The Arizona Physiological Society

16th Annual Meeting October 27-28, 2023

Midwestern University

Glendale, Arizona

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Directions to Midwestern University – Glendale, AZ

19555 North 59th Avenue, Glendale AZ 85308

Google Maps Link

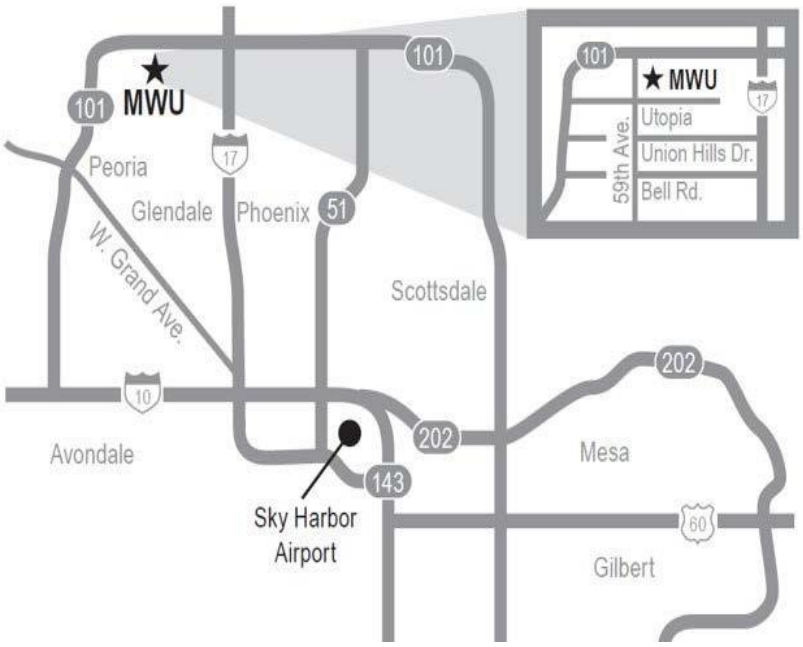
Apple Maps Link

Via Interstate 17:

- Take Interstate 17
- Exit on Loop 101 West
- Continue west on 101 to 59th Ave
- Turn left (south) onto 59th Avenue
- Turn left (east) onto Utopia
- Main campus entrance is on the left

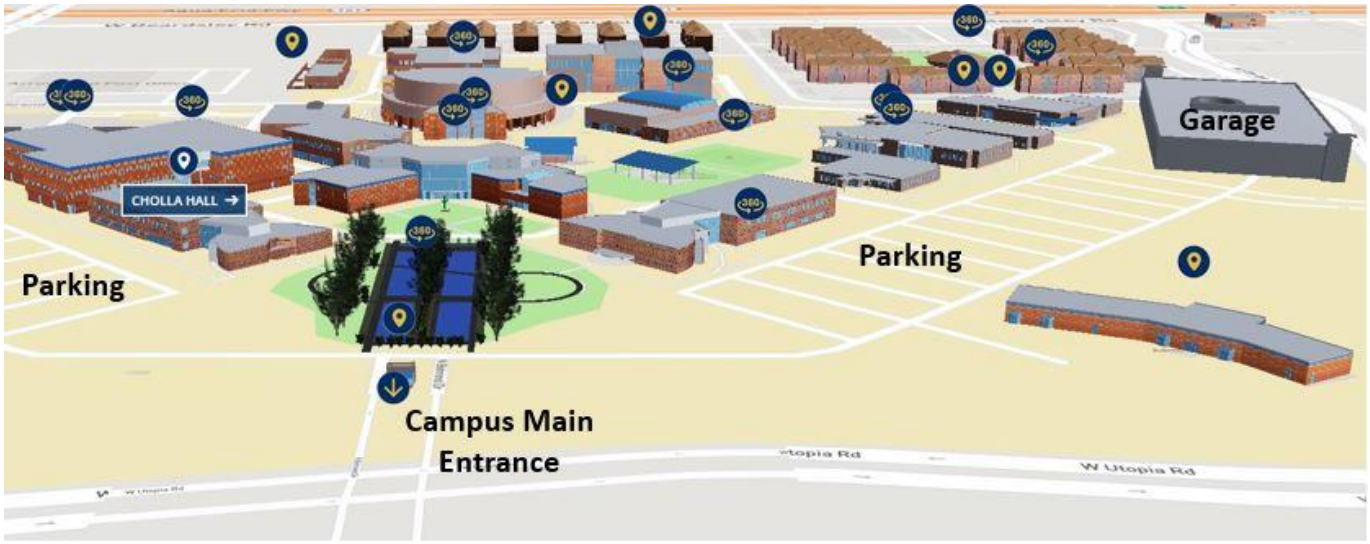
Via Interstate 10:

- Take Interstate 10 to Loop 101
- Take Loop 101 North to 59th Ave
- Turn left (south) onto 59th Avenue
- Turn left (east) on Utopia
- Main campus entrance is on the left

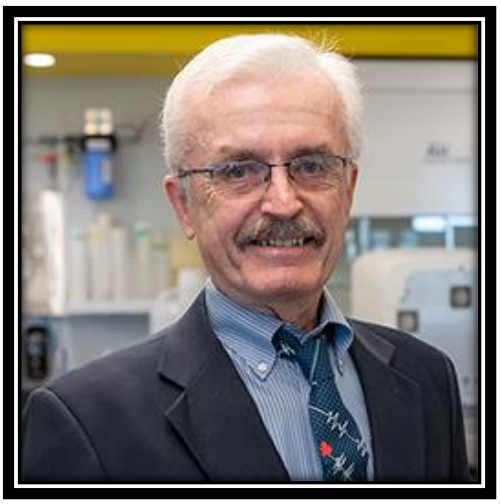


Meeting registration and regular sessions will be held in Cholla Hall
Dinner reception will be in the Sahuaro Hall Courtyard

Midwestern University Campus Map



2023 Arizona Physiological Society Senior Scientist Keynote Speaker



Dr. Chris Glembotski

Professor, Department of Internal Medicine
Director, Translational Cardiovascular Research Center
Associate Dean, Research
University of Arizona

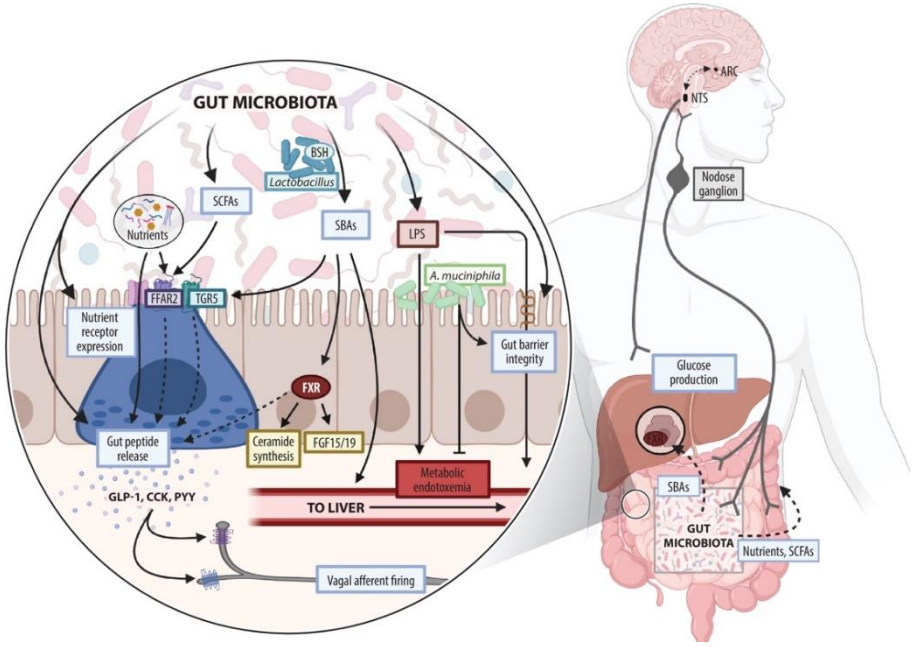
Dr. Chris Glembotski completed his doctoral studies at UCLA in Biochemistry, then did a post-doctoral fellowship in neuroscience and cell physiology at the University of Colorado Health Sciences Center, after which he joined the faculty of the University of Pennsylvania School of Medicine as Professor of Pharmacology, then became Distinguished Professor and Director of the San Diego State University (SDSU) Heart Institute, with additional grant activities and research collaborations at the University of California San Diego, Department of Pharmacology and Division of Cardiology, as well as the Scripps Research Institute in La Jolla, CA. He has had many academic administrative positions in San Diego, including Founding Director of the SDSU Genomics Research Center, Department Chair and Associate Dean for Graduate and Research Affairs. In 2019 Dr. Glembotski was also awarded the Albert Johnson Outstanding Research Award at SDSU, the institution's highest research recognition. In September of 2020, Dr. Glembotski took the position of Professor of Internal Medicine, Associate Dean for Research and inaugural Director of the Translational Cardiovascular Research Center (TCRC) at UA COMP. In this new role, Dr. Glembotski has built a strong translational research team of basic science and clinical faculty, medical and postdoctoral fellows, as well as graduate and medical students, who work in a vibrant, exciting environment at the TCRC at UA COMP. As the Associate Dean for Research, Dr. Glembotski works with scientists and physicians in many fields to enhance translational research at UA COMP. Dr. Glembotski's own research funding from the NIH has been uninterrupted for his entire career and has amounts to more than $40M in R01 as well as P01 funding, and numerous prestigious grants from the American Heart Association, including the AHA Established Investigator award. His research is focused on finding novel treatments for ischemic heart disease, cardiomyopathy and heart failure using gene therapy, stem cell and small molecule drug candidate discovery approaches. He has published more than 150 research articles in high impact peer review journals, was awarded the Translational Researcher of the Year Award in the Department of Internal Medicine in 2022 and has an H-index of 72. In addition to heart research, Dr. Glembotski is dedicated to mentoring faculty, research fellows and students to help them achieve their academic and research goals in medicine and science. Dr. Glembotski has mentored more than 50 M.S., Ph.D., and M.D./Ph.D. students, post-doctoral fellows and faculty in his lab, which focuses on finding cures for heart disease by translating scientific discoveries in the research lab to treatments for patients. His highly regarded mentoring activities were recognized by the International Society for Heart Research, prestigious Eric N. Olson Mentorship Award in 2021.

2023 Arizona Early Career Investigator Keynote Speaker

Dr. Frank A. Duca

Assistant Professor, Gastrointestinal Microbiology
School of Animal and Comparative Biomedical Sciences
College of Agriculture and Life Sciences
University of Arizona

Dr. Frank Duca is an Assistant Professor in the School of Animal and Comparative Biomedical Sciences at the University of Arizona. He obtained his PhD from Pierre and Marie Curie University in 2013, examining the impact of high-fat diets and obesity on gut-brain signaling and the gut microbiome. He was a Banting Postdoctoral Fellow at the Toronto General Hospital Research Institute, under the mentorship of Dr. Tony Lam, where he examined how metformin can directly, and indirectly via the gut microbiome, impact hepatic glucose production through a neuronal gut-brain-liver axis. At the University of Arizona, his lab is currently focused on how dietary and environmental exposures can impact gut-brain signaling mechanisms that regulate metabolic homeostasis. His lab is especially interested in how changes in the gut metagenome and metabolome can influence the development of metabolic dysregulation via alterations in nutrient-sensing, vagal signaling, and the central nervous system.



From Howard, E. J., Lam, T. K., & **Duca, F. A.** (2022). The Gut Microbiome: Connecting Diet, Glucose Homeostasis, and Disease. *Annual Review of Medicine*, 73, 469-481.

2023 AZPS ANNUAL MEETING – PROGRAM SCHEDULE

Friday, October 27, 2023

8:45 AM - 9:45 AM	**Registration/Poster Setup/Coffee & Refreshments (Cholla Hall)**	
9:45 AM - 10:00 AM	**Welcome Remarks**	
10:00 AM - 11:00 AM	**Session 1**- ***Cardiovascular Health & Beyond***	
	Session Chairs: Dr. Karen Sweazea (ASU), Dr. Ann Revill (MWU)	
10:00 AM S1.1	Chen-Wei Liu, Postdoctoral Fellow, University of Arizona Phoenix	*The molecular functions of HDAC9 in the development of e-cigarette-induced atherosclerosis by promoting endothelial-mesenchymal transition*
10:15 AM S1.2	Sukriti Bagchi, Graduate Student, University of Arizona, Phoenix	*SGK1 is a Key Mediator of Pathological Cardiac Fibrosis*
10:30 AM S1.3	Ngunyi Fuangunyi, Undergraduate Student, University of Arizona Phoenix	*The Multifaceted Nature of Cardiovascular Disease and Why Race Matters*
10:45 AM S1.4	Monique Martinez, Graduate Student, University of Arizona, Phoenix	*Impact of Mid-gestation Toll-like Receptor 7 Stimulation on Development and Anxiety-like Behavior in Offspring*
11:00 AM - 11:15 AM	**Break & Visit to Vendors**	
11:15 AM - 12:00 PM	**Session 2**- ***Beyond Binary: Exploring Sex Differences in Physiology***	
	Session Chairs: Dr. Jennifer Teske (U of A), Dr. Shirin Doroudgar (U of A)	
11:15 AM S2.1	Dana Floyd, Research Associate, University of Arizona Phoenix	*Sex-Specific Regulation of Gonadal Hormone Receptor Gene Expression Following Ang II Infusion in Spontaneously Hypertensive Rats*
11:30 AM S2.2	Sebastiao Donato Silva J., Postdoctoral Fellow, University of Arizona Phoenix	*Sex-specific effects of transient losartan treatment on angiotensin II-induced fibrogenic signaling in the heart of spontaneously hypertensive rats*
11:45 AM S2.3	Arielle Condes & Elyse Policastro, Undergraduate Student, Northern Arizona University	*Sex Differences in Redox Balance: Effects of Aging and Exercise*

12:00 PM S2.4	Arpan Sharma, Graduate Student, University of Arizona Phoenix	*Sex-Specific Regulation of Catecholamine Signaling in Rats Exposed to Dexamethasone in Utero and Angiotensin in Adulthood*
12:15 PM - 1:15 PM	**Lunch & Visit to Vendors (Cholla Hall)**	
1:15 PM - 2:00 PM	**One Minute Poster Presentation**	
2:00 PM - 3:00 PM	**Arizona Senior Scientist Keynote Speaker** **Dr. Christopher Glembotski, Professor, University of Arizona Phoenix** ***Proteostasis in Heart Health & Disease: A Degrading Proposition***	
3:00 PM - 3:15 PM	**Break & Visit to Vendors**	
3:15 PM - 4:30 PM	**Session 3** - ***From Fork to Flora: Navigating Diet, Glucose, and Gut Health*** **Session Chairs: Dr. Nafisa Jadavji (MWU), Dr. Dallin Tavoian (U of A)**	
3:15 PM S3.1	Kailin Johnsson, Graduate Student, Arizona State University	*Correlation of Plasma LPL Activity with Measures of Body Composition across Subjects with Varying Levels Insulin Sensitivity*
3:30 PM S3.2	Elizabeth Howard, Graduate Student, University of Arizona Tucson	*Impact of Plant-Derived Dietary Fibers on Energy and Glucose Homeostasis*
3:45 PM S3.3	Savanna Weninger, Graduate Student, University of Arizona Tucson	*Longitudinal characterization of the gut microbiota in the ZDSD rat model of diabetes*
4:00 PM S3.4	Nicholas Smith, Medical Student, Midwestern University	*Assessment of reversal effects on genistein and exercise on hepatic tissues*
4:15 PM S3.5	Nathan Connell, Undergraduate Student, University of Arizona Tucson	*The impact of dietary tryptophan levels on energy in glucose homeostasis in LFD and HFD-fed mice*
4:30 PM - 4:45 PM	**Break & Visit to Vendors**	
4:45 PM - 6:00 PM	**Session 4** - ***Neural Echoes: The Brain's Dance with Physiological Stimuli*** **Session Chairs: Dr. John VandenBrooks (ASU), Dr. Mingyu Liang (U of A)**	
4:45 PM S4.1	Tala Curry, Graduate Student, University of Arizona Phoenix	*Accelerated Cerebrovascular Aging and Vulnerability to Traumatic Brain Injury in Marfan Syndrome Mice*

5:00 PM S4.2	Aleanna Melliza & Alexis Osbourne, Graduate Students, Midwestern University	*Characterization of HCN channel subtypes and the contribution of "Ih" in postnatal maturation of muscarinic modulation of inspiratory bursting at hypoglossal motoneurons*
5:15 PM S4.3	Petter Burrows, Medical Student, Midwestern University	*Ischemic stroke increases levels of one carbon enzymes, the folate receptor, and choline metabolism in post-mortem male and female brain tissue*
5:30 PM S4.4	Julius Vellutato, Medical Student, Midwestern University	*Characterizing Muscarinic Receptor Subtype Roles in Inspiratory Bursting of Hypoglossal Motoneurons in Postnatal Mice*
5:45 PM S4.5	Stephenie Thai, Graduate Student, University of Arizona Tucson	*PNA5 restores BKCa function in cerebral artery smooth muscle cells of female 5x-FAD mice*
6:00 PM - 7:00 PM	**Dinner Reception (Sahuaro Hall Courtyard)**	
7:00 PM - 9:00 PM	**1st Poster Session/Wine & Desserts (Cholla Hall 112-118)**	

Saturday, October 28, 2023

8:00 AM - 9:00 AM	**Continental Breakfast & Visit to Vendors (Cholla Hall)**	
9:00 AM - 10:15 AM	**Session 5** - ***Endothelial Dysfunction: Normal & Accelerated Aging*** **Session Chairs: Dr. Tinna Traustadottir (NAU), Dr. Delrae Eckman (MWU)**	
9:00 AM S5.1	Josiane da Silva, Postdoctoral Fellow, University of Arizona Tucson	*Age-dependent cerebral microvascular dysfunction in ApoE4 knock-in mice*
9:15 AM S5.2	Sara Djurich, Graduate Student, University of Arizona Tucson	*Modeling conducted responses in microvascular networks: current rectification in endothelial cell gap junctions*
9:30 AM S5.3	Trevor Wendt, Graduate Student, University of Arizona Phoenix	*PM2.5 Temporally Decreases Human Brain Microvascular Endothelial Barrier Proteins and Concomitantly Increases Inflammation and Autophagy in a Dose Dependent Manner*
9:45 AM S5.4	Hoai Huong Le, Graduate Student, University of Arizona Phoenix	*Role of exosomal miRNAs in the crosstalk between endothelial cells and macrophages following e-cig exposure*
10:00 AM S5.5	Felipe Polk, Graduate Student, University of Arizona Tucson	*Endothelial KIR2 channel dysfunction in aged cerebral parenchymal arterioles*

10:15 AM - 10:30 AM	**Break & Visit to Vendors**	
10:30 AM - 11:30 PM	**AZ Early Career Lecture** **Dr. Frank Duca, Assistant Professor, University of Arizona Tucson** ***Impact of Small and Large Intestinal Microbiota on Metabolic Homeostasis***	
11:30 AM - 2:00 PM	**2nd Poster Session & Lunch** **(Cholla Hall Lobby & Rooms 112-118)**	
2:00 PM - 2:45 PM	**Session 6** - ***Integrative Pathophysiology: Bridging Systems & Disciplines*** **Session Chairs: Dr. Frank Duca (U of A), Dr. Haiwei Gu (ASU)**	
2:00 PM S6.1	Keila Espinoza, Graduate Student, University of Arizona Tucson	*Loss of Acid Ceramidase in Myeloid Cells Alleviates Chronic Colitis in IL10-/- Mice*
2:15 PM S6.2	Dominick Rodriguez, Graduate Student, Northern Arizona University	*Effects of Ex Vivo Sulforaphane Stimulation in Human PBMCs Before & After Exercise*
2:30 PM S6.3	Andrew Yang, Graduate Student, Midwestern University	*Progranulin and Lysosomal pH: implications for potential new therapeutic strategy for neurodegenerative diseases*
2:45 PM - 3:00 PM	**Break & Visit to Vendors**	
3:00 PM - 4:00 PM	**Awards & Business Meeting**	

Poster Sessions

*Posters **P1 – P26** will be available in **Session 1**: Friday October 27th, 7:00 PM - 9:00 PM*
*Posters **P28 – P55**: will be available in **Session 2**: Saturday October 28th, 11:30 AM - 1:30 PM*

