensitivity and specificity required for early detection. In a case-control study analyzing first-trimester blood samples from healthy and PE women, we identified several epigenetic biomarkers including microRNAs (miR). To decipher miR's role in PE pathogenesis, we focused on miR-17-5p in placental development. First, we investigated the effect of miR-17-5p on cell invasion through 3D matrix assays. We found that human umbilical vein endothelial cell migration was significantly inhibited by miR-17-5p mimic and promoted by miR-17-5p inhibitor. Furthermore, examination of placental tissues from E16.5E mice with miR-17-5p overexpression at E2.5 revealed PE-associated complications, including vascular malformation and placental hemorrhage. RNA-seq and single-cell sequencing analyses discovered potential miR-17-5p targets associated with cell invasion, cytoskeletal destabilization, and angiogenesis, subsequently validated in placenta from PE patients and miR-17-5p-overexpressed mouse models. In summary, our study suggests that miR-17-5p plays a regulatory role in PE pathogenesis by targeting trophoblast migration and angiogenesis. These findings contribute to our understanding of PE etiology and may inform the development of early diagnostic biomarkers.

Lymphatics and Cancer Metastasis: Bridging the Gaps

Sanjukta Chakraborty, Ph.D.
Associate Professor, Department of Medical Physiology, College of Medicine

The lymphatics are critical regulators of tumor metastasis yet no therapeutic is targeted towards lymphatic dissemination of cancer. Lymph node metastasis is a critical prognostic indicator of tumor progression and often associated with poor patient outcome. Presence of tumor cells in the lymph node is associated with tumor aggressiveness, yet the molecular mechanisms modulating tumor-lymphatic crosstalk remains grossly understudied. Further, expansion of the lymphatic network (or lymphangiogenesis) near a growing tumor plays a significant role in metastatic progression. Research in my lab, is focused on investigating how an inflammatory microenvironment modulates the tumor vasculature, promotes metabolic reprograming, endothelial to mesenchymal transition (EMT) mechanisms and enhances metastasis of tumors to the sentinel tumor draining nodes and to distant metastatic sites. Recent studies from the lab, using a rare hepatobiliary cancer model of cholangiocarcinoma, demonstrate that an active chemokine-cytokine crosstalk modulates lymphatic-tumor crosstalk in the progression of this cancer and is also associated with significant remodeling of the immune microenvironment. Using clinical models of metastatic cancer we demonstrate that alterations in the metastatic tumor draining lymph node helps in establishment of a tumor permissive niche. Our work also demonstrates that cholangiocarcinoma tumor cells exposed to LEC-derived cues acquire metabolic vulnerabilities that impact therapuetic regimens. These studies have direct relevance for translational intervention strategies and future drug development targeted to lymph node metastatic cancers.

Epigenetic Biomarkers and Regulation in Hypertension during Pregnancy

Mahua Choudhury, PhD
Associate Professor, Pharmaceutical Sciences, College of Pharmacy
Co-Director of Center for Microencapsulation and Drug Delivery

Preeclampsia (PE) is the leading cause of maternal and fetal mortality, requiring the development of early, precise biomarkers for effective diagnosis. Current biomarkers often target late gestation or lack the sensitivity and specificity required for early detection. In a case-control study analyzing first-trimester blood samples from healthy and PE women, we identified several epigenetic biomarkers including microRNAs (miR). To decipher miR's role in PE pathogenesis, we focused on miR-17-5p in placental development. First, we investigated the effect of miR-17-5p on cell invasion through 3D matrix assays. We found that human umbilical vein endothelial cell migration was significantly inhibited by miR-17-5p mimic and promoted by miR-17-5p inhibitor. Furthermore, examination of placental tissues from E16.5E mice with miR-17-5p overexpression at E2.5 revealed PE-associated complications, including vascular malformation and placental hemorrhage. RNA-seq and single-cell sequencing analyses discovered potential miR-17-5p targets associated with cell invasion, cytoskeletal destabilization, and angiogenesis, subsequently validated in placenta from PE patients and miR-17-5p-overexpressed mouse models. In summary, our study suggests that miR-17-5p plays a regulatory role in PE pathogenesis by targeting trophoblast migration and angiogenesis. These findings contribute to our understanding of PE etiology and may inform the development of early diagnostic biomarkers.

Alterations of Jak/Stat Balance in the Space Flight Lymph Node

Walter E. Cromer, PhD
Instructional Assistant Professor
Department of Medical Physiology, College of Medicine

Immune dysfunction in space is a growing concern and is a complex problem that has yet to be treated using an exogenous countermeasure. Dysfunction in T-cells is a particularly concerning topic as they have an incredibly diverse set of functions within the host organism.

The JAK-STAT pathway is critical to the development and function of T-cells and has to date not been explored in the lymph nodes during or after flight. We utilized RNAseq data from inguinal lymph nodes from space flown mice (RR9) to assess the prevalence of members of the JAK-SAT pathway including regulators and downstream effectors. We no significant gross changes in expression levels of individual members of these pathways. Pathway analysis of the same data revealed a broad change to the immunology of the tissue. To better understand this we performed correlation analysis to determine if interactions in the pathway were compromised. We found several cases of interaction between inhibitors and signaling molecules, as well as signaling molecules and effector molecules were altered by spaceflight suggesting defective JAK-STAT signaling.

These findings are critical to the developing picture of immune dysfunction in space. The driving factors could include DNA damage or methylation, lack of physical signal transduction as co-factors in signaling, changed metabolomic input from the environment but we cannot say for certain. This data does provide evidence to pursue the JAK-STAT pathway as a druggable target to alter space flight induced immune dysfunction.

Leveraging biomaterials to enhance lymphatic formation and function

J. Brandon Dixon, PhD
Woodruff Professor, Georgia Institute of Technology, Atlanta, GA

The lymphatic vasculature provides essential physiologic support to a variety of tissues throughout the body through its roles in maintaining fluid balance, providing a route for protein and waste clearance from the interstitium, facilitating immune cell and antigen trafficking to lymph nodes, and absorbing dietary lipid from the intestine. While significant advances have been made in the last two decades in our understanding of many of the molecular mechanism underlying lymphatic formation and function, translating this knowledge into functional therapies has been limited. In this talk I will summarize two different technologies developed by our research lab and network of collaborators that deliver mRNA to lymphatic endothelial cells, and deliver small molecule calcium channel agonists to lymphatics to enhance lymphatic pumping.

S-(−)-Bay K8644 (BayK), a small-molecule agonist of L-type calcium channels was loaded into plutonic-propylene sulfide based nanoparticles of 30 nm in diameter, that have previously been shown to have high lymphatic targeting when delivered intradermally in vivo. When formulated within lymph-draining nanoparticles (NPs), BayK acutely improved lymphatic vessel function, affects not seen from treatment with BayK in its free form. By preventing rapid drug access to the circulation, NP formulation also reduced BayK's dose-limiting side effects. When applied to a mouse model of lymphedema, treatment with BayK formulated in lymph-draining NPs, but not free BayK, improved pumping pressure generated by intact lymphatic vessels and tissue remodeling associated with the pathology.

In a second study, a large in vivo screen of over 100 different lipid nanoparticle formations was conducted in the mouse for LNPs to deliver mRNA to lymphatic endothelial cells. Each formulation was loaded with a unique DNA barcode and mRNA that encoded for an exogenous protein that would be synthesized and expressed on the cell surface. Several unique formulations, including LNP7, were identified that were highly effective at enhancing mRNA delivery to LEC. When compared to a standard commercially available LNP formulation of similar size, made with the lipid MC3, LNP7 showed a 3-fold increase in mRNA delivery to LEC in the draining lymph node and in the collecting lymphatic vessel. Lastly, when loaded with VEGF-C mRNA, LNP7 resulted in targeted LEC proliferation in vivo and improved lymphatic drainage in an injury model.

This work reveals the utility of two different lymph-targeting NP platforms to pharmacologically enhance lymphatic pumping in vivo with small molecules and to deliver mRNA to LEC in vivo and highlights promising new approaches to treating lymphatic dysfunction.

Metabolic Disease, Cerebral Vasculopathy and Depressive Symptoms: Pulling Signals from the Noise

Jefferson C. Frisbee, PhD
Ting-Yim Lee Endowed Chair and Professor, Western University, Ontario, Canada

Increasing evidence supports linkages between chronic metabolic disease, the resulting evolution of cerebral vasculopathy, and the emergence of cognitive impairments. Findings from human studies suggest that a sexual dimorphism exists in these relationships, attributed to a relative sex-based protection from vasculopathy in females with elevated metabolic disease risk. However, these relationships are inconsistent and understanding the underlying mechanisms between evolving risk states and poor health outcomes remains elusive. This seminar will present results from a translationally relevant model of chronic metabolic disease, the obese Zucker rat, and the progressive evolution of cerebral vasculopathy. Building from this, we will discuss the emergence of depressive symptoms, stemming from vasculopathy and metabolic disease risk, in both male and female rats and, using machine learning approaches, identify potential mechanisms that can predict both the timing and the severity of depressive behaviors. Finally, we will present new evidence that may help to address the paradox in the differences in depressive symptom development under conditions of metabolic disease and cerebral vasculopathy between males and females. Our most recent results suggest that not all “protections against vasculopathy” may be equal, and the benefits a sex-based protection for acute cerebrovascular events in female rats may predispose them to poor depressive symptom outcomes as compared to their male counterparts.

Lymphatics and Renin-Angiotensin System

Brett Mitchell, PhD
Professor, Department of Medical Physiology, College of Medicine

The renin-angiotensin system (RAS) plays a large role in whole body fluid homeostasis as well as vascular structure and function. Chronic augmentation of the RAS can lead to numerous conditions including arterial remodeling, sodium and fluid retention, immune system activation, inflammation, and cardiovascular and renal disease. However, less is known about how the RAS affects lymphatic vessels. RAS components in the interstitial fluid interact with lymphatic and other present cells, however the direct and indirect effects on lymphatic function have not been fully elucidated. This session will cover what is known currently about the effects of RAS mediators on lymphatics as well as potential future directions for research.