Poster ID	Lead Author (s)	Institution	Poster Title
P1	Bin Liu	University of Arizona	*Fatty acid-binding proteins promote pulmonary hypertension via glycolysis*
P2	Baylee Reed	University of Arizona	*Inspiratory Muscle Strength Training to Improve Cardiometabolic Health in Patients with Type 2 Diabetes: Protocol for the Diabetes Inspiratory Training (DIT) Clinical Trial*
P3	Marjan Aghajani	University of Arizona	*The E3 Ubiquitin-Protein Ligase Synoviolin (Syvn1/Hrd1) Promotes Adaptive Decreases in Cardiac Myocyte Protein Synthesis via eIF2α/ATF4 Pathway Activation*
P4	Spencer Vroegop	Midwestern University	*Long-term intermittent fasting induces changes to glucose metabolism and limits apoptosis in the SAMP8 aged murine jejunum*
P5	Alisha Harrison	Midwestern University	*Marfan Syndrome Increases Apoptotic Neurons Female Mice*
P6	Sean Noudali	University of Arizona	*SNAP23 is a Novel Regulator of Autophagy in Cardiomyocytes*
P7	Colton Lane	Midwestern University	*Cadaveric investigation of posterior interventricular artery variation and review of clinical implications*
P8	Thalia Olson	Midwestern University	*Cadaveric investigation of anatomical variants in the thyroid region and clinical implications for emergency airway procedures*
P9	Bhavik Rajaboina	University of Arizona, Phoenix	*Impact of Aging After Traumatic Brain Injury: Evaluation of neuropathology, axonal injury, neuroinflammation, autophagy, and pTau pathology in the dentate gyrus at 6-months post-injury*
P10	Sanika Joshi	Midwestern University	*Vascular dementia results in increased levels of methylenetetrahydrofolate reductase in cortical brain tissue of elderly female patients*
P12	Alina Bilal	University of Arizona, Phoenix	*SGK1 Promotes Atrial Pathology in HFpEF*

Poster ID	Lead Author (s)	Institution	Poster Title
P13	Ela Romanoski	University of Arizona	*Levels of dietary carbohydrate, sleep, and noise exposure affect PERK protein levels in biofluids*
P14	Ranon Plett	University of Arizona	*Glycodeoxycholic Acid Impacts Metabolic Homeostasis in High Fat Fed Mice*
P15	Jonathan Tuscano	Midwestern University	*Impact of Heavy Metals on Bone Porosity in North American River Otter*
P16	Jinhua Chi	Arizona State University	*Direct Evidence of Metabolic Interactions between PBDEs and Gut Microbes: an In Vitro Metabolomics Study*
P17	Nolan Dunn	University of Arizona	*Acute effects and vascular response to inspiratory resistance training*
P18	Marjan Fakhrizadeh Esfahani	University of Arizona, Phoenix	*Regulation of Cardiokine Secretion and Cardiac Function by Peptidylglycine α-Amidating Monooxygenase (PAM)*
P19	Ananya Shah	University of Arizona	*Inconsistent Sleep Decreases Urinary and Salivary PERK Levels*
P20	Jared Alvarez	Arizona State University	*Sex-Specific Regulation of Catecholamine Signaling in Rats Exposed to Dexamethasone In Utero and Angiotensin in Adulthood*
P21	Ernest Sandoval	University of Arizona, Phoenix	*IRE1α protects against cardiac fibrosis via regulating selective mRNA degradation*
P22	Trevor Wendt	University of Arizona, Phoenix	*OxLDL/LOX-1 Mediated Sex, Age, and Endothelial Dependent Alterations in Vascular Reactivity in Murine Thoracic Aortic Rings*
P23	Trevor Wendt	University of Arizona, Phoenix	*OxLDL preconditioning temporally intensifies ischemic-like injury mediated alterations in human male brain endothelial cell tight junction protein levels and proinflammatory mediators*
P24	Michael Britton	Arizona State University	*Aerobic scope in tropical amphibians: Evolutionary patterns and implications for climate change vulnerability*
P25	Mohammad Shahidullah	University of Arizona	*TRPM3 activation reduces Na,K-ATPase activity in cultured mouse lens epithelium*

Poster ID	Lead Author (s)	Institution	Poster Title
P26	Theresa Thomas	University of Arizona, Phoenix	*Early circuit-directed rehabilitation reduced severity of late-onset symptoms and corresponding neurotransmission after diffuse traumatic brain injury in rat*
P28	Mitchell L. Haddock/Theresa Thomas	University of Arizona, Phoenix	*Sex-dependent chronic growth hormone dysregulation after experimental diffuse traumatic brain injury in rats*
P29	Qiongzi Qiu	University of Arizona	*The single-cell and spatial transcriptional landscape of advanced diabetic and hypertensive kidney disease in humans*
P30	Rory Lockett	Arizona State University	*Impact of urban diets on the nutritional physiology of mealworms*
P31	Riley Hamel	Midwestern University	*Mn Porphyrins Affect Hydrogen Peroxide Levels in Parkin Loss-of-Function Drosophila melanogaster*
P32	Adrienne C. Scheck	University of Arizona, Phoenix	*Preclinical and Clinical Data Supporting the Use of Ketogenic Therapy for the Treatment of Diffuse Intrinsic Pontine Glioma*
P33	Samuel Danoff	University of Arizona	*Age- and Aging-with-Injury: Temporal Microglial Morphological Profiles Indicate Unique Pathological Processes in Behaviorally Relevant Circuit Relays*
P34	Carrie Standage-Beier	University of Arizona	*Associations between EDARV370A and Glycemic Traits in Southwest Hispanics*
P35	Alec Robitaille	Midwestern University	*Effects of Macromolecular Crowding on the Enzyme Kinetics of Glutamate Dehydrogenase*
P36	Siddarth Gunnala	Midwestern University	*Understanding functional outcomes of hypoxia associated with over-supplementation of folic acid in Drosophila melanogaster*
P37	Christine Lee	Midwestern University	*Characterization of Serine protease inhibitors from Schistosoma mansoni as targets for public health intervention*
P38	Gia Vu	Grand Canyon University	*Cytotoxicity effects of Cyanidin Chloride and Withaferin-A on SHSY-5Y and CHLA-03 cell growths using MTT assay*
P39	Emran Hassanzada	Midwestern University	*Title: A case of a giant solitary trichoepithelioma*

Poster ID	Lead Author (s)	Institution	Poster Title
P40	Hunter Delmoe	Midwestern University	*Utilizing Biomarker Expression to Assess Platelet Activation During CPB*
P42	Shelby McMurray	Midwestern University	*Allelic modulation of small mesenteric artery mechanical properties in adult APOE3 & APOE4 Mice*
P43	Gaurika Shah	Arizona State University	*Efficacy of Rapamycin for Increasing Female Reproductive Longevity in Old Rhesus Macaques*
P45	Brikena Gusek	Midwestern University	*Vascular Manifestations of Marfan Syndrome: Insights into Aorta, Cerebral, Carotid, Coronary, and Pulmonary Arteries*
P46	Mobin Doost	Arizona State University	*Synergism of Novel Rexinoids and Vitamin D for the Potential Treatment of Human Diseases*
P47	Michael Sausedo	Arizona State University	*Development of Novel Drugs to Combat Alzheimer's Disease*
P48	Flavio Beas	Arizona State University	*Next Generation Novel Rexinoids as Potential Therapeutic Agents for Prevention and Treatment of Cancer and Alzheimer's Disease*
P49	Matt Lyons	University of Arizona, Phoenix	*Novel Nanoparticle Drug Delivery System Improves Brain Endothelial Cell Barrier Properties Following Acute Ischemia Reperfusion-like Injury*
P50	Ngunyi Fuangunyi	University of Arizona	*The Multifaceted Nature of Cardiovascular Disease and Why Race Matters*
P51	Brikena Gusek	Midwestern University	*Age-dependent cardiac and vascular changes in hAPOE3 and hAPOE4 mice: gender-specific insights*
P52	Randall Ordovich-Clarkson	Grand Canyon University	*Comparing Psilocybin to Metformin as Neuroprotective Agents Against Parkinson's Dementia*
P54	Jose Ek-Vitorin	University of Arizona	*Lens epithelium and mechanosensor channels*
P55	Lila Wollman	University of Arizona	*Saccharin exposure blunts the ventilatory response to hypoxia in adult rats*

Faculty

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P51: Age-dependent cardiac and vascular changes in hAPOE3 and hAPOE4 mice: gender-specific insights

Brikena Gusek, Zi Q Liu, Ashley N Christensen, Johana Vallejo-Elias, T Bucky Jones, Carleton (Buck) Jones and Delrae (Del) M Eckman

Midwestern University, Department of Biomedical Sciences, Glendale, AZ

Alzheimer's disease (AD) is the most common form of dementia and is the 6th leading cause of death in the US. Growing evidence supports a link between AD and cardiovascular disease (CVD). Variant isoforms of apolipoprotein E (APOE) are risk factors for both AD and CVD. Compared to the most common APOE isoform, APOE3, APOE4 increases AD risk. Pathogenic alterations in carotid artery (CA) function are known to contribute to neurodegenerative diseases including AD. In this study, we compared the neurovascular and cardiac function of young (3 to 4-month), adult (12 to 14-month), and aged (18 to 20-month) mice expressing human-APOE targeted replacement of APOE3 or APOE4. In vivo high-resolution ultrasound imaging was performed to evaluate the function of the heart, aorta, coronary, carotid (CA), and posterior cerebral artery (PCA) blood flow in young, adult, and aged hAPOE3 and hAPOE4 mice. Our data showed no significant change in the PCA and coronary artery peak blood flow velocity between groups. There was an age-related increase in carotid and aortic PWV in both male and female hAPOE3 and hAPOE4 mice ($p < 0.05$). Cardiac output (CO) showed no significant change in the female hAPOE3 or hAPOE4 mice. A significant increase in CO was observed in the aged hAPOE3 male compared to the young group, and a decrease in the aged male hAPOE4 group compared to the male aged hAPOE3 group ($p < 0.05$). There was a significant age-related increase in the stroke volume (SV) in the male hAPOE3 group and a decrease in the male aged hAPOE4 group compared to the male aged hAPOE3 group ($p < 0.05$). No changes were observed in the female groups. A significant age-related increase was evident in the LV mass of both male and female hAPOE3 and hAPOE4 groups ($p < 0.05$). The results suggest that vascular changes in these mice are primarily driven by age. The changes in CO and SV were driven by age-related changes in male APOE3 mice vs male APOE4 mice. CA PWV exhibited age-related changes, with allelic differences observed in female APOE-3 mice vs female APOE 4 mice. These data suggest modest, yet significant allele-related changes in CV structure and function in both male and female mice.

Presenting author: **Brikena Gusek**
Corresponding author: Del Ekman, deckma@midwestern.edu

Funding: ABRC / ADHS18-205211 (DME, JVE, CJ, JP, TV, TBJ). Arizona Alzheimer's Consortium (funded by the Arizona Department of Health Services, Contract No. CTR040636) and matching funds from Midwestern University (DME). Kenneth Suarez Research Fellowship (ZQL, AC), Biomedical Sciences (BG, DME), Biomedical Sciences Start-up Funds (DME)

Back to Friday Sessions Back to Saturday Sessions Back to Posters

Faculty

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P54: Lens epithelium and mechanosensor channels

Ek-Vitorin JF and Delaere NA

Department of Physiology, University of Arizona, Tucson, AZ

The lens epithelium expresses several mechanosensors, including Piezo1 and transient receptor potential (TRP) channels. While all these channels allow the entrance of calcium from the extracellular space, their specific roles in lens homeostasis are only partly defined and seem to differ. Thus, TRP channels of the vanilloid type 1 (TRPV1) open in response to cell shrinking, triggering an increase in Na/K/2Cl cotransporter, NKCC1, activity. The vanilloid type 4 (TRPV4) channels open in response to cell swelling, triggering an increase in Na, K-ATPase activity. Some data suggest that Piezo1 might operate upstream of TRPV4. We are currently exploring the role of the melastatin-related TRPM3 channel. In humans, an isoleucine-to-methionine mutation (I65M) of the TRPM3 channel has been linked to inherited cataract and glaucoma. When the TRPM3-I65M is expressed in the human lens epithelial cell line HLE B3, the cells display intriguing responses to agonists. Preliminary experiments using patch clamp techniques showed that groups of cells expressing the WT or the mutant TRPM3-I65M responded to pregnenolone (100 µM) with a fast shift of the resting membrane potential (RMP) toward more negative values (WT: from -20.7 ± 0.8 to -30.3 ± 5.7 mV, n = 5; I65M hemizygous: from -21.6 ± 1.7 to -30.5 ± 2.1 mV, n = 5; I65M homozygous: from -20.7 ± 0.8 to -34.5 ± 1.0 mV, n = 11; Mean ± SEM). This phenomenon is more remarkable because the HLE B3 cell line displays depolarized RMP values and small K+-like outward currents. In contrast, primary cultures of (mouse) lens epithelial cells (mLEC) displayed more negative RMP values (-52.3 ± 2.1 mV; n = 6) and larger outward currents in control conditions. Interestingly, in groups of mLEC, mechanical stimulation (external solution stream from a patch pipette) of a single cell produced a fast depolarization response in a separate neighbor cell, followed by a gradual recovery toward initial levels after the interruption of the stimulus. This simple experiment demonstrates 1) that the lens epithelium is sensitive to mechanical stimuli, and 2) that the mechanical stimulus caused a depolarizing response in contiguous neighbor cells. Whether this propagation occurs through gap junction channels and/or hemichannels remains to be determined. Using this direct approach to mechanical stimulation in combination with selective channel antagonists, we intend to explore the role of specific mechanosensitive channels and connexin channels, in the response of lens epithelium to mechanical stimuli.

Presenting author: **Jose Ek-Vitorin**, ekvitori@arizona.edu

Funding: 5R01EY029171-04, 2R01EY009532-28A1

Back to Friday Sessions Back to Saturday Sessions Back to Posters

Faculty

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P55: Saccharin exposure blunts the ventilatory response to hypoxia in adult rats

Wollman LW and Fregosi RF

University of Arizona, Tucson, AZ

Saccharin is the oldest zero calorie sweetener that is approved by the FDA and is one of the most important and widely used sweeteners worldwide. Saccharin is commonly used in animal studies as an additive to increase the palatability of other pharmacological treatments that are delivered through drinking water. For instance, in our own lab, we expose rats to nicotine mixed in 1% saccharin water, with 1% saccharin water alone as our experimental control. In preliminary experiments studying the ventilatory response to hypoxia in adult rats using plethysmography, we inadvertently found that female rats who drank 1% saccharin solution for four weeks (experimental control) did not achieve the same increase in tidal volume (true control: 2.28±0.36 mL, saccharin: 1.57±0.31 mL, P=0.0133) or overall ventilation (pulmonary ventilation; true control: 116.4±19.72 mL/min/100g; saccharin: 77.75±9.78 mL/min/100g, P=0.0328) during hypoxia compared to rats who drank regular tap water (true control). Importantly, while 1-2% saccharin water is typically found in the literature as a vehicle for nicotine delivery, this concentration equates to doses more than 10 times what is considered the safe daily dose for human consumption (5 mg/kg/day). Therefore, we tested the hypothesis that, like high-dose saccharin, exposure to low-dose saccharin impairs the ventilatory response to hypoxia in adult rats. Male and female rats drank tap water, 1% saccharin (high-dose), or 0.1% saccharin (low-dose) water for 4 weeks. We then measured tidal volume, breathing frequency, and pulmonary ventilation (tidal volume x frequency) during baseline breathing and during a brief 5-minute episode of isocapnic hypoxia (10% oxygen/balance nitrogen) and compared groups using a one-way ANOVA. In male rats, neither high- or low-dose saccharin exposure significantly altered breathing at baseline, however low-dose saccharin exposure significantly blunted the tidal volume response to hypoxia (Control: 2.7±0.38 mL, low-dose: 1.9±0.63 mL; P=0.0134). In female rats, low-dose saccharin significantly increased baseline tidal volume (Control: 0.91±0.13 mL, low-dose: 1.54±0.31 mL; P=0.0006) and pulmonary ventilation (Control: 28.07±8.25 mL/min/100g, low-dose: 42.70±11.25 mL/min/100g; P=0.0266) but had no effect on the ventilatory response to hypoxia. These data suggest that saccharin exposure alters breathing and the ventilatory response to hypoxia, which should be considered and further studied in both the context of saccharin solution as a vehicle in experimental models and saccharin exposure at levels like what is experienced by typical dietary consumption in humans.

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Funding: NIH/NHLBI 5K99HL164973-02 (Wollman)

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Faculty

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P24: Aerobic scope in tropical amphibians: Evolutionary patterns and implications for climate change vulnerability

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We measured aerobic scope of minimum and maximum metabolic rates (as both net and factorial) in tropical amphibians and determined patterns across evolutionary groups and environmental conditions. We measured metabolic rates of 54 species of amphibians across a 3,000 meter elevational gradient in the tropical Andes of southeastern Peru. Metabolic rates were measured using an infrared gas analyzer in a flow-through respirometry system to detect changes in carbon dioxide while amphibians were at rest and while constantly flipped onto their backs (to measure maximum metabolic rates). Aerobic scope can be described as net aerobic scope (NAS = maximum metabolic rate – resting metabolic rate) or factorial aerobic scope (NAS = maximum metabolic rate / resting metabolic rate), and the use of these measures varies across taxonomic groups. We found that NAS is redundant with the measure of maximum metabolic rate ($R2 > 0.95$ for both day and night), and that FAS may be a better measure of aerobic scope for amphibians that is more independent of resting and maximum metabolic rates. Phylogenetic analysis suggests that direct developing frogs in the family Craugastoridae have lower aerobic scopes than other amphibians. Direct developing amphibians may have evolved this life history by manipulating the rate of differentiation (i.e., development through metamorphosis) while still within terrestrial eggs. As temperatures increase across the globe, all amphibians are expected to have increased rates of differentiation as compared to growth, leading to latent effects (smaller body sizes, lower survival, lower reproductive rates, and more) across life stages. Our research suggests that in addition to many of the known latent effects in amphibians, higher temperatures may reduce aerobic scope and capacity in amphibians that could have important implications for vulnerability to climate change impacts.

Presenting author: **Michael Britton**, michael.britton.1@asu.edu

Funding: American Society of Ichthyologists and Herpetologists; Tinker Foundation Incorporated; Florida International University - Tropical Conservation Institute; Florida International University - University Graduate School

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Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P25: TRPM3 activation reduces Na,K-ATPase activity in cultured mouse lens epithelium

Mohammad Shahidullah[1], Faiz Ur Rahman[1], Jose EK Vitorin[1], Alan Shiels[2] and Nicholas A Delamere[1]

1. Department of Physiology, University of Arizona, Tucson, Arizona;
2. Department of Ophthalmology & Visual Sciences, Washington University in St. Louis.

The lens epithelium shows rich expression of a calcium permeable nonselective cation channel, TRPM3, and it is known that a single point mutation of TRPM3 gene (substitution of isoleucine by methionine at codon 65; I65M) causes early onset autosomal dominant human cataract. The normal role of lens TRPM3 is unknown. However, ion homeostasis is abnormal in cataractous human lenses from human subjects with the I65M TRPM3 mutation. From studies on transgenic mice, we have evidence the same mutation also disrupts Na-K homeostasis. Here we explore the effect of TRPM3 activation on ion transport in cells that express WT or the I65M mutant TRPM3. Intracellular calcium was measured in single cells by the Fura-2 ratiometric method. Rubidium (Rb) uptake, a measure of potassium entry, was measured in confluent monolayers by atomic absorption spectrophotometry. A TRPM3 agonist, CIM0216 (1 to 50 µM), reduced Rb uptake by ~20% in primary cultured WT mouse lens epithelium as well as human lens epithelium cell line (HLEB3). HLEB3 cells that had been stably transfected with the I65M mutant TRPM3 responded similarly but it was notable that CIM0216 had a 10-fold higher potency in the mutant v WT cells. TRPM3 activation by the agonist pregnenolone (100µM) was observed to cause a robust increase in cytoplasmic calcium that was inhibited by a TRPM3 antagonist primidone (50 µM). The Rb uptake response to CIM0216 was absent in cells that were bathed in calcium-free solution and blocked by primidone. The Rb uptake response to CIM0216 also was reduced by olgecepant (1µM) which is a calcitonin gene related peptide (CGRP) receptor antagonist. One of the principal roles of the CGRP receptor is to increase cellular cAMP and it was found that agents that increase cellular cAMP, including IBMX, forskolin and 8p-CPT-cAMP, all caused a marked reduction of Rb uptake. The findings are consistent with a reduction of Na,K-ATPase activity due to calcium entry that occurs on opening of TRPM3 channels. TRPM3-mediated activation of the CGRP receptor and subsequent stimulation of cAMP signaling might be involved in TRPM3 response. Studies are under way to test whether the I65M mutation of TRPM3 might cause an alteration in channel function that causes cataract.