Using single nuclei transcriptomics to uncover the effect of exercise on myeloid and lymphoid cells in the epicardial adipose tissue

Annie E. Newell-Fugate, DVM, MS, PhD
College of Veterinary Medicine and Biomedical Sciences
Texas A&M University

Epicardial adipose tissue (EAT) plays a critical role in regulating coronary artery function through modulation of immune cell recruitment. However, the effect of aerobic exercise on EAT immune cell populations and their role in coronary artery disease is unknown. We hypothesized that aerobic exercise fosters an anti-inflammatory environment in EAT from female pigs, characterized by increased M2 myeloid cell number and up-regulation of anti-inflammatory cytokine transcripts. Female Yucatan pigs (n=7) were allocated to sedentary or exercised groups, and coronary arteries were surgically occluded or were left non-occluded. EAT was processed for bulk (RNA-seq) and single nucleus transcriptomic sequencing. Sub-clustering identified immune, endothelial, smooth muscle, adipocytes, adipocyte progenitor, and neuronal cells, with adipocytes and adipocyte progenitor cells being dominant. Bulk RNA-seq found that exercise upregulated chemokine signaling and phagocytosis pathways, whereas exercise downregulated pathways related to fatty acid metabolism, oxidative phosphorylation, and peroxisome proliferator receptor (PPAR) signaling in EAT from female pigs. Non-occluded sedentary EAT had the largest percentage of inflammatory M1 myeloid cells and CD8+ lymphoid cells. Irrespective of its occlusion status, sedentary EAT had the largest fraction of CD8+ lymphoid and myeloid cells expressing genes in the tumor necrosis factor superfamily. Sedentary EAT had the highest percentage of inflammatory M1 myeloid cells, whereas exercised EAT had the highest percentage of naïve M0 myeloid cells. Irrespective of subtype, myeloid cells had increased PPAR gamma expression. Myeloid and lymphoid cells in non-occluded EAT interacted with adipocytes to foster cell migration, adhesion, and cytoskeletal changes, with more molecules involved in EAT from sedentary animals. In occluded exercised EAT myeloid and lymphoid cells signaled to adipocytes via the adiponectin pathway. However, in occluded sedentary EAT myeloid and lymphoid cells signaled to adipocytes via growth factor and cytokine pathways. In conclusion, aerobic exercise mitigates the proinflammatory nature of EAT in coronary artery occlusion via decreasing M1 myeloid and CD8+ lymphoid cell numbers and upregulating cell migration and adhesion and adiponectin signaling pathways. Future research on the interaction between EAT cell populations and signaling molecules and coronary artery function in exercised states will further elucidate the mechanisms through which exercise fosters improved coronary artery health.

World's first revelations of calcium to cross-bridge coupling within intact beating hearts and TAMU launches novel prospective clinical study on multisensory remote monitoring of rural heart failure patients

Joshua Hale, Laticia Ellankil, **Kia Parsi MD, Carl Tong MD, PhD, FACC**

Background. Elucidating key mechanisms of cardiac contraction/relaxation can lead to new treatments for heart failure. Intact papillary muscles produce maximum force at much lower [Ca^{2+}] than de-membraned cardiac tissue and show [Ca^{2+}] to force hysteresis relationship. We then hypothesize that cross-bridge (CB) attachments sustain force generation independent of [Ca^{2+}] after [Ca^{2+}] enabling as a key driver of contraction.
Method. We acquired transgenic mouse model with cardiac myocyte specific endogenous fluorescent calcium sensor GCaMP8. GCaMP8 is green fluorescent protein coupled with calmodulin. We made a novel system using commercial parts and in-house software that can quantify GCaMP8-[Ca^{2+}] fluorescence of *in vivo* beating heart. We then made simultaneous intra-cardiac pressure, intra-cardiac volume, and [Ca^{2+}] measurements of *in vivo* beating hearts.
Results. By echocardiography, GCaMP8 hearts demonstrated similar size, reduced left ventricular ejection fraction, slowed maximal myocardial contraction velocity S, similar maximal myocardial relaxation velocity e', and similar E/e' ratio in comparison to WT. Thus, GCaMP8 hearts have depressed systolic function but preserved diastolic function. Western blotting did not show any expression differences in SERCA2a or phospholamban. Simultaneous intracardiac pressure and [Ca^{2+}] measurements showed peak [Ca^{2+}] occurring well before peak pressure. Normalizing delay to adjust for different heart rates, peak pressure occurs at 19%±3%SD delay from peak [Ca^{2+}] of heart-beat duration, $p<0.0001$ $n=5$. Plot of [Ca^{2+}] *vs.* pressure showed hysteresis relationship where pressure rises to peak as [Ca^{2+}] falls after initial concordant rise. Pressure rises to only 48%±5%SD of peak at peak [Ca^{2+}], $p<0.0001$ $n=5$. We then challenged the hearts with dobutamine and trans-aortic constriction (TAC). Dobutamine caused prolongation of elevated [Ca^{2+}] plateau while myocardium showed accelerated relaxation. TAC caused prolongation elevated [Ca^{2+}] plateau but the myocardium relaxed despite during prolongation.
Conclusions. We demonstrated that CB attachment sustains contraction independent of [Ca^{2+}] within beating *in vivo* hearts after initiation of contraction. Unlike systole, calcium chelation has little impact on diastolic function. Modulation of CB function can be a new treatment class.

New Prospective Clinical Study. Heart failure (HF) carries prevalence of 6.7M in the US and 64M worldwide. HF patients have high 5-year mortality rate ~ 50% and high frequent 30-day hospital re-admission rate > 20%. Rural HF patients fare worse. HF patients decompensating will exhibit ↑ respiration rate, ↑ heart rate, ↑ low frequency of heart vibrations, and ↓ intrathoracic impedance. With support from Blue Cross-Blue Shield and Analog Device Inc., Texas A&M University is launching a new prospective clinical study using multi-sensor remote monitoring of rural HF patients of the forementioned parameters to improve their care.

Sex Differences in Cardiometabolic Effects of the Androgens: Challenging the Dogma

John N. Stallone, PhD

Department of Veterinary Physiology, College of Veterinary Medicine, Texas A&M University, College Station, TX USA 77843

Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide and in the Western world, one-third of all deaths are attributed to CVD. A conspicuous characteristic of this healthcare epidemic is that most CVD is higher in men than in age-matched premenopausal women, yet reasons for these obvious sex differences remain poorly understood. A strong dogma emerged early on that testosterone (TES) exerts deleterious effects on cardiovascular health and exacerbates development of CVD and metabolic dysfunction in men. However, more recent animal and human clinical evidence overwhelmingly suggests that it is the progressive, age-dependent declines in TES in men (and perhaps women) that exacerbate CVD and metabolic dysfunction. Indeed, studies from our lab and others reveal that TES exerts beneficial vasodilatory effects on the vasculature, resulting in systemic hypotension. Further, TES also protects against metabolic syndrome (MetS) and type2 diabetes mellitus (T2DM). Recent findings reveal the existence of bi-directional modulation of glucose and fat homeostasis by TES in females *vs.* males, such that age-dependent declines in TES levels in males and abnormal increases in normally low TES levels in females both result in similar dysfunction in glucose and fat homeostasis, resulting in development of MetS and T2DM, central risk factors for development of CVD in men as well as women. These findings suggest that the long-held view that TES is detrimental to male health should be discarded in favor of the view that, at least in men, TES is beneficial to CV and metabolic health, while aging exacerbates loss of TES in males and effects of TES excess in females. The bi-directional effects of TES in males *vs.* females may significantly impact long-term health of female to male transexuals.

Neurogenic Contributions to Hypertension: How neural circuit-specific persistent plasticity can sustain high blood pressure

Glenn M. Toney, PhD, FAHA, FAPS
Professor and Head, Department of Medical Physiology, College of Medicine

This presentation will introduce evidence that inappropriately high renin-angiotensin-aldosterone system activity relative to plasma sodium concentration represents a "double-hit" that triggers persistent maladaptive plasticity in brain autonomic circuits that promote exaggerated sympathetic nerve discharge, contributing to renal and vascular dysfunctions that sustain high blood pressure.

Tissue Engineering Strategies for Lymphatic and Cardiac Tissue Regeneration

Feng Zhao, PhD
Department of Biomedical Engineering, Texas A&M University

Human cell-derived extracellular matrix (ECM) closely mimics the native tissue environment, offering structural proteins and growth factors essential for tissue repair and regeneration. To address the limitations of allogenic tissue availability and the risks of xenogenic tissue rejection, we have developed a "bottom-up" approach to generate ECM scaffolds with customized architecture from cultured human cells. This method provides precise control over key factors such as pore size and mechanical properties, which are critical for directing cell behavior and promoting effective tissue regeneration. Additionally, our approach enables comprehensive pathogen screening, significantly reducing the risks of immune rejection and inflammatory responses typically associated with non-human tissues. In my presentation, I will discuss how we have applied these strategies to human cell-derived ECM for the development of lymphovascularized tissues and vascularized anisotropic cardiac patches. Our work underscores the potential of human cell-derived ECM to deliver safer and more effective therapeutic solutions for tissue engineering and regenerative medicine applications.

Poster Presentation Abstracts

(in alphabetical order by presenter)

Distinguishing the molecular signatures of tip-like cells during angiogenic sprout initiation

Authors: **Colette A. Abbey**[1,2], Solimar Alvarez[2], Guillermo Perralta[2], Tamara Natour[1,3], Ashley Coffell[2], Sanjukta Chakraborty[1], Gregg B. Wells[4], Carl Gregory[1], and Kayla J. Bayless[1,2]

Affiliations: Texas A&M Health, Department of [1]Medical Physiology; [2]Molecular & Cellular Medicine; [3]Medical Psychiatry; [4]Cell Biology & Genetics; Texas A&M College of Medicine, Bryan, TX, 77807; USA

ABSTRACT

During angiogenic sprout initiation, a subset of endothelial cells undergoes a dramatic phenotypic change by transforming from quiescent cells that line the interior of the vasculature into tip cells that contain extensive filopodia and initiate sprouting. Using a defined three-dimensional model of human endothelial cell sprout initiation, we isolated tip-like cells separately from cells that do not immediately differentiate and remain as non-invading cells. Single cell sequencing analyses were performed to selectively identify gene expression changes in each population. Transcriptomic analyses revealed a gene signature consistent with cell proliferation, angiogenesis, and activation of endothelial morphogenesis. The invading population was marked by a significant number of upregulated genes, including RND3, that drive endothelial to mesenchymal transition and filopodia formation. Silencing of RND3 reduced filopodia formation, characteristic of tip cells, *in vitro* and during retinal angiogenesis *in vivo*. The majority of genes upregulated in the non-invading population were transcriptional targets of Yes Associated Protein (YAP) and WW Domain Containing Transcription Regulator 1 (WWTR1/TAZ), which are known to be required for angiogenesis and promote cell proliferation in cancer. To determine the contribution of the cell cycle, we quantified S-phase entry using a PIP-FUCCI reporter and Edu labeling and found that non-invading cells entered S-phase at significantly higher rates than invading cells, which remained in G_0/G_1 at higher rates. Measuring YAP and TAZ localization also revealed significantly higher nuclear to cytoplasmic ratios of YAP and TAZ in non-invading cells, consistent with increased proliferation rates. Silencing of YAP and TAZ revealed significantly less invasion compared to control groups, consistent with what has been reported in transgenic mice. Isolation and culture of non-invading and invading cells revealed cobblestone and mesenchymal morphologies, respectively, suggesting short-term retention of phenotypic characteristics in culture following removal from a 3D environment. Ongoing studies silencing YAP and TAZ will quantify changes in endothelial proliferation during sprout initiation to test if Hippo signaling drives proliferation of endothelial cells and limits differentiation of tip cells. This study expands the list of genetic markers that are associated with the acquisition of a tip-like phenotype during endothelial cell sprout initiation. The data indicate to reliably distinguish tip and non-tip cell phenotypes, with the latter strongly exhibiting YAP/TAZ activation and maintenance of an undifferentiated state.

Fibroblast-Generated Extracellular Matrix Guides Anastomosis during Wound Healing in an Engineered Lymphatic Skin Flap

Alvis Chiu[1], Wenkai Jia[1], Yumeng Sun[1], Jeremy Goldman[2] and Feng Zhao[1,]

[1] Stem Cell and Tissue Engineering Lab, Department of Biomedical Engineering, College of Engineering, Texas A&M University, College Station, TX 77843, USA
[2] Vascular Materials Lab, Department of Biomedical Engineering, College of Engineering, Michigan Technological University, Houghton, MI 49931, USA

A healthy lymphatic system is required to return excess interstitial fluid back to the venous circulation. However, up to 49% of breast cancer survivors eventually develop breast cancer-related lymphedema due to lymphatic injuries from lymph node dissections or biopsies performed to treat cancer. While early-stage lymphedema can be ameliorated by manual lymph drainage, no cure exists for late-stage lymphedema when lymph vessels become completely dysfunctional. A viable late-stage treatment is the autotransplantation of functional lymphatic vessels. Here we report on a novel engineered lymphatic flap that may eventually replace the skin flaps used in vascularized lymph vessel transfers. The engineered flap mimics the lymphatic and dermal compartments of the skin by guiding multi-layered tissue organization of mesenchymal stem cells and lymphatic endothelial cells with an aligned decellularized fibroblast matrix. The construct was tested in a novel bilayered wound healing model and implanted into athymic nude rats. The in vitro model demonstrated capillary invasion into the wound gaps and deposition of extracellular matrix fibers, which may guide anastomosis and vascular integration of the graft during wound healing. The construct successfully anastomosed in vivo, forming chimeric vessels of human and rat cells. Overall, our flap replacement has high potential for treating lymphedema.

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Learning mouse work to investigate epigenetic regulation in cardiometabolic diseases

Erin Chua[#], Laura Packer[#], Jhanvi Karthik[#], Samuel Salazar[#], Raina Hummel[#], Katie Edmonds[#], Sunil Venkategowda, Mahua Choudhury

Department of Pharmaceutical Sciences, College of Pharmacy, Texas A&M Health Science Center, College Station, Texas 77845

[#]All contributed equally

The field of epigenetics, defined as the study of gene expression without changes to the genetic sequence, is and has been a fast-growing field of study due to its applications in studying and diagnosing cardiometabolic diseases which have become prevalent in the modern population. With the rise of obesity, insulin resistance, and metabolic dysfunction-associated steatotic liver disease, exploring if there is an epigenetic explanation for the prevalence of these disorders in the population has become a high priority. To determine an epigenetic basis for these disorders, our lab has chosen to use several mice models to explore the effect of a deletion of a long non-coding RNA (lncRNA), in both whole body and isolated tissues. The isolated tissues being primarily studied are the liver, various types of white adipose tissue, heart, and brown adipose tissue. With this research, we aim to find an answer to the prevalence of the above-mentioned metabolic disorders, and to determine if there are biological and epigenetic markers which can be developed for preventative screening of such diseases. In order to explore the purpose of the lncRNA in question, it is essential that the animal model chosen, in this case mice, are properly cared and housed to ensure there are no confounding variables in the resulting data. After a series of CITI trainings in animal studies, we, a team of undergrads, started to learn how to carry out mice studies. Daily activities include ensuring each mouse has adequate food, water, and bedding. We also learned weaning of mice after 3 weeks of their birth. Further, hands on training on weaning, breeding, and single/group housing were provided by our postdoctoral mentor. Furthermore, a series of safety techniques are being trained to investigate cardiometabolic diseases.

Arterial Access in Peripheral Vascular Interventions (PVIs)

Ghadi Moubarak, MD[1], Mohammed Salih, MD[2],Talia Meidan[3], **Malak Ezzat**[1],Rahul Gunukula[1], Natalie Volz[1],Chadi Dib[1], Srinivasa Potluri[4], Sameh Sayfo, MD[5]

[1]Baylor Scott & White Health The Heart Hospital, Plano, Texas, USA; [2]Baylor University Medical Center/ The Heart Hospital Plano, Plano, Texas, USA; [3]Baylor Scott & White Research Institute, Dallas, Texas, USA; [4]Baylor Scott & White The Heart Hospital - Plano, Plano, Texas, USA; [5]Baylor Scott & White, The Heart Hospital Plano, Plano, Texas, USA

The choice of arterial access in cardiovascular interventions is crucial as it affects risk stratification and postoperative outcomes. The transradial (TR) access for coronary procedures has proven to be a safe and efficient alternative to the transfemoral (TF) approach. However, limited data is available on arterial access in peripheral vascular interventions (PVIs). Herein we assess the safety and efficacy profile of the TR vs TF approaches in PVIs. In this single-center retrospective review of 138 patients with iliac artery disease, we evaluated procedural success, access site bleeding, length of stay, in-hospital stroke, surgical reintervention, and mortality rates. Among these patients, 66 and 72 underwent TR and TF approaches, respectively. TR and TF approaches showed similar rates of procedural success, procedure time, access-site hematomas, and all-cause mortality. In conclusion, the TR approach proved to be safe and non-inferior to the TF approach in PVIs. Larger studies are needed to confirm these findings.

Keywords: transradial, transfemoral, iliac, vascular

ABAMCO, an Ambulatory Breath Analyzer for Measuring Cardiac Output

Authors: Joshua Hale[1,2], Dr. Hans Schuessler[2], Dr. Alexandre Kolomenski[2], Dr. Carl Tong[1,2]

Background: Knowing the status and the trends of cardiac output in heart failure patients can revolutionize medical care. Cardiac output measured in an outpatient setting allows for faster optimization of medical therapy and provides early detection of heart failure decompensation. Current methods for tracking the condition of heart failure patients either follow lagging indicators (e.g., thoracic impedance decrease due to pulmonary edema, weight gain due to edema), or cannot be practically performed outside specialized settings (e.g., invasive right heart catheterization with indwelling pulmonary arterial catheter at catheterization lab or intensive care unit). We hypothesized that cardiac output could be measured non-invasively in real-time by measuring the rate and concentration of carbon dioxide (CO_2) exhaled, as the heart is responsible for delivering CO_2-laden blood to the lungs for exhalation. We developed a device which is ambulatory, easy to use, and can measure cardiac output in a variety of outpatient settings.

Methods: We designed and tested a novel breath analyzer which measures cardiac output from exhaled breath. This device uses CO_2 concentration and volume of exhaled breath as inputs. Exhaled flow rate of CO_2 is measured, then divided by the difference between venous and arterial CO_s. The difference is calculated from exhaled CO_2 input to a novel formula. We built and tested a prototype to implement this method. The prototype features a heated breath flow path with baffles to combat the high humidity in breath. Custom software then calculates cardiac output in real time. We used this prototype to measure the cardiac output of volunteers at rest and after set pace treadmill exercise of 10 minute/mile.

Results: The prototype features small dimensions, light weight, and compatibility with a typical laptop computer. Reliability testing showed a 1.85% standard deviation in volume detection over 70 test breaths. CO_2 detection was compared to high-sensitivity cavity ringdown spectroscopy with an error of 1.14%. Measurement of cardiac output was performed on 11 human volunteer subjects. Echocardiogram measurement of stroke volume X heart rate was used as reference. Cardiac output measurements from our device correlated strongly with echocardiogram reference for at rest measurement, post exercise measurements, and measured change in cardiac output, giving a Pearson correlation $R=0.83$ with $p=3X10^{-6}$.

Conclusion: We developed a novel method and a device that measures cardiac output from exhaled breath; however, validating our invention in heart failure population is needed. This device can be used to measure cardiac output at outpatient settings, drastically improving the quality of care for a great many patients.

[1]Department of Medical Physiology; [2]Department of Physics and Astronomy.

IMPACT OF AGING AND SEX ON NEURAL RETINA MORPHOLOGY AND OCULAR VASCULAR FUNCTION IN C57BL/6 MICE

Gabrielle Hightower, Dylan Pham, Hyoseon Kim, Samuel Padgham, Lih Kuo, Andreea Trache, Travis Hein

Department of Medical Physiology, Texas A&M University College of Medicine, Bryan, TX

The aging population is known to have an increased risk of vascular-related diseases due to structural and functional changes causing vasomotor dysfunction and dysregulation of blood flow. Evidence suggests that ocular vascular complications may contribute to age-related retinal neurodegeneration and vision impairment. However, the assessment of both ocular vascular function and neural retina morphology has not been evaluated in the same subjects. Also, the underlying mechanisms contributing to age-related ocular vascular dysfunction and the potential sex-dependent differences with age on ocular neurovascular components remain unknown. Therefore, we are studying the effects of natural aging on neural retina morphology and ocular vascular function in young (3-4 months) and old (24-25 months) male and female C57BL/6 mice. In vivo imaging via optical coherence tomography (OCT) was used to assess total retinal
thickness (TRT). OCT analysis revealed comparable TRT thickness in young female and male mice. By contrast, only old female mice had a decreased TRT compared to their younger counterparts. These findings indicate that, at least in the female C57BL/6 mice, there appears to be neurodegeneration of the retina with aging. Future work aims to analyze the OCT images for specific retinal layer thickness changes with age and perform qPCR of retinal tissue for age-related neurodegeneration genes. We will also use the isolated vessel approach to study the impact of aging on the vasomotor function of ophthalmic arteries and to culture vascular
smooth muscle cells from ophthalmic arteries for qPCR analysis of specific vascular function genes. Furthermore, we plan to perform Doppler ultrasound and/or super-resolution ultrasound to assess the impact of age on central retinal artery and ciliary artery blood flow velocities. These additional experiments will help determine whether the age-related retinal neurodegeneration observed in the OCT studies is associated with ocular vascular dysfunction and potential sexual dimorphism in neurovascular mechanisms.