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Funding: This work was supported by NIH grants 5R01EY029171-04 and 2R01EY009532-28A1

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Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P52: Comparing Psilocybin to Metformin as Neuroprotective Agents Against Parkinson's Dementia

Ordovich-Clarkson R, Jabbour M, Pelayo DA, Lara D, La Croix S, Mumman M, Stukas S, Anderson R, Meraz D, Anderson B, and Blake C

Grand Canyon University, Phoenix, AZ

Treatment of Parkinson's disease (PD) has remained largely unchanged and focuses primarily on symptomatic relief through activation of dopaminergic pathways. Currently, there are no proven prophylactic approaches to the prevention of PD. This systematic review seeks to compare two separate compounds, metformin (MTF) and psilocybin, as potential prophylactic therapeutics against the development of PD. The authors conducted a systematic review focusing on primary studies that test these compounds on animal models to determine if they might have any neuroprotective or neurodegenerative effects. The results of this review find that MTF may halt the progression of diseases such as PD through multiple mechanisms including reduced oxidative stress at the level of the mitochondria, thereby reducing α-synuclein related damage. Psilocybin, on the other hand, may increase repair of damaged neurons through psychoplastogenic activation of serotonergic pathways, particularly 5-HT2A receptor activation, ultimately increasing the release of brain derived neurotropic factor (BDNF) and the reduction of α-synuclein accumulation. Implications of this study include a need for further research in off-label use of MTF as well as further research into serotonergic compounds such as psilocybin for the treatment and prevention of neurodegenerative diseases.

Presenting author: **Randall Ordovich-Clarkson**, randall.clarkson@gcu.edu

Funding: All funding for the Parkinson's Project has been provided through the auspices of Grand Canyon University's Research & Design Program (RDP), including cost of publication. No additional funding has been obtained for this preliminary systematic review

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Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P26: Early circuit-directed rehabilitation reduced severity of late-onset symptoms and corresponding neurotransmission after diffuse traumatic brain injury in rat

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Nearly 6 million Americans currently cope with long-term disabilities after traumatic brain injury (TBI). While the benefits of neurorehabilitation are compelling to improve functional outcome, it remains unknown whether early rehabilitation can prevent or mitigate the severity of long-term post-TBI symptoms. In addition, it is not clear whether early rehabilitation can promote adaptive circuit reorganization to alleviate neurological symptoms. In this study, we tested the hypothesis that early circuit-directed, behavioral shaping rehabilitation will attenuate persisting symptom severity and corresponding glutamate neurotransmission after fluid percussion injury (FPI) in rats. Young adult, male and female Sprague-Dawley rats received midline FPI or sham surgery and were randomized to either whisker stimulation therapy (ST; 3 times a week for 2 consecutive weeks) or no stimulation (NS) groups (n=5-8/group). Data indicate that at 28 DPI, in both males and females had significantly higher ($p<0.001$) whisker sensory sensitivity scores after FPI indicating persistent hypersensitivity symptomatology postinjury that was mitigated by ST ($p<0.05$) (males: 42% and females: 50%) to Whisker Nuisance Task. Further, at 49 DPI, we observed that FPI increased potassium-evoked glutamate overflow in the ventral posteromedial nucleus (VPM) of the thalamus that was attenuated in male FPI rats (46%) treated with ST. These findings would seem to indicate that circuit-directed rehabilitation reduces persisting sensory sensitivity and glutamate overflow and supports the potential translational relevance of a model of sensory rehabilitation focused on specific brain-injured circuits at an early time-point post-injury to reduce chronic morbidities.

Presenting author: **Theresa Thomas**, theresathomas@arizona.edu

Funding: Funding: NIH (R01NS100793), VRP (P1-4010), PCH Mission Support

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Faculty

Postdoc/Research Associate

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P32: Preclinical and Clinical Data Supporting the Use of Ketogenic Therapy for the Treatment of Diffuse Intrinsic Pontine Glioma

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2. Cedars-Sinai Medical Center, Los Angeles, CA
3. MaxLove Project, Savannah, GA
4. Imperial College, London, UK

Diffuse intrinsic pontine glioma (DIPG) is an incurable, highly aggressive tumor arising in the brainstem of children. The average age at diagnosis is 7 years and patients have a median survival of less than 12 months. Radiation is the only known effective therapy for these tumors; however, this is only palliative. New therapies are needed to improve survival and quality of life. One promising therapeutic target is aberrant cancer cell metabolism which can be targeted using a therapeutic ketogenic diet (KD). We, and others, have used malignant glioma models and cultured cells to demonstrate that ketones have a variety of anti-tumor effects including reductions in tumor cell growth, growth factor expression, hypoxia, peritumoral edema, inflammation and pro-tumor transcriptional activators, enhancement of the anti-tumor immune response and increased histone deacetylase inhibitor activity. The KD also causes changes in the expression of specific microRNAs that contribute to these effects, as well as alterations in genomic and mitochondrial DNA acetylation. Many of these targets have been found in DIPG, making the KD a logical addition for the treatment of DIPG. This led to our current preclinical investigations of the effects of the ketone β-hydroxybutyrate (BHB) on cells from DIPG. BHB inhibits the growth of DIPG cells and potentiates the anti-tumor effects of radiation, due at least in part to inhibition of radiation-induced DNA damage repair. Furthermore, we see changes in mitochondrial proteins in DIPG cells treated with BHB. In light of increasing information about the potential utility of the KD, some parents of children with DIPG have been turning to the KD as a monotherapy or adjuvant therapy with radiation. We will report on the results obtained with 3 children treated with the KD as a monotherapy and in addition to other therapies. In all 3 cases the KD was well tolerated and the children showed improvements in physical function, energy, and reductions in tumor size. This preclinical and clinical data provides support for the use of a KD as an adjuvant therapy for children diagnosed with DIPG.

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Funding: Students Supporting Brain Tumor Research to ACS, Brain Tumour Research (BTR) and Brain Tumour Research Campaign (BTRC) to NS

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Postdoc/Research Associate

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P5: Marfan Syndrome Increases Apoptotic Neurons Female Mice

Harrison AM[1], Barrameda ME[1], Curry T[1,2], Anwar F[1], Nuthi M[1], Thomas TC[2], Esfandiarei M[1,2] and Jadavji NM[1,2]

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Marfan Syndrome (MFS) is an autosomal dominant genetic disorder that affects connective tissue throughout the body via mutations in the FBN1 gene. Fbn1 encodes the fibrillin-1 protein, a matrix glycoprotein responsible for the formation of structural support of elastin and collagen network via microfibrils, controlling the bioavailability of cytokines such as the transcription growth factor-beta and activation of matrix metalloproteinases. Individuals with MFS display symptoms of vascular dysfunction in addition to impaired skeletal and visual function, but the mechanisms of this multi-system dysfunction are still under investigation. While connective tissue disorders are known to present vascular abnormalities via their involvement in endothelial homeostasis and extracellular matrix turnover, there is still a gap in our understanding of the impact of monogenic connective tissue aberrations on the brain. This study aims to determine the impact of MFS on neurodegeneration, in brain tissue of male and female MFS mice as compared to controls. Mice with the Fbn1C1041G/+ mutation serve as a well-established MFS model that recapitulates the classic manifestations of aortic root aneurysm that is common in human MFS patients. Using this model, brain tissue was collected from mice, cryosectioned at 20µM thickness and serially mounted onto slides. Sections were stained for active caspase-3 and neuronal nuclei (NeuN). Stained tissue was imaged using a Leica TCS SPE confocal microscope to create z-stacks. Observers blinded to experimental conditions completed cell count colocalization of active caspase-3 and NeuN analysis using ImageJ (NIH). Data revealed increased levels of active caspase 3 in neurons within the sensory and motor areas of female MFS mice compared to controls, indicating a heightened susceptibility for neurodegeneration. Investigating neurodegeneration in brain tissue of an MFS mouse model system will provide understanding of the effects of Marfan Syndrome to inform specific clinical considerations.

Presenting author: **Alisha Harrison**, aharrison@midwestern.edu

Funding: AHA (20AIREA35050015), NIH (R15HL145646)

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Postdoc/Research Associate

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P1: Fatty acid-binding proteins promote pulmonary hypertension via glycolysis

Bin Liu, Dan Yi, Xiaomei Xia, Karina Ramirez, Michael Fallon and Zhiyu Dai

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We are seeking to elucidate the endothelial fatty acid metabolism role for obstructive vascular remodeling in the pathogenesis of PAH. In this study, we bred a severe mouse model of PH Egln1Tie2Cre mice with Fabp45-/- mice to generate Egln1Tie2Cre/Fabp45-/- mice. We applied single-cell RNA sequencing (scRNA-seq) to profile the pulmonary cells in Egln1Tie2Cre mice and Egln1Tie2Cre/Fabp45-/- mice. Human hPAEC from idiopathic PAH patients and healthy donors were used to measure fatty acidbinding protein 4 and 5 (FABP4 and FABP5) expression. siRNA-mediated knockdown of FABP4 and FABP5 and lentivirus-mediated FABP4 and 5 overexpression were performed to study cell proliferation, apoptosis, and glycolysis. Our scRNA-seq analysis demonstrated that both FABP4 and 5 were highly induced in the ECs of Egln1Tie2Cre mice. PAECs from IPAH patients also showed higher expression of FABP4 and 5. Knockdown of FABP4-5 reduced EC proliferation, starvation-induced Caspase 3/7 activity, and glycolysis. Overexpression of FABP4-5 promoted EC glycolysis and proliferation. Genetic deletion of Fabp4 and 5 in Egln1Tie2Cre mice exhibited a reduction of RVSP, RV hypertrophy, and reduction of EC glycolysis gene programming compared to Egln1Tie2Cre mice. In conclusion, we found that FABP4 and 5 control EC glycolysis and contribute to the development of PAH.

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Funding: R00HL138278; R01HL158596-01A1; R01HL162794-01A1; 20CDA35310084; RFGA2022-01-06

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Postdoc/Research Associate

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P45: Vascular Manifestations of Marfan Syndrome: Insights into Aorta, Cerebral, Carotid, Coronary, and Pulmonary Arteries

Gusek B, Kuechenmeister B, Barrameda E and Esfandiarei M

Midwestern University, Glendale, AZ

Marfan syndrome (MFS) is a multisystemic, connective tissue disorder caused by mutations in the fibrillin-1 gene with notable vascular effects leading to aortic aneurysm, dissection, and rupture. In the recent decades, better diagnostics, medical and surgical treatments have increased the life expectancy of MFS patients; hence, issues beyond the aortic root aneurysm, such as other central and peripheral vascular diseases, have become more concerning. Previous studies have reported evidence of carotid artery tortuosity and atherosclerosis in MFS patients. The prevalence of intracranial aneurysms in MFS patients is quadrupled compared to the general population. Fifty percent of school-age children with MFS have one or more neuropsychologic deficits. MFS patients also present with respiratory disorders such as chronic obstructive pulmonary disease and sleep disordered breathing. Cases of coronary artery aneurysms (CAA) and pulmonary artery dilation have also been described in MFS patients. CAAs are common in adult patients with MFS and are associated with a more severe aortic phenotype. However, no clear correlation between the aortic events and changes in other central and peripheral arteries, and their potential effects on cerebral blood flow and general vascular pathology in MFS has been established yet. The aim of this study is to investigate the structural and functional changes in the aorta and carotid artery (CA), and the velocity of blood flow in posterior cerebral artery (PCA), coronary and pulmonary artery in a mouse model of MFS using high resolution in vivo ultrasound imaging. At 7 months of age, in vivo ultrasound imaging was performed in male and female MFS and control mice to measure the CA pulse wave velocity (PWV), wall thickness and distensibility. Using color Doppler, we also measured the PCA, coronary and pulmonary artery blood flow velocity. Our data shows that the CA PWV, an index of arterial wall stiffness, was significantly increased in MFS male and female mice compared to controls. CA wall thickness was also significantly increased, while CA wall distensibility was decreased in MFS mice. The blood flow velocity in PCA, coronary and pulmonary artery was significantly decreased in MFS mice when compared to healthy controls. This study provides an early insight into the disease progression of MFS and shows the presence of vascular dysfunction in the CA, PCA, coronary, and pulmonary artery in MFS mice. Future correlation analyses of all vascular events in the mouse model will provide a roadmap for all vascular events in MFS, assisting clinicians in designing preventive regimens to slow down or block multi-organ vascular dysfunction in MFS patients.

Presenting author: **Brikena Gusek**, bgusek@midwestern.edu

Funding: Midwestern University, NIH (R15HL145646)

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Postdoc/Research Associate

Talk: Friday October 27th, 10:00 AM

S1.1: The molecular functions of HDAC9 in the development of e-cigarette-induced atherosclerosis by promoting endothelial-mesenchymal transition

*__Liu CW__[1], Le HHT[1], Denaro P 3rd[1], Attaluri A[2], Wendt TS[1], Ma XK[1], Qiu SF[1], Hale TM[1], Gonzales RJ[1], Ong SG[3] and Lee WH[1]

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3. University of Illinois College of Medicine, Chicago, IL

The process of endothelial-mesenchymal transition (EndMT) is known to play a role in the development of several cardiovascular diseases (CVDs), including atherosclerosis. Recently, the use of electronic cigarettes (e-cigs) has been associated with atherosclerosis, but the underlying mechanisms remain unclear. The present study endeavors to explore the impact of e-cigs on EndMT and its association with atherosclerosis, with a specific focus on the role of histone deacetylase 9 (HDAC9), using in vitro and mouse models. We found that exposure to e-cigs induces EndMT in ECs, which is marked by significant alterations in epigenetic modifications. This mechanism shows reduced histone modifications associated with gene activation, such as H3K9 and H3K27 acetylation, with a concomitant increase in H3K9 and H3K27 trimethylation. Of the known HDACs, only HDAC9 was found to be impacted by e-cigs use in endothelial cells (ECs). Importantly, we observed that HDAC9 inhibition prevented EndMT in ECs following e-cigs exposure. Further experiments have demonstrated that HDAC9 was found to interact with 14-3-3 proteins and that the binding of 14-3-3 to HDAC9 leads to the sequestration of these proteins in the cytoplasm. To investigate whether the potential impact of e-cigs on the expression of histone deacetylase 9 (HDAC9) during atherosclerosis, 12-week-old ApoE−/− mice were exposed to either room air or e-cigs aerosol for 2 hours/day for five days/week for 12 weeks while on a high-fat diet. Our result has revealed that mice exposed to e-cigs exhibited elevated levels of atherosclerotic lesions and aortic oxidative stress, as evidenced by Oil Red O and DHE staining. Additionally, there was a notable increase in HDAC9 expression and EndMT in the aorta and mouse aortic ECs of these mice, in comparison to those exposed to fresh air. Furthermore, e-cigs-exposed mice had increased vascular EC fibrosis and endothelial dysfunction as detected by Masson's trichrome staining and wire myography, respectively. Collectively, these findings indicate that e-cigs are associated with vascular dysfunction that is correlated with heightened HDAC9 and EndMT activation, which could lead to long-term adverse vascular consequences in patients with atherosclerosis.

Presenting author: **Chen-wei Liu**, cwliu0617@arizona.edu

Funding: University of Arizona RII Faculty Seed Grant (to Dr. Lee), Arizona Department of Health Services (ADHS) New Investigator Awards (to Dr. Lee)

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Research Associate

Talk: Friday October 27th, 11:00 AM

S2.1: Sex-Specific Regulation of Gonadal Hormone Receptor Gene Expression Following Ang II Infusion in Spontaneously Hypertensive Rats

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Hypertensive heart disease is characterized by cardiac fibrosis in the left ventricle (LV). Angiotensin II (Ang II) promotes cardiac fibrosis through direct actions on cardiac fibroblasts. Gonadal hormones are known to impact cardiac fibrosis either through direct actions on fibroblasts or through modulation of Ang II receptors. We have previously shown that Ang II infusion alters collagen gene expression in a sex-specific manner. The present study seeks to further understand our observed sex difference by investigating the impact of Ang II on gonadal hormone regulation in the left ventricle (LV) during Ang II infusion. Male and female SHR (15-week-old) were infused with Ang II (400ng/kg/min, s.c.) or vehicle for 2 weeks via an osmotic mini pump (n=8-11 per group per sex). Col1a1, estrogen receptors α and β (ER-α, ER-β), androgen receptor (AR), 5α-reductase (5α-R), and aromatase gene expression in the left ventricle was assessed via RT-qPCR and data analyzed by Two-Way ANOVA. Ang II infusion significantly increased ER-α gene expression in males, but not females (sex x Ang II interaction p=0.0303). ER-β gene expression was also significantly increased in the males (p=0.0066), but not females. AR gene expression remained unchanged in the Ang II-infused males, but was significantly reduced in females when compared to control (sex x Ang II interaction p=0.0084). Ang II significantly increased 5α-R gene expression in male (p=0.0024), but not female LV. Aromatase gene expression was near the limit of detection yet showed an increasing trend for both male and female Ang II-infused animals when compared to control. Changes in gonadal hormone gene expression did not significantly correlate with Col1a1 gene expression. Future studies will seek to understand the consequences to changes in local gonadal hormone regulation on cardiac structure and function during Ang II infusion.

Presenting author: **Dana Floyd**, danabaileywoods@arizona.edu

Funding: NHLBI (R01HL153112)

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Postdoc/Research Associate

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P16: Direct Evidence of Metabolic Interactions between PBDEs and Gut Microbes: an In Vitro Metabolomics Study

*Jinhua C[1, 2], Yan J[2], Freeman L[2], Kyle K[3], Matthew JC[4], Julia YC[3] and Haiwei G[1, 2]

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2. Florida International University, Port St. Lucie, FL
3. University of Washington, Seattle, WA
4. University of New Mexico Health Sciences, Albuquerque, NM

Microplastics (MPs) are small plastic fragments that have diameters less than 5 mm in size, and they can be found in natural environments, everyday essentials, and living organisms. Due to their detrimental impacts on aquatic and terrestrial ecosystems, MPs have emerged as a severe public health concern. The hypothesis of this study is that MPs exposure will impact the gut microbiome in multi-omics levels. Three bacterial strains, including wild-type Escherichia coli (E. coli) MG1655 and two probiotics Nissle 1917 and Lactobacillus rhamnosus (L. rhamnosus), were first used in this study to comprehensively investigate the impacts of MPs exposure. The bacterial strains were individually cultured in an anaerobic chamber and exposed to 1 µm polystyrene MPs with different concentrations in the culture medium. Our results showed that MPs exposure caused a significant reduction of bacterial viabilities for all three bacterial strains in a dose-dependent manner. In addition, metabolomics showed that there are significant in multiple metabolic pathways, especially in pyrimidine metabolism, arginine biosynthesis, and tryptophan metabolism. Interestingly, targeted analysis on tryptophan metabolism showed that all of the three bacterial strains have affect in serotonin pathway. Furthermore, we extracted the gut microbiota from the fecal samples freshly collected from C57BL/6 mice, and we employed 16S rRNA sequencing to investigate alterations in taxonomic data due to exposure to MPs. In order level, Lactobacillales and Erysipelotrichales componence are changed after MPs exposure. Our metabolomics findings unveiled that tryptophan related metabolites were altered by MPs. In summary, this study showed that MPs exposure causes comprehensive changes to healthy gut microbiota at multi-omics levels, which could provide insights to understand the mechanistic effects of MPs exposure to humans.

Presenting author: **Jinhua Chi**, jinhua.chi@asu.edu

Funding: NIH (1R01ES030197, 1P01HL146369-01A1)

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Postdoc/Research Associate

Talk: Saturday October 28th, 9:00 AM

S5.1: Age-dependent cerebral microvascular dysfunction in ApoE4 knock-in mice

Silva JF and Pires PW

University of Arizona, Tucson, AZ

Apolipoprotein E (ApoE) is involved in the transport of cholesterol through its interaction with ApoE receptors. ApoE is found in three isoforms: ε2, ε3, and ε4, of which the ApoE4 isoform is strongly linked to an increased risk of Alzheimer's disease, a condition associated with significant vascular dysfunction. Although there has been significant progress in understanding how ApoE4 drives amyloid pathology in the brain, its effect on cerebrovascular function remain poorly defined. We hypothesized that presence of ApoE4 allele will lead to age-dependent cerebral microvascular dysfunction in mice. Parenchymal arterioles from 6-months-old and over 18-months-old male and female ApoE4 and ApoE3 (controls) knock-in mice were isolated for ex vivo using pressure myography. Basal cortical perfusion and neurovascular coupling were evaluated by laser speckle contrast imaging. Data are means ± SEM, analyzed by two-tailed Student's t-test. Arterioles from 6-months-old ApoE4 mice have significantly lower myogenic tone compared with aged-matched ApoE3 mice, a difference that was not present in arterioles from mice >18 months-old. Further, although 6-months-old ApoE4 mice did not show significant structural and biomechanical arteriolar changes, our preliminary data showed that arterioles from 18-months-old ApoE4 mice have increased vessel and lumen diameters with no changes in wall thickness when compared to arterioles from ApoE3 mice, suggesting the occurrence of outward eutrophic remodeling. As a consequence of the increase in lumen diameter without adaptations in wall thickness, arterioles from ApoE4 mice showed high levels of radial wall stress when compared with ApoE3. Basal cerebral perfusion shows a trend to be higher in 6-months-old ApoE4 mice when compared with ApoE3. There was no change in neurovascular reactivity in mice with 6-month-old or over 18-months-old. In conclusion, our preliminary data suggest that presence of the ApoE4 allele leads to an age-dependent increase in spontaneous myogenic tone and structural outward arteriole remodeling in parenchymal arterioles of mice.