Endothelin-1 Promotes Angiogenic Sprouting of Endothelial Cells via ET_B receptor Activation and Rho Kinase Signaling

Joseph Hoppe, Colette Abbey, Kayla Bayless, Travis Hein
Department of Medical Physiology, Texas A&M University College of Medicine

Abnormal growth of pre-existing blood vessels through angiogenesis contributes to pathological conditions such as cancer and proliferative diabetic retinopathy. However, the underlying mechanisms of pathologic angiogenesis that are amenable to effective treatment are limited. Herein, we examined whether endothelin-1 (ET-1), a vasoactive protein that is elevated in the plasma of patients with cancer and diabetic retinopathy, promotes angiogenesis. We used an in vitro 3D collagen-based model to evaluate the sprout initiation of human umbilical vein endothelial cells (HUVECs) in the presence and absence of ET-1 (1 pM to 1 nM). The angiogenic sprouting characteristics of invasion density and distance were quantified. To assess the potential downstream signaling mechanisms of ET-1, HUVECs were treated with ET_A receptor antagonist BQ-123 (1 μM), ET_B receptor antagonist BQ-788 (1 μM), and Rho-kinase (ROCK) inhibitor H-1152 (1 μM). ET-1 at 0.1 nM and 1 nM significantly increased the migration distance of HUVECs into the collagen matrix, however, it did not alter the density of invading cells. In the presence of BQ-788 but not BQ-123, the ET-1 (1 nM)-promoted migration was significantly decreased. H-1152 significantly decreased the invasion distance of HUVECs in the presence and absence of ET-1 (1 nM). Finally, no treatments significantly affected the density of invading HUVECs. Collectively, these data support the role of ET-1 acting through ET_B receptor activation and ROCK signaling in the endothelial cell migratory process of angiogenesis. Future studies will examine the impact of ET-1 on angiogenic sprouting of human retinal microvascular endothelial cells.

LYMPHATIC STRUCTURE AND FUNCTION ARE ASSOCIATED WITH DUCHENNE MUSCULAR DYSTROPHY PATHOGENESIS IN A CANINE MODEL

Shedreanna Johnson[1*], Bhuvaneshwaran Subramanian[1], Akshaya Narayanan[1], Alexandria Aceves[2], Sarah E. Frazier[2], Alexis Rutledge[2], Jay Griffin[2], Bonnie Seaberg[3], Mendell Rimer[3], Peter P. Nghiem[2], Mariappan Muthuchamy[1]

[1] Department of Medical Physiology, Texas A&M University, Bryan, TX, USA

[2] College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX, USA

[3] Department of Neuroscience and Experimental Therapeutics, Texas A&M University, Bryan, TX, USA

ABSTRACT

Duchenne Muscular Dystrophy (DMD) leads to progressive disability in 1 of every 5000 males due to an X-linked mutation in the DMD gene. The absence of functional dystrophin protein leads to muscle degeneration, necrosis, and an ongoing immune response triggered by muscle contractions, resulting in an extended and heightened inflammatory condition. This persistent inflammation not only exacerbates tissue damage but also plays a pivotal role in the progression of the disease. Previous studies have indicated elevated extracellular water and intramuscular fat infiltration, hinting the presence of edema—a secondary consequence of inflammation in DMD boys. Since the lymphatic system's primary role is fluid movement from the tissue, maintaining tissue homeostasis, as well as modulating inflammation, we hypothesized that impaired structure and function of the lymphatic vasculature in skeletal muscle are one of the key factors contributing to the progression of DMD. We employed the canine model, golden retriever muscular dystrophy (GRMD) to determine lymph transport function and inflammatory status of skeletal muscle and diaphragm. Results from the gadolinium-enhanced magnetic resonance imaging (MRI) showed a significant decrease in lymph transport in GRMD dogs compared to the control group. Additionally, inflammatory markers were significantly increased in pelvic limb skeletal muscle as well as in the diaphragm of GRMD dogs. Furthermore, the expression of key lymphatic markers was significantly increased in GRMD compared to normal dogs, indicating inflammatory lymphangiogenesis. Additionally, the adeno-associated virus (AAV)-microdystrophin-5 (μDys5) treatment that showed improved muscle function in the GRMD dogs, significantly decreased inflammation, specifically IL-6 and decreased podoplanin expression. Our findings provide the first evidence that: 1) a reduction in lymph transport function in the GRMD model and 2) a link between an elevated inflammatory state in skeletal muscle, both contributing to increased inflammatory lymphangiogenesis in dystrophic muscle. Additionally, treatment with μDys mitigates inflammatory lymphangiogenesis.

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Therapeutically-induced lymphangiogenesis is ineffective in resolving established kidney disease in mice

Saranya Kannan[1], Thien T Phan[1], Heidi A. Creed[1], Andrea J. Reyna[1], Gaurav Baranwal[1], Aubrie L Rich[1], Dawson L. Weiss[1] and Joseph M Rutkowski[1]
[1] Department of Medical Physiology, Texas A&M University, Bryan, TX 77807

ABSTRACT

Background: Chronic kidney disease (CKD), a major contributor to global mortality, counts acute kidney injuries (AKI) as one of its many underlying causes. Lymphatic vessels are important in modulating inflammation post-injury. Manipulating lymphatic vessel expansion thus has the potential to alter CKD progression. Previously, we demonstrated that renal lymphatic expansion prior to injury reduced CKD progression following an AKI. Here we test whether inducing lymphangiogenesis impacts established CKD.

Methods: Following progression to CKD, kidney lymphatics were expanded by transgenic induction of kidney-specific overexpression of vascular endothelial growth factor-D (KidVD) in aristolochic acid (AA) nephropathy and cisplatin injury aggravated with chronic high phosphate diet (CisPi) models or by infusion of kidney-targeting nanoparticles (NP) loaded with the VEGFR-3 specific ligand VEGF-C C156S in the podocyte apoptosis and progressive proteinuria (POD) model. Renal fibrosis and lymphatic density were determined by picrosirius red staining and immunofluorescence, respectively. Renal function was assessed by creatinine clearance rate, serum creatinine, blood urea nitrogen, urinary protein creatinine ratio and urinary albumin creatinine ratio. Renal pro-inflammatory and fibrotic markers expression were measured by qRT-PCR.

Results: KidVD+ mice demonstrated expanded renal lymphatics while NP treatment minimally expanded lymphatics. In neither the AA nor POD model did lymphangiogenesis improve renal function or fibrosis; expansion worsened function in CisPi CKD and increased fibrosis. CisPi kidneys also demonstrated increased expression of *Mcp-1*, *Il1b, Col1a1*, and *Tgfb1*. AA mice showed decreased *Tgfb1* expression and POD mice showed increased *Col4a1* expression. Kidney lymphangiogenesis and fibrosis thus appeared correlative, rather than corrective.

Conclusion: Therapeutically induced lymphatic expansion is ineffective in resolving established CKD and has the potential to further worsen CKD progression.

Protection of the Rat Heart Against Heavy Ion-radiation-induced Elevation of Inflammatory Cell Invasion, Elevation of RANKL, Damage, and Fibrosis by Combined Fish Oil and Pectin in the Diet

Kim, Joo-Hyun[a], Khaled Y. Kamal[a,b], Mariam Othman[a], John R. Ford[c], Nancy D. Turner[d], John M. Lawler[a,e]

[a]Redox Biology Laboratory, KNSM, Texas A&M University; [b]Dept.of Kinesiology & Health, Iowa State University; [c]Dept.of Nuclear Engineering, Texas A&M University; [d]Dept.of Nutrition, Michigan State University; [e]Dept.of Nutrition, Texas A&M University

Travel into deep space beyond the Van Allen belts and sojourns to the moon and Mars will expose astronauts to two profound stressors: microgravity (i.e., weightlessness) and space radiation. Space radiation includes a mix of heavy ions (HZE), protons, and high energy gamma rays and can cause invasion of inflammatory cells and oxidative stress in the heart. Elevated inflammation and damage from high energy radiation exposure can lead to fibrosis and thus an elevated risk of arrythmias and cardiovascular disease. Nutraceuticals that target redox and inflammatory signaling could prevent or mitigate the radiation-induced pathology in the heart. Thus, we proposed that a combination of fish oil (15% by weight) and pectin (6%) in the diet (FOP) would attenuate the elevation of damage, inflammatory cell invasion, RANKL, NADPH oxidase-2 (Nox2), and fibrosis after HZE exposure. Astronaut-age (40-42 weeks) mice were exposed to 28Si and 48Ti (0.5Gy) at the Brookhaven National Laboratory and split into four groups (n=6/group): controls (CON), controls with pectin + fish oil (CFP), X-ray irradiation
(RAD), and X-ray irradiation with fish oil + pectin (RFOP). FOP dietary inclusion began three weeks prior to radiation exposure, and mice were sacrificed 4 weeks after HZE radiation exposure. Heart mass was unaltered by radiation and fish oil + pectin. Markers of T-Cell (CD-8+) and leukocyte infiltration (CD45+) in the heart were doubled after radiation but significantly prevented by FOP. In addition, upregulation of redox signaling by HZE exposure, using RANKL and Nox2 (p67phox) as markers, by radiation exposure were also reduced by FOP. In addition, cardiac damage (IgG infiltration) was significantly reduced by fish oil and pectin in the diet. Finally, fish oil + pectin in the diet mitigated the upregulation of transforming growth factor-beta (TGF-ß1), a marker of fibrosis, in the heart. In conclusion, the combination of fish oil and pectin in the diet was effective in attenuating markers of inflammatory cell invasion, redox signaling, damage, and fibrosis in the heart four weeks after heavy ion radiation exposure.

Hemadyne: Ultrafast pump recreates clinical hemodynamics and endothelial responses in preclinical human biology-modeling microsystems

Authors: **Ankit Kumar**, Rushangi Patel, Dr. Abhishek Jain

Affiliation: Texas A&M University, Department of Biomedical Engineering

Introduction: The vascular endothelium plays a crucial role in mediating a range of vital physiological functions. Endothelial cells are continuously exposed to various hemodynamic forces such as shear stress, pressure, and tensile strain, which profoundly influence their function, structure, and signaling. These factors ultimately affect vascular health and disease progression. Blood flow, inherently pulsatile due to the rhythmic heartbeat, exhibits unique transient waveforms depending on the physiological status and anatomical location of vessels. However, current in-vitro perfusion pumps inadequately replicate hemodynamic flow patterns at physiological time scales due to low flow responsivity. Consequently, clinical hemodynamics has remained irreproducible in experimental models. To address this limitation, we have developed a novel tissue perfusion system capable of modeling the transient vessel-specific flow patterns with high temporal resolution. As a proof-of-concept, we used this system to examine the impact of diastolic flow reversal, a phenomenon associated with sedentary lifestyles and aging, on endothelial function and vascular health.

Materials and Methods: Our perfusion system features a custom-built pump that pneumatically drives flow in vascularized organ-on-chips. An inline flow sensor connected to the pump facilitates closed-loop control for maintaining precise flow conditions. We derived waveforms from published clinical Doppler ultrasounds and programmed them into our pump. We seeded human umbilical vein endothelial cells (HUVECs) into collagen-I coated vessel-chips. Subsequently, we connected the chips to the pump and applied either atheroprotective (no-flow reversal) or atheroprone (diastolic flow reversal) waveforms.

Results, Conclusion & Discussion: We began by characterizing the pump's performance and observed a linear (R^2 >0.99) displacement-pressure response and high responsivity (20 ms), essential for modeling physiological waveforms, but not possible to achieve in syringe, peristaltic or commercial pulsatile pumps. We programmed the pump with in-vivo human flow waveforms obtained from Doppler ultrasound of internal carotid artery, external carotid artery, superior mesenteric artery (both pre- and post-prandial), and common femoral vein. The pump accurately modeled all waveforms (Pearson correlation >0.95), capturing vessel-specific hemodynamic heterogeneity.. Similar results were observed when using patient-specific waveforms for brachial artery flow patterns in individuals with and without diastolic flow reversal. Upon applying these waveforms to the endothelialized vessel-chip, we discovered that one-day exposure to the diastolic reversal waveform significantly increased oxidative stress in ECs. This was accompanied by a reduction in eNOS production and loss of barrier integrity, indicative of endothelial dysfunction. Conversely, exposure to the waveform without diastolic reversal not only conserved eNOS production but also maintained barrier integrity, underscoring its potential atheroprotective effects.

An Epigenetic Perspective into Obesity from a Young Graduate Student

Kathryn Kunz and Mahua Choudhury

Department of Pharmaceutical Sciences, Irma Lerma Rangel College of Pharmacy, Texas A&M Health Science Center, College Station, TX, USA

Epigenetics is the process by which the body regulates gene expression through heritable and reversible chagnes to the genome while leaving the DNA sequence intact. Through epigenetics, we gain insight to how the environment can impose changes in how our genes express themselves which could potentially risk disease development. Some of these environmental factors include polluiton, stress, and more importantly, Western diet. According to the CDC, the prevalance of obesity grew 11.9% in the past 20 years. While diet and nutrition are a major contributing factors in this disease progression, it is important to consider other underlying factors. By looking into the epigenetic regulations of metabolic diseases, it could provide better understanding into this growing issue. Our lab focuses on the relationship between disease condition, and epigenetic regulation. By evaluating the roles of microRNAs, long noncoding RNAs, histone modifications, and DNA/RNA methylation in various tissues such as adipose, heart, liver, bone marrow, and kindey. Our lab has demonstrated how Western diet can influence expression of a long noncoding RNA in relation to hepatic metabolism, leading to obesity and other metabilic and cardiological disregulations. These findings are instrumental in discovering methods to mitigate metabolic risk factors and identifying epigenetic regulations in order to target with epigenetic interventions to facilitate the prevention and treatment of metabolic diseases, cardiovascular metabolic disorders, and obeisty.

Epigenetic technologies to investigate cardiometabolic diseases: a tale from the enthusiastic and motivated undergraduate students

James Kwong[#], Stephanie Han[#], Joshua Glanz[#], Liliana Guzman[#], Sunil Venkategowda, Mahua Choudhury
Department of Pharmaceutical Sciences, College of Pharmacy, Texas A&M Health Science Center, College Station, Texas 77843

[#]All contributed equally

Epigenetics, an emerging frontier in science, focuses on the study of changes in the regulation of genes without alterations to the genetic sequence itself. As emerging young scientists in this area, our research laboratory utilizes a variety of techniques to explore these complex regulatory mechanisms and gain insight into gene expression and epigenetic modifications. This project showcases an overview of essential methodologies employed in our epigenetics laboratory, highlighting their relevance in studying how genes are regulated. First, we will introduce genotyping, a technique that enables the identification of genetic variants that help to identify the mice's genetic/epigenetic background. Secondly, learning mRNA and miRNA extraction is crucial for examining how genes are turned on or off and understanding how gene expression is regulated at the transcriptional level. We also learned to measure these RN A using nanodrop spectrophotometry, which provides a precise quantification and purity assessment of isolated nucleic acids, which is essential for further experiments. Furthermore, the creation of specific buffers tailored to our experiments is designed to keep biological molecules stable and functional during various procedures. Another crucial technique, Gel electrophoresis, is then used to detect the protein level of the altered transcriptional changes at the translational level. Collectively, these techniques form a comprehensive toolkit for investigating the complex interactions in epigenetics, allowing for a deeper understanding of how gene expression is regulated and maintained in various conditions. While these techniques are used in our lab to cater to the epigenetic focus in cardiometabolic diseases, this presentation will guide other undergraduate student researchers seeking to employ these methodologies in their work across multiple research areas fields.

ENGINEERING VESSELS WITH COMPLEX ARCHITECTURES: ENHANCED MODELING OF SPATIALLY INTRICATE BLOOD VESSELS

Jennifer D. Lee[1], Ankit Kumar[1], Tanmay Mathur[1] and Abhishek Jain[1,2,3]
[1]Department of Biomedical Engineering, Texas A&M University, College Station, TX, USA.
[2]Department of Medical Physiology, Texas A&M Health Science Center, Bryan, TX, USA
[3]Department of Cardiovascular Sciences, Houston Methodist Research Institute, Houston, TX, USA

Background: The complex structures observed in human vasculature such as stenosis, branches, tortuosity, aneurysm, etc. cannot be recapitulated in a uniform vascular model. Therefore, it is essential to incorporate the spatial variations into the engineered vessels to better reflect the hemodynamics and subsequentially mechanobiology observed *in vivo*. Gravitational Lumen Patterning (GLP) is a biofabrication technique applied to vessel-chips to produce vessels embedded in ECM. In this study, GLP is employed to create spatially relevant vessels, and fluid dynamics simulations are performed to determine the relationship between the altered hemodynamics and observed cell morphology.

Methods: We prepare a 5mg/mL collagen type I mixture that is perfused into various microfluidic channels. The lumen is patterned by introducing PBS, and the collagen is polymerized at 37˚C inside an incubator. After complete polymerization, the patterned lumens are visualized using fluorescent microbeads. Important vessel characteristics are measured, and statistical analysis is performed using Student's t-test. The different 3D lumen structures are reconstructed, and computational fluid dynamics (CFD) are simulated in COMSOL to compute calculated time averaged wall shear stress (TAWSS) and quantified relative residence time (RRT). One vessel of each type is endothelialized, and a laminar flow is applied. The CFD data is analyzed in correlation to the endothelial cell orientations.

Results: We observe that GLP in complex microfluidic channels formed vessels with varying diameter, stenosis, branches, tortuosity, and aneurysm. It is inspected that the structure of the microfluidic channel dictates the patterning of collagen lumen to an extent, and the lumen follows the trend of the external channel. The fluid dynamic simulation displays changes in TAWSS and RRT in the region of diseased structures, which is fairly reflected through the decrease in cell alignment to the direction of flow.

Conclusion: We demonstrate a powerful application of GLP in generating spatially intricate vessels *in vitro*. The engineered complex vessels better recapitulate hemodynamics and subsequential endothelial cell activation hence increasing the predictive power of the vascular models. These vessels with complex architectures can be used to investigate vascular complications that are closely associated with vessel architectures.

Characterizing Becker Muscular Dystrophy Lymphatics and Muscle Damage in a Swine Model

Authors: **Macie Mackey** (BA)[1], Haley Russell[1], Connor Hendrie[1], Aaron Morton (PhD)[3], Shedreanna Johnson[2], Mariappan Muthuchamy (PhD)[2], Peter Nghiem (DVM, PhD)[1]

Affiliation:
[1]Texas A&M University: College of Veterinary Medicine and Biomedical Sciences
[2]Texas A&M University: College of Medicine
[3]Texas A&M University: School of Education and Human Development

Background: Becker Muscular Dystrophy (BMD) is characterized by progressive muscle wasting due to partial loss of dystrophin. A porcine model was utilized to evaluate the effect of exercise on the progression of BMD. Methods: Creatine Kinase (CK), a muscle damage biomarker, was assessed pre/post treadmill exercise. To further characterize the model, a treadmill protocol was deployed three times weekly for one month at 5 mph with a 10% decline (to induce eccentric contraction decrements). This protocol was designed to mimic the type of exercise that induces the most muscle damage in Duchenne MD patients and the frequency and intensity were chosen based on previous research on exercise interventions for muscular dystrophy. Before (baseline) and after exercise, biopsies were collected from the vastus lateralis muscle followed by cryosectioning, H&E staining, and light microscopy. MRI lymphangiograms were conducted to determine if the flow of lymphatics was altered. Additionally, several pro-inflammatory cytokines, chemokines, and pro-lymphatic associated markers were measured via qPCR.

Hypothesis: We hypothesized that downhill treadmill exercise would induce muscle damage and dysregulate lymphatic structure and function.

Results and Discussion: The CK values for BMD pigs (mean=1,438 U/L) trended higher than normal at baseline ($p=0.0968$, mean=558.3 U/L) and increased significantly after exercise ($p=0.0057$). The CK values post-exercise support that muscle damage was taking place in affected animals. H&E staining and light microscopy supported that exercised pigs, compared to non-exercised ones, exhibited more connective tissue deposition (fibrosis) and central nuclei (regeneration). Preliminary results of reconstructed MRI images of the lymphatics in the pelvic limbs from normal and BMD pigs that did not exercise revealed two main collecting lymphatic vessels in the lower tibial area. However, only one lymphatic vessel was only identified in exercised BMD pigs. qPCR indicated proinflammatory cytokines/chemokines CSF1, CCL2, and CCL19 were significantly reduced in exercised BMD pigs compared to non ($p<0.050$). Pro lymphatic marker CCL21 was significantly reduced in exercised vs non-BMD pigs.

Conclusion: Downhill treadmill exercise can induce muscle damage and changes in lymphatic structure. Further analyses are needed to quantify muscle strength and lymphatic function.