Presenting author: **Josiane da Silva**, josianefs@arizona.edu

Funding: National Institutes of Health (R01 AG073230) and the Alzheimer's Association (AARGD-21-850835)

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Postdoc/Research Associate

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P3: The E3 Ubiquitin-Protein Ligase Synoviolin (Syvn1/Hrd1) Promotes Adaptive Decreases in Cardiac Myocyte Protein Synthesis via eIF2α/ATF4 Pathway Activation

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As the heart undergoes pathologic remodeling, an imbalance between protein synthesis and degradation in cardiac myocytes due to the increases in protein synthesis relative to protein degradation, may happen, leading to the activation of endoplasmic reticulum stress response (ERSR). Activated ERSR can be either protective or may lead to cell death. We previously found Synoviolin (Syvn1), also known as HMG-CoA reductase degradation protein 1 (Hrd1), as an ER-localized protein is upregulated in cardiac myocytes during ER stress and mediates degradation of toxic misfolded proteins, providing an adaptive remodeling response. Nevertheless, the potential effects of Hrd1 on protein synthesis and cardiac myocyte growth remain unknown. Upon ER stress, the PERK (protein kinase RNA (PKR)-like ER kinase) branch of the ERSR, modulates protein synthesis by phosphorylation of the α-subunit of translation initiation factor 2 (eIF2α). This inhibits global translational initiation, reducing the load of unfolded proteins entering the ER. PERK activation also results in the induction of translation of selective mRNAs, including activating transcription factor 4 (ATF4), which activates the transcription of a wide range of genes involved in adaptation to stress conditions. We hypothesized that eIF2α/ATF4 pathway activation constitutes a newly-discovered mechanism for balancing the proteome in cardiac myocytes. To examine the effects of Hrd1 overexpression on cardiac myocyte growth, we generated an adenovirus encoding Hrd1 (AdV-Hrd1), which resulted in overexpression of Hrd1 in cultured neonatal rat ventricular myocytes (NRVM) by about 3-fold over control. Using photomicroscopy and morphometry we determined cell size and found overexpression of Hrd1 decreased NRVM surface area. Moreover, when we measured protein synthesis using 3H-leucine incorporation into TCA-precipitable proteins in cardiac myocyte cultures, a decrease in protein synthesis rate was found following Hrd1 overexpression. We next focused on identifying the mechanism of Hrd1-mediated growth inhibition and found increases in Hrd1 lead to activation of PERK, increased eIF2α phosphorylation, and ultimately ATF4 induction and increased ATF4 target gene expression. Moreover, treatment of cultured cardiac myocytes with ISRIB, a chemical inhibitor of the PERK pathway, blocked Hrd1-mediated ATF4 target gene induction. These findings suggest Hrd1 is a critical regulator of cardiac myocyte protein synthesis and subsequent growth and that increases in Hrd1 lead to activation of the PERK branch of the ER stress response, which results in inhibition of global protein synthesis, and activation of ATF4.

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Funding: University of Arizona - Phoenix

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Postdoc/Research Associate

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P29: The single-cell and spatial transcriptional landscape of advanced diabetic and hypertensive kidney disease in humans

*Qiu Q[1], Liu D[2], Liu Y[2], Wu X[2], Liu Y[1], Liu Z[2], Wang F[2] and Liang M[1]

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Diabetes and hypertension, the two most common causes of chronic kidney disease (CKD), can both lead to renal inflammation and fibrosis through a complex interplay among multiple cell types. However, the similarities and differences between the two pathogenic mechanisms remain understudied, including the involvement of cell organization and related biological processes. We generated an integrative cell landscape of CKD using single-nucleus gene expression and spatial transcriptome profiling in kidney samples from five patients with advanced diabetic nephropathy (DN), six patients with advanced hypertensive nephropathy (HN), and three normal controls. We obtained a total of 107,350 nuclei and 7,463 spatial spots to investigate the cell composition and the context of spatial niches. Significant hallmark changes were observed in both types of CKD, including elevated immune cell infiltration and fibrosis. Some alterations were more pronounced in HN, such as more severe podocyte loss, a greater increase of myofibroblasts, and more T cell infiltration. Molecularly, HN showed distinct gene expression variations and pathways in multiple epithelial cells, including POD, PEC, Inj. PT, TAL. Additionally, we unveiled the temporal trajectory of PT damage through spatial co-localization patterns, showing early recruitment of Tregs, DCs, and myofibroblast. Our findings provide a cell landscape of advanced diabetic and hypertensive CKD in humans, shedding light on the cellular and molecular basis of these diseases.

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Funding: US National Institutes of Health grants DK129964, HL149620, and HL121233

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Postdoc/Research Associate

Talk: Friday October 27th, 11:15 AM

S2.2: Sex-specific effects of transient losartan treatment on angiotensin II-induced fibrogenic signaling in the heart of spontaneously hypertensive rats

Silva Jr SD, Floyd DB and Hale TM

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Angiotensin II (Ang II) is a primary mediator of the renin angiotensin system (RAS) with strong profibrotic effects, mediated in part through increased levels of reactive oxygen species (ROS). Although there are no therapies able to reverse fibrosis, inhibition of the RAS can decelerate the advance of fibrosis. Our goal was to investigate the impact of prior transient losartan (AT1 receptor antagonist) treatment in the oxidative stress response and fibrotic signaling profile in the left ventricle (LV) in response to Ang II. Male and female spontaneously hypertensive rats were initially treated with vehicle or losartan (30mg/kg per day) for two weeks. To assess long term protection of losartan treatment, after two-weeks of washout, the rats then received Ang II (400ng/kg/day) for 2 additional weeks (n=3/group). Protein levels of pro-oxidant (NOX-2) and antioxidant (SOD1, SOD2) enzymes, fibrosis marker (OPN, LOX) in the LV were measured by western blotting. Collagen 1, 3 and 4 gene expression were measured by qRT-PCR. Cardiac hypertrophy was evaluated by the LV/tibia Length (LV/TL) ratio. Data were analyzed by 2-way ANOVA. OPN expression was differentially impacted by losartan in male vs. female rats (2-way interaction, $p=0.0097$), resulting in a 30% lower expression in female rats transiently treated with losartan vs saline, with no change in males. LOX expression was 10% lower in male and 34% in female rats pretreated with losartan vs saline (treatment effect of $p < 0.026$). SOD2 expression was significantly higher vs saline controls in Ang II treated male (↑47%) and female (↑33%) LV of rats transiently treated with losartan (treatment effect, $p=0.0099$). NOX2 and SOD1 expression was not affected by sex nor treatment. There was a tendency toward a reduced gene expression for collagen 1 in males and collagen 3 in females transiently treated with losartan – although neither reached statistical significance. Collagen 4 gene expression was significantly reduced in both male (↓50%) and female (↓30%) rats previously treated with losartan, compared to saline (treatment effect, $p < 0.04$). Prior losartan treatment resulted in a 13% lower LV/TL in males, with no impact in female rats (sex x treatment interaction: $p=0.014$). In summary our data indicate a sex-specific fibrotic response to Ang II following transient losartan treatment that may modulate cardiac remodeling and function. Due to the lack of specific anti-fibrotic drugs, identifying the mechanisms involved in transient losartan mediated cardio-protection, and how these effects differ between males and females is essential to improve the negative outcomes triggered by fibrosis.

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Funding: NHLBI R01HL153112

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Graduate/Professional Student

Talk: Friday October 27th, 5:00 PM

S4.2: Characterization of HCN channel subtypes and the contribution of Ih in postnatal maturation of muscarinic modulation of inspiratory bursting at hypoglossal motoneurons

Melliza AM, **Osbourne A**, Lee C and Revill AL

Midwestern University, Glendale AZ

The inspiratory phase of breathing is characterized by stiffening of the upper airway, mediated in part by excitatory output from the hypoglossal (XII) motor nucleus. The magnitude of this excitation is decreased during sleep, likely due to decreasing levels of noradrenaline and increasing levels of acetylcholine. Perplexingly, however, the effects of muscarinic acetylcholine receptors (mAChRs) have an excitatory effect on inspiratory bursting in neonatal preparations, which becomes inhibitory in adult preparations. mAChRs modulate several ion channels and characterizing muscarinic effect changes at the XII nucleus will help to explain the mechanism of the inhibitory shift over postnatal maturation. The hyperpolarization activated cyclic nucleotide gated (HCN) channel is positively modulated by mAChRs. HCN channels give rise to Ih, a mixed cation current activated at hyperpolarized membrane potentials that contribute to membrane depolarization. Ih increases dramatically with postnatal maturation in XII motoneurons (MNs). Thus, we hypothesize that 1) the effects of muscarinic modulation of Ih increases with postnatal maturation, and 2) that muscarinic activation of Ih contributes to the net inhibitory component of muscarinic modulation of inspiratory bursting at XII motoneurons. To test our hypotheses, we will use molecular and neuroanatomical techniques to evaluate changes in expression pattern of the four HCN genes and proteins at the XII nucleus across postnatal maturation in CD1 mice. We used the rhythmic medullarly slice preparation to test the functional effects of muscarinic modulation of Ih on inspiratory bursting in neonatal CD1 mice (postnatal day, P0-P4) in combination with pharmacological block of Ih with ZD7288. Local application of muscarine (100μM, 30s) in the XII motor nucleus increased inspiratory burst amplitude (189 ± 58% of baseline, n = 9). Contrary to our hypothesis, there was no statistically significant difference between inspiratory burst amplitude elicited by muscarine in the presence of ZD7288 (192 ± 47% of baseline, n = 9) versus with the aCSF vehicle control (174 ± 43% of baseline, p = 0.098). These data suggest that blocking the Ih does not significantly change the response of inspiratory burst activity to muscarine when compared with an aCSF vehicle control in P0-4 mice. Since the magnitude of Ih increases with postnatal maturation in XII MNs, future research will elucidate whether the Ih contribution to muscarinic modulation of inspiratory bursting changes with postnatal maturation.

Presenting authors: **Aleanna Melliza** and **A. Osbourne**, Aleanna.Melliza@midwestern.edu

Funding: NIH/NHLBI Funding: R15HL148870

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Graduate/Professional Student

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P35: Effects of Macromolecular Crowding on the Enzyme Kinetics of Glutamate Dehydrogenase

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The purpose of the study is to determine the effects of macromolecular crowding on the enzyme kinetics of glutamate dehydrogenase (GDH). Macromolecular crowding is a measure of the intracellular concentration of macromolecules which ranges from 80-400 mg/mL and corresponds to 5%-40% of the cell volume. This so-called "macromolecular crowding" has significant consequences on cellular processes. These crowding conditions can be simulated in vitro using crowding agents such as polyethylene glycol (PEG), Ficoll, dextran 150 (Dex150), and other large, inert polymers. Crowding agents range in size and structure and can also include proteins such as egg white or bovine serum albumin (BSA). Spectrophotometry was used to measure the mean absorbance over time at varying concentrations of glutamate dehydrogenase. Slopes were plotted over time and Michaelis Menten curves were created to calculate a Vmax and Km for each run in the presence of various macromolecular crowding agents. Results showed that macromolecular crowders have significant effects on GDH kinetics. Dex150 decreases GDH Vmax. The relative Km is significantly different in BSA versus Dex150 when varying glutamate or NAD+, but it is not when using NADP+. Crowder concentration appears to increase the effect of macromolecular crowding in GDH. Various crowding agents do not have significant effects on GDH denaturation. The effect of a carboxylic group has significant effects on kinetics. The conclusions demonstrate that crowding agents have significant impacts on kinetics and pose interesting questions about how organic crowding in vivo affects cellular processes and physiology.

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Funding: Hobart and William Smith Colleges Undergraduate Research Fund

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Graduate/Professional Student

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P12: SGK1 Promotes Atrial Pathology in HFpEF

Bilal AS, Hahn SA, Murray VB, MacDonnell LF, Glembotski CC and Blackwood EA

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Heart failure with preserved ejection fraction (HFpEF) has emerged as the greatest unmet medical need in cardiovascular medicine, comprising 50% of all heart failure cases, with a US prevalence of ≥3 million. HFpEF uniquely affects the function of both cardiac atria and ventricles independently where in atria it leads to pathological atrial remodeling that includes atrial myocyte dysfunction and marked collagen deposition arising from increased myofibroblast activation. Pathological atrial remodeling has become widely recognized as a primary prognostic criterion in the clinic that best predicts the incidence of HFpEF and its severity long-term, underscoring the need for studies of atrial myopathy and fibrosis in this context. A recent report suggests the serum/glucocorticoid kinase 1 (SGK1) plays a deleterious role in the myocyte in obesity-induced atrial fibrillation (AF). Because AF is a comorbidity of HFpEF, we reasoned SGK1 may have a similarly deleterious role in the atria during HFpEF. The purpose of this study is to elucidate the role of SGK1 in the atria of HFpEF, with the hypothesis that SGK1 promotes pathological atrial remodeling. Wild-type or cardiac-specific SGK1 loss-of-function (SGK1cKO) mice were subjected to either a normal or HFpEF diet and monitored longitudinally. To specifically focus on the role of SGK1 in atrial myocytes and atrial fibroblasts, primary neonatal rat atrial myocytes (NRAMs) and fibroblasts (NRAFbs) were used and subjected to siRNA-mediated knockdown of Sgk1 (siSgk1) or a small molecular inhibitor of SGK1. NRAMs were further subjected to SGK1 gain-of-function (GOF) studies facilitated by adenovirus-mediated expression of either wild-type or a kinase-dead mutant of SGK1 (SGK1 KD). SGK1cKO mice subjected to HFpEF were protected from cardiac pathology and fibrotic remodeling induced by HFpEF. Mechanistically, SGK1 GOF studies in NRAMs showed a significant increase in mTORC1 signaling that was repressed with SGK1 KD or siSgk1. Because mTORC1 signaling has been implicated in adverse metabolic remodeling, these results suggest the protective effect of SGK1cKO, in vivo, is in part mediated through decreased mTORC1 signaling. In NRAFbs SGK1 LOF repressed myofibroblast differentiation. Together, these data suggest SGK1 contributes to atrial pathology in HFpEF via promoting mTORC1-mediated pathological remodeling in atrial myocytes and an enhanced fibrotic state in atrial fibroblasts. Future studies are aimed at delineating the mechanism by which SGK1 regulates atrial fibrosis in HFpEF and whether targeting SGK1 represents a novel therapeutic strategy for AF and HFpEF.

Presenting author: **Alina Bilal**, asusanab@gmail.com

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New Investigator Award from the Arizona Biomedical Research Centre (RFGA2022-010-10)

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Graduate/Professional Student

Talk: Saturday October 28th, 2:00 PM

S6.3: Progranulin and Lysosomal pH: implications for potential new therapeutic strategy for neurodegenerative diseases

Yang A, Harrison A, Uppalapati CK, Pascual AS, Biparva P, Leyva KJ and Hull EE

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Progranulin (PGRN) deficiency and lysosomal dysfunction have been independently linked to Alzheimer's disease. Several lines of evidence suggest that there is a link between PGRN and lysosomal function. PGRN is a pleiotropic signaling molecule whose activity depends upon differential proteolytic processing. The different PGRN subunits generated during processing can regulate inflammation, lysosomal function, and/or growth. Not only is the lysosome a site of PGRN processing, the resulting PGRN subunits promote the function of several lysosomal proteases. In addition, in models of PGRN insufficiency, increasing the levels of PGRN restores lysosomal function and reduces inflammation. Thus, this work investigates the link between lysosomal function and PGRN synthesis and processing. Experiments utilized the SW13 human adrenal carcinoma cell line that exists in two epigenetically distinct subtypes. PGRN processing and production were analyzed by both ELISA and immunoblotting using antibodies that bind to characterized epitopes. Live cell measurements of pH were performed using the ratiometric DND 160 fluorescent dye. Lysosomal proteolytic assays were performed by measuring fluorescent intensity produced after proteolysis of an endocytosed substrate. Lysosomes, purified by ultracentrifugation, were analyzed by lipidomic and proteomic mass spectrometry. Results suggest that differential processing of PGRN occurring within each SW13 subtype is correlated to both differences in rate of growth and lysosomal pH. Specifically, the slow-growing, metastatic subtype produces higher levels of PGRN and expresses increased levels of matrix metalloproteinases (MMP) 2/9. compared to the more proliferative subtype. Interestingly, when PGRN is exogenously added to the culture medium, the proteases expressed by each subtype influences whether PGRN will be processed into a product(s) promoting growth or a product(s) promoting inflammation. We also show that the pH of lysosomes in each subtype differs, with the slowly growing, metastatic subtype having a significantly higher pH than the proliferative subtype. This result suggests that lysosomal proteases, which have increased activity at a more acidic pH, may be responsible for producing a PGRN product(s) that promotes growth in the proliferative subtype, while the more alkaline lysosomal pH of the slowly growing subtype does not. Ongoing experiments address the possibility that decreasing lysosomal pH may shift the processing of PGRN, influencing the biological activities associated with this versatile signaling molecule. As mutations in the PGRN gene are implicated both in dysfunctional lysosomal pH and a variety of neurodegenerative diseases, these results may provide a novel approach to regulate proper intracellular functions to slow or prevent the development of disease.

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Graduate/Professional Student

Talk: Friday October 27th, 11:45 AM

S2.4: Sex-Specific Regulation of Catecholamine Signaling in Rats Exposed to Dexamethasone In Utero and Angiotensin in Adulthood

Sharma A[1], **Alvarez J**[2], Madhavpeddi L[3] and Hale TM[3]

1. University of Arizona College of Medicine, Tucson, AZ
2. Arizona State University, Tempe, AZ
3. University of Arizona College of Medicine, Phoenix, AZ

Pregnant women who are at risk of pre-term delivery are given the synthetic glucocorticoid dexamethasone (DEX) to stimulate fetal lung development as it is not degraded by 11ß-hydroxysteroid dehydrogenase, enabling DEX to freely cross through the placenta and act on the developing fetus. Our lab has previously found that in-utero DEX exposure increases stress-induced blood pressure and heart rate responses in female, as well as autonomic dysregulation in the adult offspring. Angiotensin II (Ang II) induces hypertension and cardiac remodeling in part through activation of the sympathetic nervous system. Given these prior findings, this project explores whether prenatal DEX exposure alters the response of Ang II on cardiac sympathetic nervous system regulation. Pregnant rats were administered either vehicle (20% w/v 2-hydroxypropyl ß-cyclodextran) or the glucocorticoid DEX (0.4 mg/kg body weight, i.p) on gestation days 18-21. When offspring reached ~15 weeks of age, groups were administered either subcutaneous AngII (200 ng/kg per min) as a cardiovascular challenge or saline as experimental control for four weeks. To measure local sympathetic signaling, tyrosine hydroxylase (TH) was analyzed as it serves as the rate limiting step of catecholamine synthesis while catechol-O-methyltransferase (COMT) was selected as it catalyzes catecholamine breakdown. Gene expression of adrenoreceptor ß1 (Adrb1) was measured to assess receptor availability for sympathetic activity. Data were analyzed by 3-way ANOVA with sex, prenatal treatment (i.e., DEX vs. Vehicle), and postnatal treatment (i.e., saline vs. AngII) as the variables. There was an overall main effect of prenatal treatment to reduce TH expression in the LV ($p=0.018$), although this effect was more pronounced in males. COMT expression was found to be significantly impacted by sex, prenatal treatment, and post-natal treatment (3-way interaction, $p=0.016$). Thus, the degree to which DEX and Ang II impacted COMT expression differed by sex. There was a sex x postnatal treatment interaction ($p=0.013$) on ADRB1 expression whereby expression was increased by Ang II only in female hearts. Although prior studies have shown that Ang II can increase local sympathetic activity in the heart, the present data suggest that prenatal treatments disrupt this response in a sex-specific manner. Moreover, sex and prenatal treatment were greater drivers of local sympathetic regulation than Ang II.

Presenting authors: **Arpan Sharma** and **J. Alvarez**, arpans44@arizona.edu

Funding: NIMH/ORWH 1U54MH118919

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Graduate Student/Medical

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P2: Inspiratory Muscle Strength Training to Improve Cardiometabolic Health in Patients with Type 2 Diabetes: Protocol for the Diabetes Inspiratory Training (DIT) Clinical Trial

Reed BL, Tavoian D, Bailey EF, Funk JL and Coletta DK

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Type 2 diabetes mellitus (T2DM) is a complex, chronic metabolic disease that carries with it a high prevalence of comorbid conditions, making T2DM one of the leading causes of death in the US. Traditional lifestyle interventions (e.g., diet, exercise) can counter some negative effects of T2DM, however, participation in these activities is low. Thus, it is critical that we develop and investigate novel management strategies that effectively reduce cardiometabolic disease risk and address barriers to adherence. High-resistance inspiratory muscle strength training (IMST) is a timeefficient and simple breathing exercise that significantly reduces BP and improves vascular endothelial function in adults with above-normal blood pressure. Herein we describe the study protocol for a randomized clinical 78 trial to determine the effects of a 6-week IMST regimen on glycemic control and insulin sensitivity in adults with T2DM. Our primary outcome measures include fasting plasma glucose, fasting serum insulin, and insulin resistance. Secondary outcome measures include casual systolic BP and endothelialdependent dilation. Further, we will collect plasma for exploratory proteomic analyses. This trial seeks to establish the cardiometabolic effects of 6 weeks of high-resistance IMST in patients with T2DM.

Presenting author: **Baylee Reed**, bayleereed@arizona.edu

Funding: Spark funding, University of Arizona

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Graduate/Professional Student

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P34: Associations between EDARV370A and Glycemic Traits in Southwest Hispanics

Standage-Beier CS[1], Klimentidis YC[2], Soltani L[3] , Spegman DJ[3], Garcia LA[4], De Filippis E[5], Shaibi GQ[6], Parra OD[4], Mandarino LJ[4, 7] and Coletta DK [4, 7]

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Ectodysplasin A, a transmembrane protein and member of the TNF family, along with its receptor, EDAR, are pivotal in the development of human ectodermal tissue, including hair, sweat glands, teeth, and mammary glands. Recently, a single nucleotide polymorphism (SNP) in EDAR, rs3827760 or EDARV370A, has garnered attention due to its associations with breast density and metabolic syndrome (MetS) traits in Southwest Hispanic participants from the Arizona Insulin Resistance (AIR) registry and Sangre por Salud (SPS). In this study, we performed a replication association analysis of EDARV370A in Hispanic participants from El Banco por Salud (El Banco). El Banco sample comprised 1,030 participants with 69% female, age 51.8 ± 0.47 years, and body mass index (BMI) 32.1 ± 0.21 kg/m2. We performed SNP genotyping of EDARV370A, analyzing its association with MetS traits using linear regression models in El Banco individually and combined with AIR and SPS. Genotype frequencies in El Banco were (TT:344, TC:511, CC:175), met Hardy Weinberg Equilibrium (HWE), and had a minor allele frequency (MAF) of 42%. Combined El Banco, AIR, and SPS analysis had genotype frequencies of (TT:784, TC:1211, CC:530), meeting HWE, and had an MAF of 45%. Analyses were all adjusted for age, sex, and BMI. In El Banco individually, we observed significant associations with hemoglobin A1c (HbA1c) and fasting plasma glucose, with p-values and means by genotype of p=0.008 (TT:7.23, TC:7.79, CC:7.69) and p=0.04 (TT:7.74, TC:8.24, CC:8.43), respectively. When we combined El Banco data with AIR (n=502) and SPS (n=993), creating a total sample size of 2,525 individuals, we continued to find an association with HbA1c (p=0.03). Interestingly, in sex-stratified fully adjusted models, we found that females exhibited a significant association with hemoglobin A1c (p=0.03), whereas males did not reach statistical significance. Our findings provide further evidence supporting the role of EDARV370A in MetS, particularly with glycemic traits. Notably, this study identifies a novel association in females, shedding light on the potential gender-specific effects of EDARV370A. In conclusion, these results highlight the importance of targeted research in understanding the impact of carriers of this SNP on health outcomes.

Presenting author: **Carrie Standage-Beier**, cstandagebeier@arizona.edu

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Graduate/Professional Student

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P37: Characterization of Serine protease inhibitors from Schistosoma mansoni as targets for public health intervention

Lee C, Hall B, Sanford Leah and Molehin AJ

Midwestern University, Glendale, AZ

Schistosomiasis is a neglected tropical disease caused by blood flukes belonging to the genus Schistosoma. Over 250 million people in over 78 countries result in over 280,000 deaths annually. Infections in definitive vertebrate hosts are caused by one of three clinically relevant Schistosoma species: Schistosoma haematobium, S. japonicum, and/or S. mansoni. Serine protease inhibitors (serpins) are a superfamily of proteins that antagonize the activity of serine proteases and play key roles in various physiological functions including inflammation, complement activation, fibrinolytic pathways, and blood coagulation. In pathogens, serpins are thought to have evolved specifically to limit host immune responses. The roles played by serpins in parasitic helminths are less well understood, although some are thought to be associated with host immune modulation. In this study, we aimed to characterize serpins from Schistosoma mansoni and evaluate their role in schistosome immune modulation and/or evasion. Using bioinformatics and proteomic tools, we have identified two S. mansoni-specific serpin genes termed Sma1 and Sma2 and successfully cloned both genes for recombinant protein production. Sma1 and Sma2 genes were identified through database mining of previously published microarray data, cloned and detailed sequences, structural analysis and comparative modelling carried out using various bioinformatic and proteomics tools. Sma1 and Sma2 contain an open reading frame of 1360 and 1654 encoding proteins of 406 amino acid residues and 387 amino acid residues respectively. Detailed sequence analysis, comparative modeling and structural-based alignment revealed that Sma1 and Sma2 contain the essential structural motifs and consensus secondary structures typical of inhibitory serpins. The presence of an N-terminal signal sequence in Sma2 suggests that it is a protein secreted through the classical pathway, while Sma1 lacking an N-terminal signal sequence might be secreted through other non-classical pathways. Gene transcriptional profiling for both Sma1 and Sma2 across all Schistosoma mansoni life cycle stages as well as their native protein expression determination are currently underway. Future studies are aimed at immunolocalizing Sma1 and Sma2 and evaluating the functions of both serpins using in vitro immune-related serine protease inhibition assays. We also plan to determine the immunological profile of these proteins in mice immunized with recombinant Sma1 and Sma2. We believe data obtained from this study will increase our understanding of the roles played serpins in S. mansoni host immune modulation.

Presenting author: **Christine Lee**, christine.lee1@midwestern.edu

Funding: Biomed MBS Intramural grant and CGS Intramural Seed Grant

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Graduate/Professional Student

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P7: Cadaveric investigation of posterior interventricular artery variation and review of clinical implications

Lane CP[1], Douglas M[1], Mckoy M[1], Karupakula ES[2], Patel HC[2], Ruble KP[2], Campbell TL[2,] Ritzman TB[2], Smith HF[1] and Lynch L[1]

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Heart dominance is determined based on which of the coronary arteries give rise to the posterior interventricular artery (PIA). In individuals with right dominant hearts, the PIA is a branch of the right coronary artery, whereas, in individuals with left dominant hearts, the PIA is a branch of the left coronary artery. Individuals whose PIA receives contributions from both the left and right coronary arteries are described as having co-dominant hearts. In left heart dominance, the left coronary artery dominates blood supply to the left ventricle and interventricular septum, which is correlated with increased risk and poor patient outcomes in the setting of acute coronary syndrome (conditions brought on by sudden, reduced blood flow to the heart). In this study, we investigate the PIA of 147 cadaveric donors from the gross anatomy laboratories at Midwestern University Glendale and Downers Grove Campuses to evaluate the frequency of left heart dominance in our cadaveric sample. Of the 147 donors investigated, 117 (79.6%) are right dominant, 19 (12.9%) are left dominant, and 11 (7.5%) are codominant. Our sample has a slightly elevated prevalence of left heart dominance compared to previously cited estimates (5-10%), which may warrant further investigation in a larger sample. Future studies of cardiac variation will continue to examine heart dominance and potential associations with other anatomical variants such as patent ductus arteriosus and foramen ovale.

Presenting author: **Colton Lane**, colton.lane@midwestern.edu

Funding: Funding for the cadaveric donors was provided by the Anatomy Department at Midwestern University. Otherwise, this study did not receive any specific funding

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Graduate/Professional Student

Talk: Saturday October 28th, 1:45 PM

S6.2: Effects of Ex Vivo Sulforaphane Stimulation in Human PBMCs Before & After Exercise

Rodriguez D[1], Chassman C[1], Condes A[1], Policastro E[1], Eggler A[2], Buscaglia R[1] and Traustadóttir T[1]

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Redox signaling is an increasingly appreciated mechanism of exercise-induced health benefits. However, several studies show impaired redox signaling responses to exercise in older organisms. Additional interventions to augment the effects of exercise may be necessary to achieve greater health benefits. Sulforaphane is a phytochemical found in cruciferous vegetables, that is known to stimulate the main regulator of cell protection, Nrf2. The purpose of this study is to test the hypothesis that combining acute exercise (in vivo stimulus) with ex vivo sulforaphane (SFN) treatment will induce greater response of Nrf2 activation and Nrf2-regulated gene expression in human PBMCs compared to exercise alone. To date, 7 individuals have completed the study, 4 men and 3 women (mean age: 67 ± 4y). They performed a VO2max test, and a 30-minute acute exercise trial (AET) on separate visits. Blood was drawn before and immediately after the AET to isolate PBMCs and incubate samples with and without SFN treatment (Treatments: DMSO control, SFN, exercise (EX), and EX+SFN). PBMCs were harvested after 2- and 5-hours for measures of Nrf2 activation and gene expression for NQO1, HO1, GR, and GCLC targets. The effect of SFN stimulation is supported by a four-fold increase in NQO1, HO1, and GR over control ($p<0.05$), in the group as a whole. Looking at individual responses for gene expression data, two distinct patterns emerged: individuals who had a lower response to exercise but an improved response to the combined EX+SFN treatment (group 1, n=4, average fold change from control; EX: <2-fold, EX + SFN: 4-5 fold) and individuals who had a higher response to exercise and a worse response to the combined treatment (group 2, n=3, average fold change from control; EX: 2-3 fold, EX+SFN:<2-fold). These divergent responses were not sex specific but could be influenced by fitness level and basal redox balance. Additional data collection and analysis are in progress. Overall, these preliminary data suggests that the combined treatment of EX+SFN may only benefit certain individuals. Furthermore, we are testing whether a sulforaphane supplementation (in vivo) prior to acute exercise will have a similar effect to the ex vivo SFN treatment.

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Funding: NIH/NIA 1 R15 AG074088

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Graduate/Professional Student

Talk: Friday October 27th, 3:30 PM

S3.2: Impact of Plant-Derived Dietary Fibers on Energy and Glucose Homeostasis

Howard EJ, Meyer RM, Weninger SN, Kangath A and Duca FA

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The gut microbiota contributes to the development of metabolic disease, and it is well known that diet shapes the gut microbiota, emphasizing the need to better understand how diet impacts metabolic disease via alterations in the gut microbiota. Dietary fiber intake is linked with improvements in metabolic homeostasis in humans, and specific fibers beneficially alter the gut microbiota, promote weight loss, and improve glucose homeostasis. In a previous study, we found that specific plant-based flours, including wheat and barley, supplemented into a high-fat diet (HFD) reduced body weight and adiposity and improved glucose tolerance in rats. However, whether this was due to specific fibers within the flours remains unknown. To test the impact of various dietary fibers on energy and glucose homeostasis, we supplemented HFD-fed mice with 5 different fibers (beta-pectin, beta-glucan, wheat dextrin, resistant starch, or cellulose as a control) at 10% (w/w) for 18 weeks (n=12/group), measuring body weight, adiposity, indirect calorimetry, and glucose tolerance. We found that only beta-glucan supplementation in a HFD decreased adiposity and body weight gain and improved oral glucose tolerance compared to HFD with cellulose, while all other dietary fibers failed to improve metabolic homeostasis. Supplementation with beta-glucan increased energy expenditure and locomotor activity in mice compared to HFD-cellulose. Despite a lack of metabolic effect for most dietary fibers, all fibers supplemented into a HFD shifted the cecal microbiota composition and exhibited increased SCFA levels. However, only beta-glucan supplemented mice specifically exhibited an increase in Ileibacterium relative abundance, as well as higher cecal butyrate levels compared to HFD-cellulose. These findings demonstrate that beta-glucan is a promising therapeutic option for diet-induced obesity and glucose tolerance, possibly via increased energy expenditure. Future studies will investigate the role of the gut microbiota and butyrate in the metabolic improvements observed with beta-glucan supplementation in HFD-feeding.

Presenting author: **Elizabeth Howard**, elizabethhoward@arizona.edu

Funding: USDA National Institute of Food and Agriculture, AFRI 2019-67017-29252

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Graduate/Professional Student

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P39: A case of a giant solitary trichoepithelioma

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2. Midwestern University, Arizona College of Osteopathic Medicine, Glendale, AZ

Patient History: 62-year-old female with a history of intellectual disability, mild cerebral palsy, bipolar disorder was seen in clinic for a 4 cm 2 bump on her right scalp. On exam, the lesion was mobile, soft and rubbery with no surface changes and observation was elected. She returned 18 months later with the lesion having more than doubled in size to 10.64 cm 2 .

Histology: Within the dermis there is a neoplasm composed of well-circumscribed aggregations of basaloid epithelial cells that form immature follicular structures and are surrounded by dense fibrous connective tissue.

Diagnosis: Given the size of the tumor, it was best characterized as a "giant solitary trichoepithelioma" (GST), which is a rare variant of a trichoepithelioma. 1 There have been less than 30 cases reported in the literature, and less than a handful to have occurred on the scalp. 2 GST is a benign tumor of the follicular germ cells that is defined as a trichoepithelioma that is larger than 2 cm. 1,2 GST most commonly presents in the 6th decade and has the potential to ulcerate and grow large within a matter of months. 3,4,5 With the largest reported case measuring 17 cm, GST's have the ability to continually grow and cause damage to local structures. 6 There is a theoretical risk of malignant transformation, however, to our knowledge there have not been any reported cases of this.

Treatment: Our patient's neoplasm, given its size and location, warranted surgical excision. Mohs surgery was performed and the tumor was cleared after 2 stages.

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Presenting author: **Emran Hassanzada**, emranhassanzada@gmail.com

Funding: Financial Disclosures/Conflicts of Interest: None

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Graduate/Professional Student

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P21: IRE1α protects against cardiac fibrosis via regulating selective mRNA degradation

Parker S, **Sandoval E**, Hahn S, Glembotski C and Blackwood E

University of Arizona College of Medicine - Phoenix, Phoenix, AZ

Upon cardiac injury, cardiac fibroblasts are activated and differentiate into myofibroblasts, which work to maintain cardiac structure and function by secreting extracellular matrix (ECM) components. However, if this persists, it will lead to stiffening of the myocardium and heart failure. The unfolded protein response (UPR) responds to an increased demand for folding of nascent secreted ECM proteins trafficked through the endoplasmic reticulum such as collagen. IRE1α, the most evolutionarily conserved arm of the UPR, acts adaptively both by enhancing the folding of secreted proteins and reducing protein synthesis burden as occurs during pathologic cardiac fibrosis. The following experiments investigated a novel mechanism of IRE1α which protects against the differentiation of cardiac fibroblasts into myofibroblasts, with the goal of developing new therapeutic interventions. In vitro experiments utilized primary cardiac fibroblasts (CFBs) which were cultured with transforming growth factor beta (TGF-β) to promote activation. Small molecule targeting approaches were utilized to specifically inhibit or activate IRE1α. IRE1α-floxed mice were injected with AAV9 to knockout IRE1α specifically in myofibroblasts (IRE1mfbKO) and were subjected to transverse aortic constriction (TAC) as a model of heart failure to stimulate fibroblast activation, in vivo. While small molecule activation of IRE1α significantly blunted CFB activation in response to TGF-β, specific inhibition of IRE1α's endonuclease domain enhanced CFB responsiveness to TGF-β. Importantly, this effect occurred independent of IRE1α's canonical mechanism of activating the transcription factor, XBP1s, implicating regulated IRE1α-dependent decay (RIDD) as a novel anti-fibrotic protective mechanism. Transcriptomics and targeted RT-qPCR analysis of CFBs identified TMEM100 as a novel RIDD target that contributes to fibrotic pathology upon impaired degradation. Finally, in response to TAC, IRE1mfbKO mice exhibited an exacerbated decrease in cardiac function and marked increase in interstitial fibrosis. IRE1α was shown to provide protection against pathologic differentiation of CFBs in response to TGF-β or TAC via regulating the degradation of the transmembrane protein TMEM100. Thus, small molecule targeting of IRE1α represents a novel approach to mitigating cardiac fibrosis.

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Graduate/Professional Student

Talk: Saturday October 28th, 10:00 AM

S5.5: Endothelial KIR2 channel dysfunction in aged cerebral parenchymal arterioles

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2. Loma Linda University, Loma Linda, CA

Aging is associated with cognitive decline via incompletely understood mechanisms. Cerebral microvascular dysfunction occurs in normative aging, particularly impaired endothelium-mediated dilation. Parenchymal arterioles are bottlenecks of the cerebral microcirculation, and dysfunction in those arterioles cause a mismatch in nutrient demand and delivery, leaving neuronal populations at risk. Extracellular nucleotides, such as ATP and ADP, elicit parenchymal arteriole dilation by activating endothelial purinergic receptors (P2Y), leading to opening of K+ channels, including inwardly-rectifying K+ channels (KIR2). These channels can amplify hyperpolarizing signals, resulting in robust dilation. However, it remains unknown if endothelial P2Y and KIR2 signaling are altered in brain parenchymal arterioles during normative aging. We hypothesized that aging impairs endothelial P2Y and KIR2 function in parenchymal arterioles. We observed reduced dilatory response to the purinergic agonist 2-methyl-S-ADP (1 μM) in pressurized arterioles from Aged (>24-month-old) mice despite similar hyperpolarization in endothelial cells tubes. No differences were observed in vasodilation or endothelial cell hyperpolarization to activation of small- and intermediate-conductance Ca2+-activated K+ channels (KCa2.3 / KCa3.1) by NS309. Freshly-isolated endothelial cell tubes from Aged mice had a smaller hyperpolarization to 15 mM [K+]E than Young mice (4-6-months-old). Paradoxically, dilatory responses of Aged arterioles to 15 mM [K+]E was larger than in Young, and was unchanged by endothelium removal. Further, we observed a significant increase in myogenic tone in Aged parenchymal arterioles, which was not enhanced by endothelium removal. We conclude that aging impairs endothelial KIR2 channel function in the cerebral microcirculation with possible compensation by smooth muscle cells.

Presenting author: **Felipe Polk**, fpolk@arizona.edu

Funding: Funding: National Institutes of Health (RO1 AG073230), National Heart, Lung and Blood Institute (R00140106), and the Alzheimer's Association (AARGD-21-850835)

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Graduate/Professional Student

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P48: Next Generation Novel Rexinoids as Potential Therapeutic Agents for Prevention and Treatment of Cancer and Alzheimer's Disease

Flavio F. Beas, Sabeeha M. Reshi, Carl E. Wagner, Pamela A. Marshall and Peter W. Jurutka.

Arizona State University, Tempe, AZ

Bexarotene, an FDA-approved synthetic retinoid-X-receptor (RXR) ligand, causes a signaling cascade that results in the transcription and control of RXR target genes. Bexarotene is used to treat all stages of cutaneous T-cell lymphoma (CTCL) by inducing apoptosis, thus reducing T-lymphocyte proliferation. CTCL is a rare type of blood cancer that can be life threatening, and the type of CTCL also determines the treatment protocol. While bexarotene can be an effective treatment in many patients with CTCL, this drug is employed at high doses and is known to exhibit potent side effects such as hypothyroidism and hyperlipemia. In addition to its use in CTCL and in "off-label" treatment of some other cancers, bexarotene has been demonstrated to decrease levels of amyloid-β in transgenic mice expressing familial Alzheimer's disease (AD), thus showing a promising reduction in neurodegenerative symptoms. The heterodimerization of RXR with liver-X-receptors (LXR) and peroxisome proliferation-active receptor-gamma (PPARγ) is thought to control cholesterol efflux, inflammation, and transcriptionally regulates the production of apolipoprotein (ApoE) in the brain. Thus, the development of more potent bexarotene analogs with lower side-effects profiles could have profound implications in the treatment of both CTCL and AD. In the present study, we synthesized 26 novel rexinoids with a similar structure to bexarotene that may be effective activators of RXR. In order to investigate the ability of these 26 novel rexinoids to bind and activate the RXR-RXR homodimer, we performed a mammalian two-hybrid assay (M2H) and an RXR response element (RXRE)-mediated luciferase assay to evaluate the efficacy of these possible RXR agonists. The M2H assay demonstrated that a subset of our analogs were able to drive RXR-RXR dimerization and the RXRE assay suggested that the same subset of analogs promoted RXRE-directed transcription. We also performed an LXRE-mediated luciferase assay to analyze the role of our novel compounds as activators of LXRE-based transcription and as inducers of ApoE mRNA in human U87 brain cells. The experiments revealed that several of these unique rexinoids expressed higher activation of LXRE-mediated transcription along with elevated ApoE gene expression versus bexarotene. Taken together, the results in these multiple assay systems show potential for novel bexarotene analogs as next-generation therapeutics that may combat neurodegenerative diseases, such as AD, and could also be promising drugs for treatment of CTCL and other cancers, while mitigating the significant side effects of high-dose bexarotene therapy.