Deep learning-based estimation of infarcted myocardium from strain imaging

RR. Mehdi[1], T. Mukherjee[1], EA. Mendiola[1], S. Neelakantan[1], R. Avazmohammadi[1]

[1] Department of Biomedical Engineering, Texas A&M University, College Station, TX, USA

Myocardial infarction (MI) induces significant remodeling of the myocardium, necessitating accurate estimation of infarct regions to understand disease progression and guide treatment strategies. Late gadolinium enhancement (LGE)-based cardiac magnetic resonance (CMR) is effective in delineating infarct regions but has limitations, including complications from gadolinium injection, safety concerns in patients with renal impairments, and extended scanning times that restrict its use in time-sensitive clinical settings. To address these challenges, we developed a deep learning (DL)-assisted method for estimating infarct regions using cardiac deformation (anatomic strains) data obtained from four-dimensional (4D) imaging.

Our approach began with generating a synthetic dataset using finite-element (FE) rodent heart models informed by in-vivo and ex-vivo data. These models simulated a range of infarct scenarios, varying in size, location, and stiffness levels. The simulated strain data were then used to train a UNet DL model. Initial validation was performed using a rodent model of MI, where ground truth data were obtained through histological analysis. This analysis confirmed that the DL model could accurately estimate the size and location of infarct regions in these preclinical models.

Building upon the success in rodent models, we extended the model to human data. The DL model was further trained and validated using cine CMR with LGE in human MI patients, where LGE served as a reliable ground truth for infarct estimation. The model's predictions in human patients demonstrated high accuracy, showing excellent agreement in identifying infarct regions when compared to the LGE-CMR obtained infarcts. This stepwise validation process—from rodent models with direct histological ground truth to human imaging data with LGE—ensures the robustness and generalizability of our method. By offering a non-invasive and efficient alternative that eliminates the need for gadolinium-based contrast agents, this approach has the potential to improve the management of MI patients by utilizing more accessible and safer imaging modalities like echocardiography.

Separation of the "active" and "passive" mechanisms of impaired filling in left ventricular diastolic dysfunction

Tanmay Mukherjee[1], Sunder Neelakantan[1], Sakthivel Sadayappan[2], Carl Tong[1], Reza Avazmohammadi[1].
[1]Texas A&M University, College Station, TX 77840, [2]University of Texas Southwestern Medical Center, Dallas, TX 75390

Introduction: Left ventricular diastolic dysfunction (LVDD) is characterized by restrictive diastolic filling and impaired left ventricle (LV) relaxation. Whereas myocardial stiffening has been thought to restrict LV filling, myofilament regulation impairments have been linked to impaired LV relaxation. However, the association of the passive mechanisms of myocardial stiffening with impaired active relaxation forces remain yet to be established. We hypothesize that investigating the “diastolic stretch” of the LV during relaxation through strain analysis may provide kinematic insight into both aspects of LV remodeling.

Methods: In this study, small animal models consisting of (i) diabetic (db/db, n=5) and (ii) transgenic aging (t3SA; = 5) murine models, with their respective wild-type controls (WT; n= 5 and tWT; n =5, respectively) were used. Doppler imaging was performed to evaluate functional indices of LV relaxation, transmitral flow and annular tissue velocities (E and e’). Cardiac magnetic resonance (CMR) and B-mode ultrasound imaging were performed to estimate cardiac strain and strain rates at end-diastole (ED) relative to early-diastole, i.e., diastolic strains and strain rates. Finally, mechanical testing was performed on harvested LV free wall (LVFW) specimens to measure passive stiffness.

Results: LVDD was confirmed by elevated E/e’ ratio (t3SA vs. tWT: 48.299 vs. 19.654; db/db vs WT: 37.535 vs. 28.997). The db/db mice presented an increase in passive LVFW stiffness measured as the tangent to the circumferential stress-strain curve at 30% strain (db/db vs WT: 102.729 vs. 52.888 kPa). Diastolic strain calculations corroborated LV filling impairment indicating significant reductions in circumferential LV strains (t3SA vs. tWT: 0.0853 vs. 0.1211; db/db vs WT: 0.0720 vs. 0.1250). Additionally, a strong positive and negative correlation was observed between passive stiffness and diastolic circumferential strains and E/e’, respectively (db/db vs. WT: $R^2 = 0.5271$ and $R^2 = 0.7149$, respectively).

Conclusion: Passive stiffening may impair LV filling by not only restraining the passive stretch of the myocardium at diastole but also by decelerating the active relaxation. Further integrated in-vivo and ex-vivo studies of LVDD can deconvolute the “active” and “passive” causes of impaired relaxation.

CMR-based Study of Torsional Behavior of Left Ventricle Post Mitral Valve Repair Surgery

Vahid Naeini[1], Tanmay Mukherjee[1], Seyed Babak Peighambari[1], Emilio A. Mendiola[1], Dipan J. Shah[2], Reza Avazmohammadi[1,3,4]

[1] Department of Biomedical Engineering, Texas A&M University, College Station, TX, USA
[2] DeBakey Heart and Vascular Center, Houston Methodist, Houston, TX, USA
[3] J. Mike Walker ’66 Department of Mechanical Engineering, Texas A&M University, College Station, TX, USA
[4] Department of Cardiovascular Sciences, Houston Methodist Research Institute, Houston, TX, USA

Cardiac function is intricately associated with the mechanical dynamics of the left ventricle (LV), particularly its torsional deformation. Mitral Valve Prolapse (MVP), a prevalent cardiac abnormality, often necessitates surgical repair (MVRe) or replacement (MVRp), which can significantly impact LV torsion and overall cardiac kinematics. This study investigates the changes in LV torsion following MVRe by employing advanced cine cardiac magnetic resonance (CMR) imaging techniques combined with non-rigid image registration to capture and quantify complex three-dimensional myocardial deformations.

A cohort of three patients was analyzed pre- and post-surgery using an approach that measures in-plane rotations as well as three-dimensional (3D) torsion. This assessment allowed for the characterization of LV torsion across different myocardial layers. Our findings demonstrate significant alterations in the torsional mechanics post-surgery, which potentially reflect improved myocardial efficiency and function. The study underscores the potential of LV torsion as a sensitive biomarker for evaluating the efficacy of surgical interventions in MVP patients and may aid in refining postoperative care for enhanced recovery trajectories.

Role of left ventricular anisotropy in the outcome of myocardial infarction: Insights from a rodent model

Sunder Neelakantan[1], Emilio Mendiola[1], Rana Raza Mehdi[1], Qian Xiang[2], XiaoXiao Zhang[2], Kyle J. Myers[1], Peter Vanderslice[2], Reza Avazmohammadi[1]
[1] Texas A&M University, College Station, TX, [2] Texas Heart Institute, Houston, TX

Introduction. Myocardial infarction (MI) leads to cardiac myocyte death and scarring, resulting in significant biomechanical remodeling of the left ventricle (LV). Maladaptive LV remodeling post-MI is known to contribute to the development of heart failure (HF). Understanding the role of LV free wall (LVFW) biomechanical remodeling in the transition of infarcted hearts to HF will improve prognostic capabilities and intervention strategies. Our objective in this study was to assess the association between LVFW anisotropic stiffening and organ-level functional adaptations.

Methods. MI was induced in WKY rats via the ligation of the LAD artery, and transthoracic echocardiography was performed to measure ejection fraction (EF). Fresh LVFW myocardial samples were harvested and subjected to biaxial tensile loading hearts were harvested at five timepoints: sham, and weekly from 1wk to 4wk post-MI (n=6 for each timepoint). The samples were stretched to 30% along the circumferential and longitudinal directions, and stiffness (slope of stress-stretch curves at 30% stretch) in each direction was measured. The ratio between longitudinal and circumferential stiffnesses was defined as the LVFW anisotropy.

Results. EF reduced post-MI, and changes in EF pre- and post-MI (denoted by ΔEF) showed a significant reduction at later timepoints. Although circumferential stiffness remained unchanged with time, longitudinal stiffness tended to increase post-MI, thus altering the overall anisotropy of LVFW tissues. The correlation between the anisotropy and EF indicated that an increased longitudinal bias post-MI was strongly correlated with reduced EF and LV decompensation.

Conclusions. Our results suggest that the myocardium stiffness changes *anisotropically* with a bias in the longitudinal direction post-MI. The strong correlation between myocardial anisotropy and EF suggests that studying alterations in LVFW biomechanical markers could provide insights into the mechanisms of transition to HF post-MI. The quantification of these markers through cardiac imaging offers to improve early prognostication of HF post-MI.

TEMPORAL IMPACT OF DIABETES ON OCULAR VASCULAR FUNCTION AND NEURAL RETINA MORPHOLOGY IN INS2(AKITA) MICE

Dylan Pham, Zahi Hussain, Gabrielle Hightower, Micah Thomas, William Wakeland, Joseph Hoppe, Xin Xu, Shu-Huai Tsai, Lih Kuo, Travis Hein

Department of Medical Physiology, Texas A&M University College of Medicine, Bryan, TX

Diabetic retinopathy is a leading cause of vision loss in working-age adults in the United States, but effective treatments are limited. Reduction of the ocular blood flow and degeneration of the neural retina are associated with diabetes before development of diabetic retinopathy. The Ins2(Akita) mouse spontaneously develops type 1 diabetes within 3 to 4 weeks of age. However, the effect of diabetes on ocular vascular dysfunction and neural retina degeneration and the potential underlying molecular mechanisms before pathologic changes in the retina in this model remain unclear. Herein, we examined the temporal impact of diabetes on retinal blood flow velocity, ophthalmic artery vasomotor function, neural retina morphology, and retinal mRNA expression of neurovascular genes arginase (Arg), Rho kinase (ROCK), and endothelin-1 converting enzyme-1 (ECE-1) in Ins2(Akita) mice. Diabetic Ins2(Akita) mice and control wild-type (WT) mice were studied from 6-8 weeks up to 24 weeks of age. Doppler ultrasound, optical coherence tomography (OCT), isolated and pressurized ophthalmic arteries, and qPCR were performed to measure central retinal artery (CRA) velocity, total retinal thickness (TRT), vascular reactivity, and retinal mRNA expression, respectively. At 8-weeks old, OCT imaging showed that TRT was thinner in diabetic mice than in control mice, which was maintained through 24-weeks old. CRA velocity was significantly lower in diabetic mice from 12 to 24 weeks. Endothelium-dependent nitric oxide (NO)-mediated dilation of ophthalmic arteries to acetylcholine decreased in diabetic mice at 10-weeks old. Endothelium-independent NO-mediated vasodilation to sodium nitroprusside and vasoconstriction to endothelin-1 were unaffected in diabetic vessels. The mRNA expressions of Arg1, Arg2, ECE-1, and ROCK1 were reduced in the retina of control and diabetic mice at 8-weeks old, whereas ROCK2 mRNA expression was comparable between groups. These findings indicate that neural retina degeneration and impaired endothelial NO-mediated dilation of ophthalmic arteries precede diminished CRA flow velocity in diabetic Ins2(Akita) mice with reductions in gene expression of retinal Arg1, Arg2, ECE-1, and ROCK1. Future studies will determine whether neurodegeneration contributes to ocular vascular dysfunction and whether therapeutic molecular targets can be identified to prevent these neurovascular changes in early diabetes and prevent progression to vision impairment or loss.