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Funding: NIH R15 CA249617

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Graduate/Professional Student

Talk: Saturday October 28th, 9:45 AM

S5.4: Role of exosomal miRNAs in the crosstalk between endothelial cells and macrophages following e-cig exposure

Le HHT[1], Liu CW[1], Attaluri A[2], Denaro P[1], Ong SG[3] and Lee WH[1]

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2. Arizona State University, Tempe, AZ
3. University of Illinois Chicago, Chicago, IL

Electronic cigarettes (e-cigs) are alarmingly popular among children, with an estimated current usage rate of over 2.5 million middle and high school students in the United States. Although often marketed as a safer alternative to traditional tobacco cigarettes, e-cigs are also known to result in endothelial dysfunction, a major risk factor for the development of cardiovascular diseases, which is the leading cause of morbidity and mortality worldwide. Despite the relationship between e-cigs and vascular function, the mechanisms involved in e-cig-induced endothelial dysfunction remain unclear. Using human induced pluripotent stem cell-derived endothelial cells (hiPSC-ECs) from healthy donors, we previously modeled cardiovascular risks associated with e-cigs. Our central hypothesis is that crosstalk between endothelial cells and macrophages following e-cig exposure, via endothelial-derived exosomal transfer of microRNAs (miRNAs), results in pro-inflammatory macrophage polarization and contributes to e-cig-induced vascular toxicity. We treated hiPSC-ECs with diluted e-cig aerosol extract to induce endothelial dysfunction for 48 hours and collected the resultant conditioned medium. Exosomes were isolated from the conditioned medium using sequential ultracentrifugation and characterized using nanoparticle tracking analysis (NTA). We initiated terminal differentiation of THP-1 monocytes into macrophages using PMA and incubated them with e-cig-induced endothelial-derived exosomes (e-cig-exos) for 48 hours. The e-cig-exos led to an M1 pro-inflammatory state in our THP-1 macrophages, resulting in production of M1-associated genes, including pro-inflammatory cytokines IL-1α/β and TNFα. RNA was extracted from the exosomes and subjected to sequencing for small RNAs. 61 miRNAs were found to be upregulated and 166 miRNAs were downregulated in the e-cig-exos. Gene Ontology and Kyoto Encyclopedia of Genes and Genome (KEGG) pathway analyses of the predicted genes of the top 10 differentially expressed miRNAs showed that pathways related to macrophage function were perturbed. Our results suggest that following e-cig exposure, the interplay between endothelial cells and macrophages via endothelial transfer of exosomes promotes an inflammatory environment that enables the progression of vascular dysfunction. The identification of exosomal miRNAs involved in e-cig-induced endothelial-vascular crosstalk can further elucidate our understanding of endothelial biology as well as the vascular complications associated with e-cig usage. However, more work is needed to determine the function of these differentially expressed miRNAs.

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Funding: Valley Research Partnership P1 Grant (VRP70 to Dr. Lee & Ms. Le); University of Arizona RII Faculty Seed Grant (to Dr. Lee); Arizona Department of Health Services (ADHS) New Investigator Awards (to Dr. Lee)

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Graduate/Professional Student

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P40: Utilizing Biomarker Expression to Assess Platelet Activation During CPB

Hunter Delmoe, Mitchell Rentschler, Meghal Sancheti, Zeyu Song, Breanne Collison, Weidang Li, Charlotte Bolch, Thomas Rath and Hamid H Darban

Midwestern University, Glendale, AZ

Cardiopulmonary bypass (CPB) triggers an inflammatory response due to blood interaction with foreign surfaces within the CPB circuit. This initiates the clotting cascade, leading to the release of platelet activation biomarkers such as platelet factor 4 (PF4). Premature platelet activation during CPB can result in post-surgery bleeding complications and an increased risk of transfusions. Therefore, measuring these biomarkers can serve as an indicator to assess platelet activation during CPB. The Balance® Biosurface from Medtronic and Xcoating™ Surface from Terumo are claimed to be biocompatible, reducing platelet adhesion during surgery. In this study, we employ these two coated CPB circuits from Medtronic and Terumo, utilizing bovine blood to measure PF4 levels while simulating typical CPB runs. We established a CPB laboratory protocol based on prior literature. To assess and compare the biocompatibility of the two circuits, we employed bovine blood donations in two different types of CPB circuits. The post-dilutional hematocrit was maintained at 25%, a Heparin bolus was added to the collected blood, and the activated clotting time was sustained at 600 seconds. Both circuits were primed with the same quantity of Crystalloid. Hypothermia (32^{o}C) was induced at 5 minutes into CPB, with normothermia (37^{o}C) achieved after 45 minutes. Blood samples were collected before the commencement of CPB and at 5 minutes, 45 minutes, and 90 minutes during CPB. These samples were subjected to centrifugation, and the collected plasma was analyzed for platelet biomarker measurements using ELISA assays. PF4 was quantified to assess platelet activation. ELISA results consistently indicated an increase in PF4 concentrations, suggesting ongoing platelet activation during CPB runs. Both Medtronic and Xcoating surfaces behave similarly and work at reducing platelet activation.

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Funding: Midwestern University

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Graduate/Professional Student

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P42: Allelic modulation of large mesenteric artery mechanical properties in adult APOE3 & APOE4 Mice

McMurray SL, Walton IW, Frantz JE, Wagner K, Gusek B, Stimpson A, Jones CB and Eckman DM

Midwestern University, Glendale, AZ

Previous studies from our lab have demonstrated age-related changes in vascular structure/function in posterior cerebral arteries and (PCA) and left common carotid artery (CA) in male and female mice expressing human-ApoE targeted replacement of APOE3 (B6.129P2-Apoetm2(APOE*3)MaeN8) and APOE4 (B6.129P2-Apoetm3(APOE*4)MaeN8) (Taconic Labs). Therefore, we hypothesized that similar changes may be observed in the systemic circulation. We isolated 4th/5th-order mesenteric arteries (MAs) from adult 6-month-old male and female mice expressing hAPOE3 (n=3) or hAPOE4 (n=4). MA segments (5-8 mm in length) were rapidly isolated and cannulated on an arteriograph to assess vascular mechanical properties; lumen diameter (LD), wall thickness (WT), wall:lumen ratio (WL), distensibility (Dist), stress/strain (SvS), compliance (C), incremental modulus of elasticity (Einc), and calculated pulse wave velocity (cPWV) under passive conditions (Ca2+-free Krebs + diltiazem) at intraluminal pressures ranging from 10mm Hg - 140mm Hg. In addition, phenylephrine-induced contraction and potassium-induced contraction were assessed using Ca2+-containing Krebs. Data was analyzed using two-way ANOVA, Student's t-test, and analysis of nonlinear fit. Values were considered statistically different at $P<0.05$. In our preliminary data, passive measures of LD, Dist, and C were similar in APOE3 and APOE4 mice. WT and WL were less, while wall stress, strain, cPWV, and Einc were greater in APOE3 versus APOE4 mice ($P<0.05$). There was a leftward shift in SvS in the APOE4 compared to APOE4 mice. Active measures of phenylephrine- and potassium-induced contraction were similar in APOE3 and APOE4 mice. This data suggests there are changes in structure of MA associated with allelotype. Furthermore, these preliminary findings suggest that MAs from APOE4 mice may exhibit a trend toward a hypertensive phenotype.

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Graduate/Professional Student

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P15: Impact of Heavy Metals on Bone Porosity in North American River Otter

Tuscano J, Valdez D and Lynch LM

Midwestern University, Glendale, AZ

The detrimental effects of heavy metal exposure on health have long been a subject of concern and while the adverse effects of heavy metals on various organ systems have been extensively studied, their impact on bone health, specifically bone porosity, remains unknown. Using the North American river otter, a bioindicator of environmental contamination, this study aims to explore the relationship between heavy metal exposure and bone porosity.

We quantified bone porosity via microCT scans of the right tibiae, femora, and radii of North American river otters from populations exposed to varying heavy metal concentration across the United States. Heavy metals of interest included aluminum, arsenic, manganese, and lead, all of which are known environmental pollutants and may accumulate in bone tissue over time. We found differences in bone porosity between populations of high heavy metal concentration, intermediate concentration, and low concentration, with populations exposed to high heavy metal concentrations having decreased bone porosity percentages in all three limb elements, on average.

Future projects will analyze changes in bone mineral density (BMD) to further assess the impact of heavy metals on bone strength, which may shed light on the potential risks posed by heavy metal exposure to bone health. This is will be essential to informing preventative public health measures aimed at preserving bone integrity in particularly vulnerable populations.

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Funding: Midwestern University

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Graduate/Professional Student

Talk: Friday October 27th, 5:30 PM

S4.4: Characterizing Muscarinic Receptor Subtype Roles in Inspiratory Bursting of Hypoglossal Motoneurons in Postnatal Mice

Vellutato J, Kurup A, Jeong KT, Dudley SK, Wealing JC and Revill AL

Midwestern University, Glendale, AZ

Loss of tongue muscle (innervated by hypoglossal (XII) motoneurons) tone is responsible for airway obstruction during sleep. Contributing factors include loss of noradrenergic drive and activation of muscarinic acetylcholine receptors (mACHRs). While noradrenergic effects are well studied, less is known about muscarinic effects. In mice, XII motoneurons express four mAChRs; M1, M3, and M5 are excitatory while M2 is inhibitory. We hypothesize that M2 is upregulated with postnatal maturation whereas M1, M3, and M5 are downregulated. We therefore expect that activation of M1, M3, and M5 receptors will potentiate inspiratory bursting early in postnatal development whereas activation of M2 receptors will inhibit inspiratory bursting later in postnatal development. To test this, we utilized rhythmic medullary slice preparations from mice at postnatal days 0-5 (P0-5) and P9-14, which contained preBötzinger Complex (site of inspiratory rhythm generation) and XII motoneurons. Blocking M1 receptors locally with pirenzepine (10 µM & 100 µM) decreased the muscarinic potentiation of inspiratory bursting in P0-5 mice to 94±15% and 72±14% of control muscarine response [n=9, $p<0.05$]. Activating M1 receptors locally with cevimeline (1 mM) for 30s and 60s increased burst amplitude to 116±7% and 117±7% of control muscarine response [n=6, $p<0.05$]. Local application of methoctramine (MTH) in P0-5 mice at 2 µM had no effect on inspiratory burst potentiation (71.14±14.59% of control, n=25). Bath application of MTH similarly had no effect (62.94±80.35% of control, n=9) while preliminary analysis suggests there may be increasing effect of blocking M2 receptors with postnatal maturation ($p=0.0452$ vs control, n=10). Bath application of M3 receptor antagonist 4-DAMP in P0-5 mice at 10 nM had no effect on muscarine-potentiated bursting (172 ± 12% vs 178 ± 30% muscarine control), whereas application at 100 nM decreased burst potentiation (133 ± 12% vs 178 ± 30% control muscarine response) [n=4, $p<0.05$]. However, bath application with another M3 receptor antagonist, J Fumarate 104129, had no significant effect in P0-5 mice (188 ± 46% at 0.6 nM [n=6], 185 ± 32% at 6 nM [n=6], and 144 ± 24% at 60 nM [n=4] vs 176 ± 34% muscarine control [n=6]). Overall, our data partially supports a role of M1 receptors contributing to muscarinic potentiation of inspiratory bursting in XII motoneurons, with the contributions of M2 and M3 appearing insignificant early in postnatal life. Preliminary analysis suggests that M2 has a larger contribution later in development, but future work will further evaluate the contribution of muscarinic receptor subtypes later in postnatal life.

Presenting author: **Julius Vellutato**, julius.vellutato@midwestern.edu

Funding: Kenneth A Suarez Grant

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Graduate/Professional Student

Talk: Friday October 27th, 3:15 PM

S3.1: Correlation of Plasma LPL Activity with Measures of Body Composition across Subjects with Varying Levels Insulin Sensitivity

Johnsson KA[1], Frietas EDS[1], De Filippis E[2], Roust L[2] and Katsanos C[1]

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2. Mayo Clinic, Scottsdale AZ

Lipoprotein Lipase (LPL) hydrolyzes triglycerides into free fatty acids in plasma for use and/or storage in tissues (i.e., adipose tissue, skeletal muscle) and subsequently controls the rate of fatty acid uptake. Impaired LPL activity (LPLa) has been associated with many unfavorable outcomes such as obesity, elevated triglycerides, and impaired glucose uptake. How LPLa relates to body composition in humans that span a wide range of obesity and insulin resistance remains unknown. Eighteen subjects of various degrees in terms of obesity (BMI 18 – 45 kg/m2) between the ages of 19 to 45 were evaluated for insulin sensitivity using an oral glucose tolerance test (i.e., Matsuda Index). Matsuda-determined insulin sensitivity ranged between 1.79 to 28.97. To resemble postprandial conditions, insulin was infused (0.5 mU/kg/min) for 30 minutes prior to the determination of LPLa to resemble increased postprandial insulin response. To release endothelial-bound LPL, subjects received an injection of intravenous heparin (75 UI/kg). Plasma samples were collected 10 minutes after the heparin infusion and analyzed for LPLa using commercialized ELISA kit (ab204721). Body composition was determined using a dual-energy X-ray absorptiometry (DEXA) scan. Group differences were compared using Person's Correlation to evaluate relationships between LPLa and several body composition parameters. Alpha level was set at $P < 0.05$. Average subject's characteristics were as follows: age = 27± 3.9, BMI = 27 ± 3.7, Matsuda = 9.62 ± 3.5. LPLa was positively correlated ($P<0.05$) with total lean mass ($r = 0.58$), free fat mass ($r = 0.56$), and BMI ($r = 0.49$). Notably, increased LPLa was positively correlated with both increased total body fat ($r = 0.54$, $p = 0.02$) and increased android fat ($r = 0.58$, $p = 0.01$). This data suggests that across tissues, intravascular plasma LPLa is associated with greater accumulation of body fat, including android fat, which has unfavorable health outcomes.

Presenting author: **Kailin Johnsson**, kjohnsso@asu.edu

Funding: American Diabetes Association Grant #7-12-CT-40

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Graduate/Professional Student

Talk: Saturday October 28th, 1:30 PM

S6.1: Loss of Acid Ceramidase in Myeloid Cells Alleviates Chronic Colitis in IL10-/- Mice

Espinoza KS, Marron MT, Snider JM and Snider AJ

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Inflammatory bowel disease (IBD) is characterized by chronic inflammation in the colon and drastically increases the risk in the development of colorectal cancer (CRC). Over expression of acid ceramidase (AC) resulting in accumulation of sphingosine-1-phosphate (S1P), which amplify inflammatory pathways, has been implicated in patients with IBD and CRC. The conditional loss of AC in myeloid cells (ACMYE) has demonstrated promise as a therapeutic target in an acute colitis model. We sought to expand the investigation AC loss in a physiologically relevant model of IBD using IL-10 deficient mice. IL10-/- mice were crossed with AC conditional knockout mice where AC is deleted in myeloid cells to generate ACMYE/IL10-/-, with ACfl/fl/IL10-/- mice used as control. Male and female animals were collected at 8, 12, and 24 weeks of age and assessed for intestinal inflammation. Upon examination of basic parameters of colitis, ACMYE mice exhibited reduced body weight and enlarged spleens at 12 weeks of age. Flow cytometry analysis was utilized to define the role of AC in immune cell recruitment. Colonic myeloid cell infiltration and antigen presenting cell (APC) MHCII expression were not altered between genotypes at 12 weeks of age. Interestingly, ACMYE expression of CD11b on macrophages and Ly6G on neutrophils were increased at 12 weeks of age. Furthermore, APC MHCII expression was significantly reduced despite alterations to circulating myeloid cell populations in the blood and spleens of ACMYE mice at 12 weeks of age. The increase in CD11b and Ly6G may indicate differential inflammatory responses between ACfl/fl and ACMYE mice with increased disease duration. Reduced MHCII expression in ACMYE mice may further indicate APC dysfunction during inflammation, blunting immune cell crosstalk. Histologic assessment revealed no difference between genotypes in colitis or colon lesion severity at 12 weeks of age. However, Female ACMYE mice demonstrated significantly lower inflammation scores when compared to both ACfl/fl females and ACMYE males, indicating a potential sex-based difference in protection from lesion severity. Realtime qPCR for the expression of proinflammatory cytokines revealed that ACMYE mice exhibited significant ablation in the expression of several proinflammatory cytokines at 24 weeks of age. Together these data implicate AC as a potential therapeutic target in reducing inflammation in chronic IBD.

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Funding: This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases R01 DK132079 (AJS)

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Graduate/Professional Student

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P18: Regulation of Cardiokine Secretion and Cardiac Function by Peptidylglycine α-Amidating Monooxygenase (PAM)

Fakhrizadeh Esfahani M and Doroudgar S

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Atrial fibrillation is a common heart arrhythmia that can lead to ischemic strokes and heart failure. Additionally, it may result in atrial remodeling over time. Aging, obesity, hypertension, diabetes mellitus, and cardiovascular diseases are all recognized as risk factors for AF. Current methods for treating AF have limited effectiveness and can result in adverse effects both within and outside the heart. Therefore, the more we know about the mechanisms of AF, the more effectively it can be treated. Calcitonin, a 32-amino acid hormone, is known to be produced by the thyroid gland's C-cells. Elevated serum calcium levels stimulate the secretion of thyroid-derived CT, which plays a protective role in preventing hypercalcemia. It was recently found that extra-thyroid CT is produced by human atrial cardiomyocytes and by binding to CT receptors on atrial fibroblasts plays a vital role in mediating anti-fibrotic and anti-arrhythmic effects. Atrial CT was found to be reduced in aging, the primary risk factor for AF, and in patients with persistent AF, suggesting it could contribute to AF. However, the underlying mechanisms of reduced CT levels in aging and AF are not yet understood. C-terminal amidation is a necessary post-translational modification (PTM) for the stability and biological activity of many secreted peptides, including thyroid-derived CT. Amidation occurs during CT maturation in thyroid cells. Peptidylglycine α-amidating monooxygenase (PAM), the enzyme responsible for C-terminal amidation of secreted peptides, exhibits notably high expression levels in atrial myocytes, where it is localized to the endoplasmic reticulum (ER) and Golgi, the sites responsible for the synthesis of secreted peptides, however, the roles for atrial PAM in peptide amidation are not examined. There is evidence suggesting a connection between PAM and the regulation of heart rhythm. For instance, genome-wide association studies have established a link between single-nucleotide polymorphisms in the PAM gene, and the presence of an abnormal PR interval, which is known to increase the risk of AF. Therefore, the hypothesis of this project is that PAM is essential for optimal atrial CT secretion, which is crucial for atrial function and AF. This project aims to label proteins secreted from the atria, including CT, using proximity labeling to examine the effects of PAM deletion on secreted proteins. The effects of PAM deletion on atrial function will also be examined. Based on the pilot data for this project, intracellular labeling of proteins destined to be secreted may be a suitable method for detecting secreted proteins.

Presenting author: **Marjan Fakhrizadeh Esfahani**, fakhrizadeh@arizona.edu

Funding: University of Arizona College of Medicine-Phoenix University of Arizona Health Sciences Career Development Grant

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Graduate/Professional Student

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P28: Sex-dependent chronic growth hormone dysregulation after experimental diffuse traumatic brain injury in rats

Haddock, ML[1], Krishna, G[2], Bromberg, C[2, 3], Yuen, KCJ[4], **Currior Thomas, T**[2, 3]

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2. University of Arizona College of Medicine-Phoenix, Phoenix, AZ
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Pituitary dysfunction, a common but underdiagnosed complication secondary to traumatic brain injury (TBI) in adolescent age-transitioning individuals, causes late-onset cognitive, somatic, and metabolic impairments (post-TBI symptoms) across all TBI severities. An estimated 40% of TBI patients develop chronic growth hormone deficiency (GHD) within months to years post-injury, which can impact downstream products of GH signaling, such as insulin-like growth factor 1 (IGF-1). Without treatment, the patient's quality of life deteriorates over time. Patients fortunate to be diagnosed require daily life-long GH replacement, associated with high costs and poor treatment adherence. While GHD has been recently studied in humans, experimental models of mild TBI are still necessary to determine the pathophysiological development of GHD and evaluate novel long-term therapeutic strategies. To test the hypothesis that experimental mild TBI can incite GHD, we administered midline fluid percussion injury or sham procedures to male and female 3-month-old Sprague-Dawley rats (N=8-11/group) using IACUC-approved protocols. At 35 days post-injury, plasma and pituitary GH levels and plasma IGF-1 levels were measured using ELISA. Plasma GH levels were significantly decreased in brain-injured male animals ($P<0.05$), and IGF-1 was significantly lower in females ($P<0.001$), with similar pituitary GH levels. These data suggest that a single experimental diffuse TBI can cause sex-dependent dysregulation of GH rather than typical GHD associated with insufficient GH release from the pituitary. Further investigation to understand temporal and sex dependent post-TBI mechanisms in the trajectory of GH dysregulation is needed to develop diagnostic and therapeutic algorithms necessary to improve patients' transition into adulthood.

Presenting author: **Mitchell L. Haddock** and **Theresa Thomas**, theresathomas@arizona.edu

Funding: NIH-R01NS100793; Valley Research Partnership P1-4010; Phoenix Children's Hospital Mission Support

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Graduate/Professional Student

Talk: Friday October 27th, 10:45 AM

S1.4: Impact of Mid-gestation Toll-like Receptor 7 Stimulation on Development and Anxiety-like Behavior in Offspring

Martinez M[1], Alvarez J[2] and Hale TM[1]

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2. Arizona State University, Tempe, AZ

Maternal immune activation (MIA) can occur during pregnancy due to exposure to infectious diseases or other inflammatory conditions. MIA is a notable risk factor for various psychiatric disorders, such as major depressive disorder, as well as cardiac disorders in the offspring. Resiquimod (R-848), a toll-like receptor (TLR) 7 agonist, induces systemic inflammatory responses and mimics responses to viral infections. Previous studies have shown that MIA with a TLR4 agonist lipopolysaccharide or the viral mimic polyinosinic:polycytidylic acid delays developmental milestones, induces anxiety-like behavior, and impairs social behavior in offspring. The current project investigates the degree to which mid-gestation MIA with R-848 impacts offspring development and anxiety-like behavior. Pregnant rat dams received vehicle (phosphate-buffered saline) or R-848 injections (1 mg/kg) on gestation day 14 (GD14). Maternal body weight and behavior were assessed, in addition to weight, developmental milestones, and anxiety-like behavior in the offspring. Although all dams gained weight throughout pregnancy, the R-848 dams displayed more pronounced weight fluctuations post-injection. At the end of gestation on GD21, the body weights between the two groups were not significantly different from each other. On postnatal day 21 (PND21), the R-848 dams had significantly lower body weights ($p=0.007$) compared to the vehicle dams. Maternal pup retrieval results confirm that behavior was not altered by R-848. Litter size, male-to-female ratio, and birth weights were also not affected by R-848. However, the R-848 exposed female offspring exhibited a lower body weight ($p=0.0195$) on PND49. A righting reflex test on PND7 yielded no discernible trends between the vehicle and R-848 pups. Vaginal opening, which marks the onset of the first estrus, was assessed from PND30-35 and appeared to show a shift towards earlier vaginal opening in rats exposed to R-848. Open field testing one day during PND49-56 revealed no locomotion differences, but female R-848 offspring trended towards reduced time in the center zone compared to R-848 males ($p = 0.0731$), suggesting increased anxiety-like behavior. In general, the female offspring spent less time in the center zone than males (main effect of sex, $p=0.0820$). These findings suggest that in-utero R-848 exposure results in attenuated weight gain, earlier onset of puberty, and increased anxiety-like behaviors in female offspring. Future exploration of pre-pubertal stages and assessments of autonomic regulation will provide further insight into the long-term consequences of immune activation during pregnancy.

Presenting author: **Monique Martinez**, moniquem15@arizona.edu

Funding: NIMH/ORWH 1U54MH118919

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Graduate Student/Medical

Talk: Friday October 27th, 4:00 PM

S3.4: Assessment of reversal effects of genistein and exercise on hepatic tissues

Smith N[1], Orosz T[1], Parameshwar Laxm S[1], Pan J[1], McDonald H[1], Vroegop S[1] and Al-Nakkash L[2]

1. AZCOM Midwestern University, Glendale, AZ
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The aim of this study was to determine what reversible impact a standard diet/water (Std), genistein treatment (Gen), moderate exercise treatment (Ex), or both (Gen+Ex) would have on hepatic pathology secondary to a diabetic and obese state in a mouse model induced by a high fat high sugar (HFHS) diet. Liver tissue and serum was collected from 60 male C57BL/6J mice randomly assigned into the following groups: 12-weeks HFHS then 12-weeks of Std, 12-weeks HFHS then 12-weeks HFHS+Gen, 12-weeks HFHS then 12-weeks HFHS+Ex, or 12-weeks HFHS then 12-weeks HFHS+Gen+Ex. Control groups were 24 weeks Std chow or 24 weeks HFHS. Gen comprised 600 genistein mg/kg diet. Exercise was 150 51 min/week moderate treadmill exercise. Hepatic fat deposition was assessed by Oil-Red-O staining, and PCR was to assess the level of collagen mRNA. Collagen deposition was quantified from Trichrome stained liver sections. We are currently investigating hepatocytic apoptosis from TUNEL stained sections. Body weight (g) was reduced by 34% with Std, 9% with Gen, and 14% with both Gen+Ex compared to HFHS. Serum ALT activity was reduced by 67% in Std ($P<0.05$) compared to HFHS. Serum TG was significantly decreased by HFHS and remained unchanged by dietary modifications or exercise. Percent fat area, total number of lipid droplets and average area were reduced by Std compared to HFHS ($P<0.05$). Caspase-3 (apoptosis executioner enzyme) levels were decreased in HFHS and restored in Std ($P<0.05$). p21 (cell cycle inhibitor) levels followed a similar trend. We are currently evaluating collagen levels (via PCR). Trichrome analysis demonstrated the presence of collagen in hepatic tissues, which was shown to be significantly reduced in STD, Gen, and Gen+Ex groups compared to LN and HFHS groups. This data will be complemented by assessments of collagen levels via PCR. We are currently evaluating images of TUNEL stained sections to assess differences in apoptotic signaling. We conclude, inclusion of Gen, Ex, or both with concurrent HFHS diet provides some improvements in hepatic steatosis and hepatic markers compared to controls. We find that removal of the HFHS diet (Std) is the most effective, resulting in maximal hepatic recovery via induction of programed cell death, reduction of steatosis, reversal of collagen deposition, and improvement in key markers of hepatic health. Along with removal of the HFHS diet, supplementation with genistein was found to have a significant impact on the prevention of collagen deposition in hepatic tissues, further supporting its beneficial effects of limiting fibrotic pathogenesis.

Presenting author: **Nicholas Smith**, nicholas.smith1@midwestern.edu

Funding: Midwestern Arizona Alzheimer's consortium and Midwestern Intramural

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Graduate/Professional Student

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P17: Acute effects and vascular response to inspiratory resistance training

Tavoian D, Mazzone JL, Craighead DH, **Dunn N** and Bailey EF

University of Arizona

Aging and sedentary lifestyles have been shown to cause unfavorable vascular remodeling in the form of endothelial dysfunction. These changes can be counteracted with regular performance of high-resistance inspiratory resistance training (IRT), however, the underlying mechanisms are unknown. In this study we assessed endothelial function and oscillatory shear patterns in the brachial artery in twenty healthy, young adults (22.9 ± 3.4 years; 10 males, 10 females) during and after a single bout of IRT. Using a randomized crossover design, participants completed either a single bout of IRT or a time-matched rest interval. Flow-mediated dilation (FMD) was assessed before (Pre), 10 minutes after (Post10), and 40 minutes after (Post40) the assigned condition, while anterograde (i.e., laminar) and retrograde (i.e., reverse) blood flow patterns were collected during IRT. Diameter of the brachial artery diameter decreased 5.0 ± 0.9% in response to IRT. FMD was significantly greater 10 minutes post-IRT when compared to pre-IRT and 40 minutes post-IRT (Pre: 7.33 ± 0.80%; Post10: 8.94 ± 0.99%; Post40: 6.98 ± 0.77%; all p-values< 0.05). FMD did not change during the rest condition (Pre-Rest: 7.00 ± 0.84%; Post10: 5.81 ± 0.73%; Post40: 6.55 ± 0.72; p-value= 0.137). During IRT, flow velocities were separated by breathing phase (i.e., resisted inhalation and unresisted exhalation). During the resisted inhalation phase retrograde flow increased (Pre: 21.7 ± 1.6 s-1; vs. Inhalation: 43.8 ± 2.9 s-1; p<0.001) and anterograde flow decreased (Pre: 105.9 ± 6.1 s-1; vs. Inhalation: 93.2 ± 5.5 s-1; p<0.001), relative to baseline. During unresisted exhalation, the shear pattern was unchanged from baseline values (all p-values>0.05). Thus, the outcomes of this study show that augmented retrograde shear stress induced in IRT could be a mechanism to improve endothelial function chronically to prevent or counteract unfavorable vascular remodeling.

Presenting author: **Nolan Dunn**, nolandunn@arizona.edu

Funding: This work was supported by NIA/NIH Grant Number: 1R01AG065346-01A1 (EFB) and NIH Training Grant Number: 5T32HL007249-44 (DT)

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Graduate/Professional Student

Talk: Friday October 27th, 5:15 PM

S4.3: Ischemic stroke increases levels of one carbon enzymes, the folate receptor, and choline metabolism in post-mortem male and female brain tissue

Burrows P[1], Dhillon H[1], Covaleski A[1], Manfredi L[1], Beach TG[2], Serrano GE[2] and Jadavji NM[1]

1. Midwestern University, AZ
2. Banner Sun Health Research Institute, AZ

Folic acid plays a central role in the closure of the neural tube in developing infants and is also a central component of one-carbon (1C) metabolism. The role of 1C is far reaching, our research group has previously shown that deficiencies in 1C lead to worsened stroke outcomes using preclinical models. However, the impact of ischemic stroke on 1C enzymes remains unknown. The objective of this study is to investigate whether ischemic stroke contributes to a change in the levels of 1C enzymes after ischemic stroke in male and female patients. Brain tissue sections from ischemic stroke patients and controls were stained, all tissue was co-stained with neuronal nuclei (NeuN) and DAPI (4',6-diamidino-2-phenylindole). The colocalization of all three markers was evaluated by two individuals who were blinded to the experimental groups. Ischemic stroke increased neuronal levels of the folate receptor and 1C enzymes, methylenetetrahydrofolate reductase (MTHFR), thymidylate synthase (TS) and serine hydroxymethyltransferase (SHMT). Choline metabolism, including acetylcholine esterase (AChE) and choline acetyltransferase (ChAT) were also increased in stroke patients. In male stroke brain tissue was observed to have increased levels of MTHFR, TS, SHMT and AChE. Female brain tissue had increases in the folate receptor and TS. The results suggest that ischemic stroke leads to increased demand on 1C and that there are some small differences between males and females.

Presenting author: **Petter Burrows**, petter.burrows@midwestern.edu

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Graduate/Professional Student

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P31: Mn Porphyrins Affect Hydrogen Peroxide Levels in Parkin Loss-of-Function Drosophila melanogaster

Hamel RP, Juba AN and Buhlman LM

Midwestern University, Glendale, AZ

The purpose of this study was to investigate how MnTnBuOE-2-PyP5+, a manganese porphyrin ring (MnP) redox-active drug, affects vulnerable dopaminergic neuron mitochondrial hydrogen peroxide levels in homozygous loss of function park mutant Drosophila. To this end, control and parkin-null flies expressing redox-sensitive green fluorescent protein 2 fused to C. elegans oxidant receptor peroxidase 1 (UAS-mito-roGFP2-Orp1) under the control of tyrosine hydroxylase expression using the GAL4>UAS expression system (THGAL4>UAS-mito-roGFP2-Orp1) were treated with 0 µM and 10 µM MNTnBuOE-2-PyP5+ from the embryonic stage to brain dissection at day 4-6 post-eclosion. Fly brains were dissected and labeled with antibodies to detect tyrosine hydroxylase-producing cells, Z-stacks were captured, and Image Pro Premier 3D software was used to measure the total volume of oxidized and non-oxidized roGFP2 within the tyrosine hydroxylase labeled volume. Ratios of oxidized and non-oxidized roGFP2 were reported for one PPL1 region per brain to compare hydrogen peroxide levels between each condition. We found that administration of 10 µM MNTnBuOE-2-PyP5+ did not significantly affect PPL1 mitochondrial hydrogen peroxide levels in control flies at day 4-6 post eclosion (n=15). However, PPL1 mitochondrial hydrogen peroxide levels were decreased in female but not male parkin-null flies (n=14, p=0.0005 for females; n=15, p=0.2621 for males). Untreated female parkin-null flies had significantly higher hydrogen peroxide levels compared to males (n=15, p=0.0093).

Our data suggests loss of parkin affects the redox state in dopaminergic neurons in a sexual dimorphic manner. Normally, ROS are converted to hydrogen peroxide by superoxide dismutase and subsequently converted to water by glutathione peroxidase. Our results suggest that there may be greater superoxide dismutase activity in untreated female parkin-null flies compared to males. Comparing levels of neurodegeneration and oxidative stress in vulnerable neurons versus non-degenerating dopaminergic neurons allows us to elucidate mechanisms by which loss of function in parkin causes selective degeneration and determine how oxidative stress is triggered.

Presenting author: **Riley Hamel**, riley.hamel@midwestern.edu

Funding: 2023 KAS Research Fellowship

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Graduate/Professional Student

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P30: Impact of urban diets on the nutritional physiology of mealworms

Rory Lockett[1], Milena Figueiredo de Sousa[1, 2] and Karen L Sweazea[1]

1. Arizona State University, Phoenix, AZ
2. Goias Federal University, Brazil

Mealworms (*Tenebrio molitor*), the larval stage of yellow mealworm beetles, are a popular feeder insect for birds, amphibians, reptiles, fish, and even human populations throughout the world. As such, the goal of this work was to understand how the diet of mealworms impacts their nutritional quality as variations in quality can impact the animals (and humans) that consume them. We divided 500 mealworms among each of the following substrates designed to model food sources available in urban versus rural, more natural areas: 100% wheat germ (control); 100% Styrofoam; mixture of soil, grasses, and leaves from urban lawns; mixture of soil, grasses and leaves from rural lawns; 50% mixture of wheat germ + carrots; natural fertilizer; or fertilizer with weed preventative. The mealworms were maintained at room temperature and the diets were replaced weekly to prevent spoilage and to remove mealworm wastes. Once a week for three weeks, mealworms were sampled from each substrate and frozen at -20degC. After 3 weeks, mealworms housed in wheat germ + carrots weighed significantly more than all other groups ($p<0.05$), whereas those housed in Styrofoam or urban lawn substrates weighed significantly less at week 3 as compared to week 1 ($p<0.01$). The urban lawn substrate resulted in greater molting and contained the highest number of pupae, but also the greatest mortality among the substrates. Total protein content of mealworms homogenized in phosphate buffered saline were measured using the Bradford method. Mealworms maintained on wheat germ had significantly greater total protein content as compared to mealworms transitioned to any other diet ($p<0.05$). In addition to that, mealworms maintained on wheat germ had the greatest increase in protein content from week 0 to week 3 as compared to any other diet ($p<0.05$). Differences recorded in body mass and total protein support our hypothesis that the nutritional quality of mealworms is altered by ingestion of urban substrates. These data suggest that mealworms (and potentially other insects) in cities may be exposed to food substrates that result in less nutritional value than those living in more natural areas as mimicked by the rural lawn substrates and wheat germ control.

Presenting author: **Rory Lockett**, rlockett@asu.edu

Funding: Funded by a Jumpstart Grant awarded to R. Lockett from the Graduate and Professional Student Association at Arizona State University

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Graduate/Professional Student

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P10: Vascular dementia results in increased levels of methylenetetrahydrofolate reductase in cortical brain tissue of elderly female patients

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3. Banner Sun Health Research Institute Brain and Body Donation Program, Sun City, AZ
4. Department of Biomedical Sciences, Midwestern University, Glendale, AZ

Vascular dementia (VD) is a form of dementia that is projected to double in prevalence within the next three decades, placing it at the forefront of health service priorities. Deficiencies in one-carbon (1C) metabolites, such as dietary deficiencies in folic acid or choline have been linked to cognitive impairment, including VD in the elderly population. However, understanding the role of 1C metabolism in VD requires further investigation. The aim of this study was to investigate the levels of 1C enzymes and receptors in post-mortem brain tissue from female and male patients diagnosed with VD. Post-mortem cerebral cortex tissue from male and female VD-diagnosed patients and healthy controls was obtained from the Banner Sun Health Research Institute Brain and Body Donation Program. Immunofluorescence staining was performed to visualize the following enzymes methylenetetrahydrofolate reductase (MTHFR), serine hydroxymethyltransferase (SHMT), thymidylate synthase (TS), choline acetyltransferase (ChAT), and acetylcholine esterase (AchE) and the Folic acid Receptor (FR). All tissue was stained with a neuronal marker, NeuN, to ensure that the staining is specific to neurons, as well as DAPI. Co-localization of the staining was quantified using microscopy imaging. In VD cerebral brain tissue, there are no changes in choline metabolism, ChAT and AChE. However there are increased levels of MTHFR in VD patients compared to controls. Additional data will be collected by staining for other 1C enzymes and receptors. The gathered data will provide valuable insights into the involvement of 1C metabolism in VD, potentially contributing to the development of novel diagnostic tools and therapeutic approaches for VD affected patients.

Presenting author: **Sanika Joshi**, sanika.joshi@midwestern.edu
Funding: Midwestern University

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Graduate/Professional Student

Talk: Saturday October 28th, 9:15 AM

S5.2: Modeling conducted responses in microvascular networks: current rectification in endothelial cell gap junctions

Djurich, S and Secomb, TW

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Neurovascular coupling is the mechanism by which blood flow is increased to active areas of the brain. A contributing mechanism is believed to be local hyperpolarization of capillary endothelial cells in active regions resulting from local elevation of extracellular [K+], which initiates an upstream conducted response in the form of an electrical current drawn from upstream arterioles. The resulting hyperpolarization of arterioles causes dilation, increasing downstream blood flow. For this mechanism to be effective in delivering increased flow to a specific location, the conducted response must travel in the upstream direction only, without reentry into adjacent parallel flow pathways. Such specificity in the response to activation has been observed in skeletal muscle, and may result from partial rectification of current in gap junctions connecting adjacent endothelial cells. The goal of this work is to simulate the spread of hyperpolarizing currents along vessel walls in microvascular networks of the cerebral circulation, including the effects of rectification in gap junctions. A theoretical model was developed for the spread of electric current in the endothelial cells of a network of microvessels, in response to local K+- induced hyperpolarization. Transmembrane currents represented in the model are a KIR-channel current, a non-voltage-dependent K+ current, and a background current. Currents along vessel walls are represented assuming asymmetric gap junction conductance between adjacent endothelial cells, with higher conductance for downstream currents (causing upstream hyperpolarization) than for upstream currents. The model was applied to a synthetic network of 45 segments, assuming 10 nS conductance for downstream currents, while a range of upstream conductance was tested. The model shows effective upstream propagation of conducted responses when the upstream gap junction conductance is 1 nS or less. These results show that partial current rectification by endothelial gap junctions can result in preferential upstream propagation of conducted responses, consistent with experimental observations of local flow regulation.