Impact of lymphangiogenesis on renal phosphate handling following kidney injury

Thien T Phan, Heidi Creed, Dawson Weiss, Myles Vu, Christiaan van der Weiden, Andrea J. Reyna, Joseph M. Rutkowski

Department of Medical Physiology, Texas A&M University College of Medicine, Bryan, TX 77807, USA

Abstract

Overconsumption of inorganic phosphate (Pi) causes tubular cell damage and kidney dysfunction, and hyperphosphatemia can lead to Ca^{2+} retention, vascular calcification, and cardiovascular disease. Conversely, kidney injury and chronic kidney disease (CKD) cause hyperphosphatemia and Pi retention. We hypothesized that the damage caused by chronic Pi consumption likely induces kidney lymphangiogenesis and that changes to renal lymphatic density may alter kidney mineral handling. We identified significant lymphangiogenesis and increased expression of the lymphatic growth factors VEGF-C/D in kidneys of mice fed a 2% Pi diet for 2 months and as early as three weeks of diet. We then utilized “KidVD” mice, a mouse model of kidney-specific inducible expression of VEGF-D, to expand renal lymphatic density and test Pi handling. Mineral handling was largely normal in male and female KidVD mice compared to littermates on Pi diet. In a Pi-driven CKD model mice were injured with 10 mg/kg cisplatin dose, allowed to recover for 2 weeks, then challenged with chow or 2% Pi diet for 3 weeks with VEGF-D induction. This resulted in Pi retention in all mice. Pi handling in both male and female KidVD mice were normal to controls. Female KidVD, however, demonstrated significantly increased Ca^{2+} excretion compared to controls. Circulating FGF23 levels were significantly elevated in male and female with VEGF-D overexpression. Gene expression of *Fgfr1* was also significantly increased in male and female KidVD mice. Renal lymphangiogenesis thus appears to specifically impact Ca^{2+} retention through the FGF23-Fgfr1 axis.

Project BP: A Student-led Blood Pressure Screening Initiative

Samantha Pozo Navarro and Abigail Hawkins

Although the number of people diagnosed with hypertension continues to increase, many people, especially those in marginalized communities with limited access to resources and without continuous access to healthcare, are unaware of their rising blood pressure. Within Brazos County, a 2022 Community Health Needs Assessment conducted by Baylor Scott & White reported that hypertension is associated with 70% of all heart disease cases. Consequently, there is an evident need in the Brazos Valley community for a method to address blood pressure; one that not only understands local barriers and social determinants of health but also educates and provides resources for these patients. This paper outlines Project BP, a medical student-initiated screening clinic, that will be implemented in Bryan, Texas to address this community need. In partnership with the Community Service Distinction Program at Texas A&M University College of Medicine, the clinic will aim to provide a free resource to obtain a current and accurate manual blood pressure reading and receive educational resources. By identifying at-risk patients early and increasing awareness of the long-term sequelae of high blood pressure, the clinic hopes to promote personal and community wellness as well as greater heart health. Implementation of the clinic has required a multidisciplinary approach with local leaders in the outreach landscape, community physicians, and health resources. Moreover, the clinic will call upon medical student volunteers to take blood pressures and to assist in providing education. A stratification system based on blood pressure and insurance status is being developed in order to refer patients to appropriate resources. Educational resources have been provided by a cardiologist in Temple, Texas and will be available on paper as well as through QR codes that patients can scan while at the clinic for further access. Additionally, to address a language barrier that may hinder access to care, the clinic will offer educational resources in Spanish and have on-site Spanish speaking personnel. Overall, the attitude, perception, and knowledge regarding the personal health of each individual that attends the clinic will be measured by a survey before and after the clinic. Through these efforts, the clinic aims to bridge gaps in healthcare access and empower the Brazos Valley community to take proactive steps towards managing hypertension and improving heart health.

Mechanistic Insight Into Global Warming-Mediated Thrombogenesis

Shahnaz Qadri[1], Fatima Z. Alshbool[2] and Fadi T. Khasawneh[1]

[1]Department of Pharmaceutical Sciences, Irma Lerma Rangel College of Pharmacy, Texas A&M University, Kingsville, TX
[2]Department of Pharmacy Practice, Irma Lerma Rangel College of Pharmacy, Texas A&M University, Kingsville, TX

There are emerging reports of life-threatening events taking place due to the body's response to high temperatures, such as heart failure, increased metabolic demand, and hypercoagulability. Indeed, there is evidence that such "disorders" are the consequences of global warming with a 1 to >2°C increase in climate temperature. Moreover, during summer heat waves and humid days, the burden of cardiovascular disease (CVD) is higher with or without preexisting conditions. Epidemiological studies revealed that the CVD mortality rate is higher by 9% when climate temperature is above 35°C. And if adaptation to rising temperatures does not happen, the mortality rate is expected to triple between 2030 and 2050. Thus, it is paramount to investigate the mechanism of heat-related CVD/illness in order to develop prevention and/or therapeutic strategies. With regard to occlusive/thrombotic CVD, studies have shown that exposure of platelets to varying ambient temperatures (AT) causes hyperactivation. However, much is unknown regarding how platelets "perceive" thermal response, and the underlying mechanisms. Indeed, platelets express thermoregulatory and mechanosensitive ion channels such as Transient Receptor Potential ion channels (TRP), the Piezo1 as cation channels having high affinity for calcium influx, as well as the anionic channel TMEM16F are found in platelets regulates phosphatidylserine (PS) exposure and microparticle release, which plays a significant role in platelet hemostasis, thrombosis and platelet integrity. Although the thermal activation of these channels is well addressed in other tissues, *their thermal sensitivity in platelets has never been studied*. Therefore, we aim to characterize thermosensitive ion channels in platelets to investigate the mechanism of heat related CVD-illness. Our data indicated that exposure to increased temperature causes activation of the chloride channel TMEM16F with significant increase in PS exposure in platelets; which is a typical procoagulant characteristic feature associated with CVD illness/stroke. Given that platelets do show some tolerance to temperatures, the observation of ionic balance in these cells during heat exposure leads us to hypothesize the presence of a thermoregulated hyperpolarizing cation channel to counterbalance the influx of chloride via TMEM16F. Indeed, our studies document that there are three isoforms of the potassium two-pore domain ion channels that are expressed: TREK1, TREK2 and TRAAK that potentially may modulate homeostasis. TREK1 and TREK2 are primarily known for efflux of potassium, and are thermoregulatory channels. Our data shows platelet aggregation and calcium signaling was significantly affected using pharmacological inhibitors of TREK-1 and TREK-2. In conclusion, our findings suggest that activation of thermosensitive ion channels, triggers a platelet procoagulant state, which may be a basic insight into heatstroke related illness due to global warming. Our ongoing research should inform the management and diagnosis of occlusive CVD-illness caused by increased temperature due to global warming.

Hypoxia impairs Kv7 channel function in porcine coronary arterioles

Authors: **Trevor S Self**[1] and Cristine L Heaps[1,2]

[1] Department of Physiology and Pharmacology, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX, United States.
[2] Michael E. DeBakey Institute for Comparative Cardiovascular Science and Biomedical Devices, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX, United States.

Ischemic heart disease is a multifaceted pathological manifestation that affects more than 80 million people in the United States, with an annual economic cost of more than $300 billion in healthcare expenses and lost productivity. Understanding the progression of this disease and the underlying regulatory mechanisms is essential for the development of novel therapeutic strategies. Using a clinically relevant swine model we designed an *in vitro* approach to isolate a reduction in oxygen tension as a single characteristic of this otherwise complicated disease. We tested the hypothesis that hypoxia would attenuate coronary arteriolar relaxation, mediated through a loss of Kv7 channel contribution. Continuous bubbling of N_2 gas, supplemented with 5% CO_2 and 1% O_2, through the tissue buffers was used to establish the hypoxic environment, and hypoxic insult was confirmed by HIF1α immunofluorescent staining. Isometric tension wire myography and electrophysiology experiments were used to investigate Kv7 channel contribution to H_2O_2-mediated relaxation and Kv channel currents, respectively, in response to a 1-hour hypoxic treatment. Our data reveal that hypoxia impairs H_2O_2-mediated vasodilation and that this is attributable to a loss of Kv7 channel activity. Further, protein kinases are known to associate with and activate Kv7 channels in other tissue types. Using our model of hypoxia, inhibition of PKA yielded a similar inhibitory response as direct blockade of Kv7 channels. Taken together, our data reveal that hypoxic insult reduces H_2O_2-stimulated contribution of Kv7 channels in vascular reactivity studies, resulting in attenuated relaxation of coronary arterioles that may be mediated through PKA.

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Inflammation and Pathological Lymphangiogenesis in the heart are associated with Duchenne Muscular Dystrophy Cardiomyopathy

Bhuvaneshwaran Subramanian[1], Shedreanna Johnson[1], Carl Tong[1], Peter P. Nghiem[2], Mariappan Muthuchamy[1]

[1]Department of Medical Physiology, Texas A&M University, Bryan, TX 77807
[2]Department of Veterinary Biosciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX 77843

Duchenne Muscular Dystrophy (DMD) is a devastating genetic disease that affects approximately 1.3 to 2.1 per 10,000 male live births. Lack of dystrophin results in the degradation of dystrophin associated protein complex resulting in progressive skeletal muscle and heart failure. DMD initially disrupts the skeletal muscle, however, cardiac failure is the predominant cause for the mortality in patients at the later stages of DMD. Myocardial inflammation is observed in DMD patients with heart failure. The cardiac lymphatic vessels modulate the status of inflammation in several cardiovascular diseases. Our data show that the skeletal muscle lymphatics of the DMD animals revealed poor lymphatic conductance when compared with the control animals. Hence, we hypothesize that changes in lymphatic structure and function causing inflammation in the heart, consequently leading to cardiomyopathy in DMD patients. To test our hypothesis, we used *D2.mdx* mice, having DMD gene mutation in the DBA/2J genetic background. The gene expression profile for inflammation and lymphangiogenesis in the 8-month-old heart tissues revealed a significant increase in the proinflammatory and lymphangiogenic markers in the *D2.mdx* mice when compared to the control group. Echocardiogram studies demonstrated that *D2.mdx* hearts exhibit a significant decrease in the left ventricular inner diameter at diastole (LVIDd) and systole (LVIDs); whereas posterior wall thickness at diastole (PWTd) and systole (PWTs) are significantly increased, indicating *D2.mdx* hearts show a concentric LV hypertrophy phenotype. Additionally, while the left ventricular ejection fraction is increased in DMD mice, stroke volume in the DMD hearts is significantly decreased, suggesting that DMD hearts resemble hypertrophic cardiomyopathy but without any diastolic dysfunction. Immunohistochemical analyses detected the occurrence of hypertrophy and pathological lymphangiogenesis in the cardiac tissues of *D2.mdx* animals. Further studies of cardiac lymphatic function in DMD animals are warranted to provide new insights into developing a therapeutic strategy targeting lymphatics for DMD cardiomyopathy.

Registered Participants

Laila Abdel-Rahim
Research Associate
Department of Medical Physiology

John August, DVM
Carl B. King Dean
College of Veterinary Medicine & Biomedical Sciences, Texas A&M University

Reza Avazmohammadi, PhD
Assistant Professor
Department of Biomedical Engineering

Shameena Bake, PhD
Research Assistant Professor
Department of Neuroscience & Experimental Therapeutics

Sakhila K. Banu, PhD
Professor
Veterinary Integrative Biomedical Sciences

Kayla J. Bayless, PhD
Associate Professor
Department of Medical Physiology

Samantha Beevers
Graduate Student
Department of Medical Physiology

Sarah Bondos, PhD
Associate Professor
Department of Medical Physiology

Zhuodong Chai
Graduate Student
Department of Pharmaceutical Sciences

Sanjukta Chakraborty, PhD
Associate Professor
Department of Medical Physiology

Alvis Chiu
Graduate Student
Department of Biomedical Engineering

Mahua Choudhury, PhD
Associate Professor
College of Pharmacy

Erin Frances Chua
Undergraduate Student
College of Pharmacy

John Criscione, PhD
Professor
Biomedical Engineering

Vince Cupit
Administrative Coordinator I
Department of Medical Physiology

Brandon Dixon, PhD
Woodruff Professor
Georgia Institute of Technology

Katie Edmonds
Undergraduate Student
College of Pharmacy

Malak Ezzat
Graduate Student
Department of Medical Physiology

Jefferson Frisbee, PhD
Ting-Yim Lee Endowed Chair and Professor
Western University, Ontario, Canada

Joshua Glanz
Undergraduate Student
College of Pharmacy

Shannon Glaser, PhD
Professor
Department of Medical Physiology

Bethany Goodlet
Research Associate
Department of Medical Physiology

Liliana Guzman
Undergraduate Student
College of Pharmacy

Joshua Hale
Graduate Student
Department of Medical Physiology

Stephanie Han
Undergraduate Student
College of Pharmacy

Raaida Hasnain
Undergraduate Student
Department of Biomedical Sciences

Travis W. Hein, PhD
Professor
Department of Medical Physiology

Connor Hendrie
Student Research Assistant
Veterinary Integrative Biomedical Sciences

Gabrielle Hightower
Graduate Student
Department of Medical Physiology

Joseph Hoppe
Graduate Student
Department of Medical Physiology

Raina Hummel
Undergraduate Student
College of Pharmacy

Jaclyn Iannucci, PhD
Postdoctoral Research Associate
Neuroscience & Experimental Therapeutics

Shedreanna Johnson
Graduate Student
Department of Medical Physiology

Saranya Kannan, PhD
Postdoctoral Research Associate
Department of Medical Physiology

Jhanvi Karthik
Undergraduate Student
College of Pharmacy

Mansoor A. Khan, PhD, RPh
Dean, Regents and Distinguished University
Professor, College of Pharmacy

Fadi Khasawneh, PhD
Professor and Department Head
College of Pharmacy

Joo Hyun Kim
Graduate Student
Department of Kinesiology & Sport Management

Hyoseon Kim, PhD
Postdoctoral Research Associate
Department of Medical Physiology

Vashishta Kolla
Graduate Student
Veterinary Integrative Biomedical Sciences

Samhita Kosuru
Undergraduate Student
College of Pharmacy

Ankit Kumar
Graduate Student
Department of Biomedical Engineering

Kathryn Kunz
Graduate Student
Department of Pharmaceutical Sciences

Lih Kuo, PhD
Professor
Department of Medical Physiology

Glen Laine, PhD
Professor, Director
Michael E. DeBakey Institute

Tatlock Lauten
Graduate Student
Department of Medical Physiology

John Lawler, PhD
Professor
Department of Kinesiology & Sport Management

Jennifer Lee
Graduate Student
Department of Biomedical Engineering

Zhenyu Li, PhD
Professor
Department of Pharmaceutical Sciences

Macie Mackey
Senior Research Associate
Veterinary Integrative Biomedical Sciences

Rana Raza Mehdi
Graduate Student
Department of Biomedical Engineering

Tina Mendoza
Business Administrator II
Department of Medical Physiology

Rajesh Miranda, PhD
Professor
Department of Neuroscience & Experimental Therapeutics

Brett M. Mitchell, PhD
Professor
Department of Medical Physiology

Aaron Morton, PhD
Assistant Professor
Department of Kinesiology & Sport Management

Tanmay Mukherjee
Graduate student
Department of Biomedical Engineering

Malea Murphy, PhD
Research Specialist III
Department of Medical Physiology

Mariappan Muthuchamy, PhD
Professor
Department of Medical Physiology

Vahid Naeini
Graduate Student
Department of Biomedical Engineering

Akshaya Narayanan
Graduate Student
Department of Medical Physiology

Sunder Neelakantan
Graduate Student
Department of Biomedical Engineering

Oksana Nekrashevych, MPH
Project Coordinator II
Department of Medical Physiology

Annie Newell-Fugate, PhD
Assistant Professor
Veterinary Physiology & Pharmacology

Peter Nghiem, DVM, PhD
Associate Professor
Veterinary Integrative Biomedical Sciences

Emily Nguyen
Undergraduate Student
Department of Biology

Mariam Othman
Graduate Student
Department of Kinesiology & Sport Management

Laura Packer
Undergraduate Student
College of Pharmacy

Samuel V. Padgham
Technician
Department of Medical Physiology

Xu Peng, MD, PhD
Associate Professor
Department of Medical Physiology

Dylan Pham, PhD
Postdoctoral Research Associate
Department of Medical Physiology

Thien Phan
Graduate Student
Department of Medical Physiology

Samantha Pozo Navarro
Medical Student
Department of Medical Physiology

Shahnaz Qadri, PhD
Research Scientist
College of Pharmacy

Jiaqian Qi, PhD
Postdoctoral Research Associate
College of Pharmacy

Ellie Rahbar, PhD
Associate Professor
Department of Biomedical Engineering

Samba Reddy, PhD
Regents Professor
Department of Neuroscience & Experimental Therapeutics

Andrea Reyna
Research Assistant
Department of Medical Physiology

Allison C. Rice Ficht, PhD
Interim Senior Associate Dean for Research
College of Medicine, TAMHSC

Mendell Rimer, PhD
Associate Professor
Department of Neuroscience & Experimental Therapeutics

Amelia Rodriguez
Business Coordinator II
Department of Medical Physiology

Haley Russell
Undergraduate Student
Veterinary Integrative Biomedical Sciences

Joseph Rutkowski, PhD
Associate Professor
Department of Medical Physiology

Samuel Salazar
Undergraduate Student
College of Pharmacy

Indira Saravanan
Graduate Student
Veterinary Integrative Biomedical Sciences

Trevor Self
Graduate Student
Veterinary Physiology & Pharmacology

Song Yi Shin, PhD
Visiting Scholar
Department of Medical Physiology

Paula Shireman, PhD
Professor
Department of Medical Physiology

Nitya Shree, PhD
Postdoctoral Research Associate
Department of Pharmaceutical Sciences

Hannah Smith
Graduate Student
Department of Medical Physiology

Farida Sohrabji, PhD
Regents Professor and Head
Department of Neuroscience & Experimental Therapeutics

John N. Stallone, PhD
Professor
Department of Veterinary Physiology & Pharmacology

Randolph Stewart, PhD
Clinical Professor
Department of Veterinary Physiology & Pharmacology

Jennifer Strande, MD, PHD
Medical Director
Amgen

Bhuvaneshwaran Subramanian, PhD
Postdoctoral Research Associate
Department of Medical Physiology

Yuxiang Sun, PhD
Professor
Department of Nutrition

Sharanee Sytha
Graduate Student
Department of Veterinary Physiology & Pharmacology

Glenn M. Toney, PhD, FAHA, FAPS
Professor and Head
Department of Medical Physiology

Carl Tong, MD, PhD, FACC
Associate Professor
Department of Medical Physiology

Andreea Trache, PhD
Associate Professor
Department of Medical Physiology

M. Nasir Uddin, PhD, FAHA
Research Associate Professor
Department of Medical Physiology

Sunil Venkategowda, PhD
Postdoctoral Research Associate
Department of Pharmaceutical Sciences

Brad Verhulst, PhD
Research Assistant Professor
Department of Psychiatry

Wei Wang, PhD
Assistant Research Scientist
Department of Medical Physiology

Yinan Wei, PhD
Professor
College of Pharmacy

Christopher R. Woodman, PhD
Associate Professor
Department of Kinesiology & Sport Management

Sydnee Woodward
Student Assistant
Department of Medical Physiology

Guoyao Wu, PhD
Distinguished Professor
Department of Animal Science

Xin Wu, PhD
Research Assistant Professor
Department of Neuroscience & Experimental Therapeutics

Chaodong Wu, PhD
Professor
Department of Nutrition

Ling Yang, PhD
Postdoctoral Research Associate
College of Pharmacy

David C. Zawieja, PhD
Regents Professor
Department of Medical Physiology

Yan Zhang, PhD
Postdoctoral Research Associate
College of Pharmacy

Ziran Zhang, PhD
Postdoctoral Research Associate
College of Pharmacy

Guoying Zhang
Research Associate
College of Pharmacy

Feng Zhao, PhD
Professor
Department of Biomedical Engineering

Yuqi Zhou
Graduate Student
College of Pharmacy