Presenting author: **Sara Djurich**, sarad2@arizona.edu

Funding: NIH U01 HL133362

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Graduate/Professional Student

Talk: Friday October 27th, 3:45 PM

S3.3: Longitudinal characterization of the gut microbiota in the ZDSD rat model of diabetes

Weninger SN, Ding A, Schiro G, Laubitz D and Duca FA

University of Arizona, Tucson, AZ

The complex development of type 2 diabetes (T2D) creates challenges for studying its progression in animal models, which often lack transition through the prediabetic state or fail to fully develop the multifaceted aspects of T2D. However, studying T2D development and progression in humans is costly with extensive limitations. A newly developed rat model of T2D, the Zucker Diabetic Sprague Dawley (ZDSD) rat, more closely parallels the progression of T2D in humans. The purpose of this study was to examine T2D progression and the associated changes in the gut microbiota in the ZDSD model and test whether the model can be used to examine potential therapeutics targeting the gut microbiota. Bodyweight, adiposity, and fed/fasting blood glucose and insulin were recorded throughout the progression of T2D in male ZDSD rats over 24 weeks. Glucose and insulin tolerance tests were performed, and feces collected for microbiota analysis using 16s rRNA gene sequencing at 8, 16, and 24 weeks. At the end of 24 weeks, half of the rats were supplemented with oligofructose (OFS) in their drinking water and tests repeated. Over the 24 weeks, we observed a transition from nondiabetic to prediabetic and overtly diabetic states, via worsened insulin and glucose tolerance and significant increases in fed/ fasted glucose values, followed by a significant decrease in circulating insulin. Microbiota analysis demonstrated alterations in the gut microbiota throughout the development of diabetes with shifts in alpha and beta diversity as well as alterations in specific bacterial genera in healthy compared to prediabetic and diabetic states. OFS treatment significantly increased body weight and adiposity, improved glucose tolerance, and shifted the cecal microbiota of the ZDSD rats during late-stage diabetes. These findings demonstrate the translational potential of ZDSD rats as a T2D model and highlight the potential for the gut microbiota to both impact the development of the disease, as well as serve as a biomarker for T2D. Additionally, OFS treatment was able to moderately improve glucose homeostasis in the ZDSD model.

Presenting author: **Savanna Weninger**, savannaweninger@arizona.edu

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Graduate/Professional Student

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P6: SNAP23 is a Novel Regulator of Autophagy in Cardiomyocytes

Noudali SN, Hahn SA, Glembotski CC and Blackwood EA

University of Arizona, Phoenix, AZ

Many forms of cardiovascular disease (CVD) are associated with pathological increased left ventricular load-induced cardiac hypertrophy, which can lead to heart failure. As they are post-mitotic, maintaining proteostasis is critical to sustaining cardiomyocyte viability in cardiac hypertrophy. An evolutionarily conserved mechanism for maintaining proteostasis is autophagy, which can become dysregulated in pathological cardiac hypertrophy and contribute to disease progression. Thus, identifying novel regulators of autophagy are of great interest as potential therapeutic targets for CVD. We identified a SNARE protein, SNAP23, to be associated with adaptive processes in cardiomyocyte proteostasis. As SNARE proteins are known to facilitate autolysosome formation in autophagy, this led to our hypothesis that SNAP23 regulates cardiomyocyte autophagy. SNAP23 was knocked down or overexpressed, in vitro, in primary cultured neonatal rat ventricular myocytes (NRVM) using siRNA or adenovirus, respectively. In vivo assessments of SNAP23 function in mouse hearts were achieved via administration of a novel adeno-associated virus followed by subjecting mice to a model of load-induced cardiac hypertrophy, transverse aortic constriction (TAC). Snap23 mRNA was increased and negatively correlated with reduced cardiac performance in left ventricle biopsy samples from heart failure patients. In NRVM, SNAP23 knockdown reduced basal and stress-induced autophagy, while SNAP23 overexpression increased autophagy. SNAP23 overexpression, in vivo, preserved cardiac function during early phases but exacerbated cardiac hypertrophy and functional decline in late phases of TAC-induced cardiac hypertrophy. These data support that SNAP23 is a novel regulator of cardiomyocyte autophagy and may be protective in early stages of cardiac hypertrophy.

Presenting author: **Sean Noudali**, noudali@arizona.edu

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Graduate/Professional Student

Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P36: Understanding functional outcomes of hypoxia associated with over-supplementation of folic acid in Drosophila melanogaster

Gunnala S, Harrison A and Jadavji NM

Midwestern University, Glendale

Folic acid is a water-soluble B-complex vitamin (B9) involved in nucleic acid synthesis, methylation, and DNA repair. It plays a central role in one-carbon (1C) metabolism, which is a metabolic network that integrates nutritional signals with biosynthesis, redox homeostasis, and epigenetics. Our previous work, along with others has shown the positive impact supplementation of folic acid can have after brain injury, such as an ischemic stroke. Recently, over-supplementation of folic acid has become a problem in many countries with mandatory food fortification laws in place to reduce the prevalence of neural tube defects. However, the impact of over-supplementation of folic acid on brain injury is not well understood. The aim of our study was to investigate the how folic acid over-supplementation impacts hypoxia outcome using Drosophila melanogaster as a model. We maintained w1118 male and female flies on control and 100uM folic acid supplemented diets. Offspring from these crosses were exposed to hypoxia (1% oxygen) for a period of two hours after which flies were returned to normoxic conditions to model reperfusion. We confirmed that flies were exposed to hypoxia by measuring escape latency of larvae from food in vials. The survival rate of flies was recorded for after hypoxia treatment for 90 days. In a separate group of flies 24 hours after hypoxia fly climbing behavior was also measured, this included the number of movements made and the motivation to fly. We observed that 100uM folic acid and hypoxia treatment increased the number of dead flies over the span of their lifetime. Furthermore, we observed a reduction in the motivation to fly in hypoxia treated and folic acid over-supplemented flies. We are currently investigating apoptosis in brain tissue of flies to determine potential mechanisms. This research provides insight into how over-supplementation of folic acid impacts brain function after hypoxia.

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Funding: Midwestern University

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Graduate Student/Medical

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P4: Long-term intermittent fasting induces changes to glucose metabolism and limits apoptosis in the SAMP8 aged murine jejunum

Vroegop S, Smith NJ, Sudler SR, Bosnoyan A, Aziz A, Singh A, Shim M, Broderick T & Al-Nakkash L

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Background: Intermittent fasting (IF) has become a popular subject in mainstream dietary interventions and is known to be effective in decreasing overall mass and promoting health in many different body systems, including the GI tract. SAMP8 (Senescence Accelerated Mouse- Prone 8) mice have a shorter lifespan of 9-12 months, exhibit age-related deficits in memory and learning, and are used as a model for studying physiological changes associated with aging. This study aimed to examine the potential for intermittent fasting to ameliorate age-associated anatomical and physiological damage to the murine small intestine. To that end, we assessed histomorphological parameters generated from jejunal samples and compared total protein expression using western blots of key absorption and senescence-related proteins in fasted and non-fasted SAMP8 mice to investigate the effects of intermittent fasting on jejunal structure and function.

Methods: Male and female SAMP8 mice were randomly assigned to either a fasting protocol (IF) or an ad-libitum diet (AL) for the study duration (n=15/group). Mice were 2 months old at the start of the study and fed accordingly for 8 months. Fasted mice followed a strict 24-hour alternate-day fasting protocol. At the end of the study, mice were euthanized and jejunum was either stored at –80 °C until use or segments fixed in paraformaldehyde for H&E histology. Fecal pellets were analyzed for total primary and total secondary bile acid content.

Results: Histomorphological analyses indicate a significant IF-induced decrease (by 21%, n=4/group, $P<0.05$) in villi length in females and a significant IF-induced increase in wall thickness (by 7%, n=4/group, $P<0.05$). Intermittent fasting also resulted in significantly less weight gain over the course of the study in both males (22% less, n=7-9, $P<0.05$) and females (33% less, n=7-9, $P<0.05$) compared to their non-fasted counterparts, respectively. This indicates the potential for decreased weight gain in fasted mice to be partially influenced by the structural changes noted above, and likely not only attributed to decreased caloric intake. In female mice, IF led to a marked 57% decrease in GLUT2 expression (n=5-6, $P<0.05$) compared to ad-libitum. Given that GLUT2 is responsible for moving glucose/galactose and fructose out of the enterocyte and into the bloodstream across the basolateral membrane, this suggests a restructuring of glucose transport and metabolism in response to fasting.
This may contribute to more stable blood glucose levels and an adaptive shift towards alternative energy substrates during fasting periods, which is supported by improved glucose tolerance testing in IF mice versus AL groups. Interestingly, we found no IF effect on GLUT5 expression (responsible for absorbing fructose across the apical membrane of the enterocyte) in male or female mice. Expression of intestinal transport proteins SGLT1 and PEPT1 in response to IF are currently under evaluation. To determine effects of IF on jejunal apoptotic activity, we investigated cleaved Caspase-3 expression, and uncovered significant decreases in both male and female IF groups compared to their respective ad- libitum groups. This reduction was particularly pronounced in female mice and suggests a protective role of IF against induction of apoptotic pathways. There was no effect of IF on total primary or total secondary fecal bile acid content in both male and female mice.

Conclusions: Intermittent fasting can help and IF also has the potential to alter carbohydrate metabolism (via reduced GLUT2 expression) and significantly decrease apoptotic activity (via decreased Caspase-3 expression) in the aged murine small intestine. These findings collectively highlight the complex effects of IF on cellular and metabolic processes, and in particular the significance of sex-specific responses. We aim to unravel the underlying molecular mechanisms driving these effects. The implications of this study point towards a better understanding of the therapeutic potential of fasting regimens to help minimize age-related deleterious changes to jejunal form and function in mammals.

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Funding: Midwestern Arizona Alzheimer's Consortium; Midwestern Intramural Funding

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Graduate/Professional Student

Talk: Friday October 27th, 5:45 PM

S4.5: PNA5 restores BKCa function in cerebral artery smooth muscle cells of female 5x-FAD mice

Thai ST, Polk FD, Silva JF and Pires PW

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Few therapeutic options exist for treatment of Alzheimer's disease (AD), the most prevalent type of dementia, particularly therapies focusing on cerebral microvascular function. AD is associated with impaired neurovascular coupling (NVC) responses in the brain, a process that ensures blood flow to regions of increased neuronal activity through functional cerebral microvascular dilation. This dilation involves opening of large conductance Ca2+-activated K+ channels (BKCa), a channel known to be a target for oxidative modulation in the early-onset 5x-FAD model of AD. PNA5, a novel agonist of the vasculo-protective Mas receptor, prevents heart failure-induced dementia, but its effects on AD remain undetermined. Thus, we hypothesized that PNA5, a novel Mas receptor agonist, improves cerebral microvascular BKCa function in 5x-FAD mice. Five-month-old female 5x-FAD mice were treated with PNA5 (100 µg/kg/day, s.c.) for 1 month; saline-treated 5x-FAD were controls. We used electrophysiology to record single-channel BKCa currents, pressure myography to investigate BKCa-dependent vasoreactivity and laser speckle contrast imaging for NVC. Data are means ± SEM, 5x-FAD + vehicle vs. 5x-FAD + PNA5. We observed an increase in BKCa open probability (Po) in cerebrovascular smooth muscle cells isolated from 5x-FAD + PNA when compared to vehicle-treated 5x-FAD (Po: 0.024 ± 0.005 vs 0.050 ± 0.013, n=13-15, $p<0.05$, Student's t-test), without additive effects of the reducing agent dithiothreitol (DTT) (0.06017 ± 0.01459, n=15). Similarly, 5x-FAD + PNA5 restored BKCa vasoreactivity, observed as a larger constriction after BKCa inhibition with iberiotoxin (30 nM, Vasoconstriction (%): 5.07 ± 0.37 vs 13.66 ± 3.34%, N = 16-7, $p<0.05$, Student's t-test), without additive effects of DTT in 5x-FAD + PNA5 (Vasoconstriction (%): 16.22 ± 4.20 vs. 11.89 ± 2.81, N = 5). Lastly, we observed a preliminary increase in NVC in 5x-FAD + PNA5 when compared to 5x-FAD + vehicle (Increase in perfusion (%): 3.551 ± 0.7801 vs 8.603 ± 1.3140%, N = 2-2). In conclusion, these data suggest that PNA5 may restore BKCa activity and improve neuro-vascular function in 5x-FAD. Ongoing studies in the laboratory will expand on these preliminary findings to further investigate mechanisms that underlie the effects of PNA5 and how it may serve as a potential therapeutic drug for AD.

Presenting author: **Stephenie Thai**, sthai1234@arizona.edu

Funding: R01 AG073230, AARGD-21-850835

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Graduate/Professional Student

Talk: Friday October 27th, 10:15 AM

S1.2: SGK1 is a Key Mediator of Pathological Cardiac Fibrosis

Murray V, **Bagchi S**, Hahn S, Glembotski C and Blackwood E

University of Arizona College of Medicine - Phoenix, Phoenix, AZ

Cardiac fibroblasts initially play an adaptive role in the injured heart, proliferating and differentiating into myofibroblasts to facilitate repair and to maintain cardiac structure and function. However, prolonged cardiac stress leads to pathological cardiac fibrosis, ultimately resulting in heart failure (HF). Thus, there is a major interest in developing therapeutic strategies to constrain fibroblast differentiation and sustained activation. We recently identified roles for the cytosolic kinase, serum/glucocorticoid regulated kinase 1 (SGK1), in promoting hypertrophy and pathological remodeling in the cardiac myocyte. However, despite reports that SGK1 may be implicated in fibrosis, mechanistic roles for SGK1 in cardiac fibroblasts in response to injury remains unknown. The following studies were performed to test the hypothesis that SGK1 promotes pathological cardiac fibrosis and exacerbates progression to HF via its role in cardiac fibroblasts. For in vitro studies, transforming growth factor beta, (TGFβ) was used in primary cardiac fibroblasts (CFBs) to stimulate differentiation, and CFBs were transfected with siRNA to knockdown SGK1 expression. Transverse aortic constriction (TAC) was used as a pressure-overload induced model of cardiac fibrosis and HF in mice. SGK1-floxed mice were injected with a novel AAV9 expressing Cre recombinase under a myofibroblast-specific promoter to delete SGK1 in myofibroblasts (SGK1 mfbKO), in vivo. SGK1 signaling was elevated in cardiac explants obtained from ischemic human HF patients, which led us to further evaluate SGK1 activity in CFBs. In cultured CFBs, SGK1 knockdown blunted TGFβ-mediated differentiation and fibrotic signaling. In the HF mouse model, SGK1 mfbKO mice subjected to TAC showed preserved systolic and diastolic cardiac function, measured by echocardiography. At the biochemical level, pathological remodeling and fibrotic gene expression were attenuated in SGK1 mfbKO mice as determined by qRT-PCR of cardiac extracts. Finally, small molecule inhibition of SGK1 in cultured CFBs attenuated differentiation and fibrotic signaling in response to TGFβ treatment. Taken together, these results demonstrate that SGK1 knockdown is protective against cardiac fibrosis, attenuating differentiation and fibrotic signaling in CFBs. Further, SGK1 mfbKO protected against pathological cardiac remodeling and functional decline in a mouse model of HF, highlighting the specific pathophysiological contributions of CFBs.

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Funding: NIH/NHLBI – T32HL007249; Arizona Department of Health Services New Investigator Award – RFGA2022-010-10; University of Arizona Sarver Heart Center – Irving J. Levinson and J.G. Murray Memorial Research Award; Valley Research Partnership Program Award – P1A-6005
University of Arizona RII – PDRG; Scott R. MacKenzie Foundation; NIH/NHLBI – R01HL149931; NIH/NHLBI – R01HL141463; NIH/NHLBI – R01HL157027

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Graduate/Professional Student

Talk: Friday October 27th, 4:45 PM

S4.1: Accelerated Cerebrovascular Aging and Vulnerability to Traumatic Brain Injury in Marfan Syndrome Mice

Curry T[1] , Curtin L[2], Barrameda ME[2], Hair C[1], Krishna G[1], Sabetta Z[1], Thomas TC[1] and (Co-senior) Esfandiarei M[2] (Co-senior)

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2. Midwestern University, Glendale, AZ

Marfan syndrome (MFS) is a connective tissue disorder associated with mutations in fibrillin-1 (Fbn1), increasing transforming growth factor-β (TGF-β) bioavailability systemically and chronically, generating vascular dysfunction by 6-months (6M) in Fbn1C1041G/+ (MFS) mice. TGF-β has been implicated in cerebrovascular dysfunction, loss of blood-brain barrier (BBB) integrity, age-related neuroinflammation, and neurological deficits. Improvements in MFS treatment and life expectancy have uncovered a risk for cerebrovascular complications such as stroke and cerebral aneurysm. Cerebrovascular dysfunction and neuropathology have been minimally investigated in MFS. We hypothesized that Fbn1-mutation promotes an accelerated aging phenotype, leaving the brain more vulnerable to TBI. Male and female 6M MFS, 6M C57BL/6 (WT) control, and middle-aged 12M WT mice were utilized (N=3-10/group, significance is $p<0.05$; G*Power®). In vivo ultrasound imaging demonstrated increased aortic root diameters and wall stiffness in MFS mice compared to 6M and 12M WT mice. Posterior cerebral artery (PCA) blood flow velocity was decreased in MFS males, where female cohorts were not different. In 6M MFS male mice, Evans blue extravasation and Immunoglobulin G staining demonstrated increased BBB permeability in the hippocampus to large and small molecules, respectively, as compared to WT and more similarly to 12M WT. Morphology of Iba-1-stained cells in 6M MFS and 12M WT indicated reactive microglia. Acute glial activation and BBB permeability can disrupt glutamate homeostasis, where in vivo hippocampal electrochemical recordings showed elevated baseline glutamate concentrations and a trend towards slower glutamate clearance in MFS and 12M WT mice. Higher neurobehavioral severity scale (NSS) scores in 6M MFS mice suggested neurobehavioral alterations more like 12M WT. Midline fluid percussion was used to induce mild traumatic brain injury (TBI), where 6M MFS male mice and both female groups required a 15% lower pressure to induce mTBI righting reflex times (5-10 minutes) compared to 6M WT male mice. Mice were evaluated at 1-day post-injury, where BBB permeability to large and small molecules and microglia activation were increased, glutamate clearance was slowed, and NSS scores were increased compared to 6M WT and were similar to 6M MFS and 12M WT mice. These novel findings support MFS as a condition with an accelerated cerebrovascular aging phenotype and increased vulnerability to mTBI that is exacerbated in males compared to females, where TGF-β may be a critical target.

Presenting author: **Tala Curry**, curryt@email.arizona.edu

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Graduate/Professional Student

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P8: Cadaveric investigation of anatomical variants in the thyroid region and clinical implications for emergency airway procedures

Olson T, [1] Mirjat D[1], Karupakula ES[2], Patel HC[2], Ruble KP [2], Ritzman TB[2], Campbell TL[2], Lynch LM[1] and Smith HF[1]

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The thyroid ima artery and pyramidal lobe are anatomical variants that may cause complications in invasive thyroid procedures. The thyroid ima artery is a variant supplying the thyroid gland that may arise from a variety of sources including the brachiocephalic trunk, aortic arch, common carotid arteries, internal thoracic arteries, or the subclavian arteries. After arising in the neck, the thyroid ima artery courses over the anterior surface of the trachea, therefore it is at risk during emergency airway procedures--i.e., if unaccounted for, it represents a potential site of hemorrhage during these procedures. Another anatomical variant in this region, a pyramidal lobe, is a supernumerary lobe of the thyroid gland that typically extends superiorly from the isthmus. It is attributable to incomplete involution of the thyroglossal duct during embryonic development. The pyramidal lobe can also complicate thyroid surgeries. For example, in complete thyroidectomies the presence of a pyramidal lobe could result in incomplete removal of the glandular tissue. To further document variation in this region, the present study examined 56 human body donors from anatomy courses on both Arizona and Illinois Midwestern University campuses for the presence or absence of these two clinically relevant anatomical variations. Of the donors sampled, 12.5% possessed a thyroid ima artery, which is higher than previous estimates and suggests an increased risk during thyrotomy. The results showed that 16.1% of donors had a pyramidal lobe, which is lower than previous findings based on clinical studies. Roughly two-thirds (67.8%) of the sample exhibited neither thyroid variant. This high occurrence of anatomical variation in the thyroid region suggests that caution is warranted during emergency airway procedures and provides potentially clinically relevant updates to the frequency of specific variants in the region.

Presenting author: **Thalia Olson**, thalia.olson@midwestern.edu

Funding: Department of Anatomy, Midwestern University

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Graduate/Professional Student

Talk: Saturday October 28th, 9:30 AM

S5.3: PM2.5 Temporally Decreases Human Brain Microvascular Endothelial Barrier Proteins and Concomitantly Increases Inflammation and Autophagy in a Dose Dependent Manner

Wendt TS[1], **Macias D**[1], Kazemifar S[1, 2], Wettbo JP[1, 2], Ansar S[2] and Gonzales RJ[1]

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2. Clinical Sciences Lund, Applied Neurovascular Research Department, Lund, Sweden

Exposure to airborne particulate matter 2.5 (particle size <PM2.5 um) pollution is a significant co-morbidity for stroke and other cardio- and cerebrovascular diseases, causing premature mortality. However, mechanisms underlying PM2.5-mediated endothelial dysfunction and integrity loss are not known. Our goal was to elucidate how PM2.5 alters brain endothelial phenotype causing inflammation and loss of barrier integrity to provide better insight to the potential pathogenesis of environment pollutants. We hypothesized that PM2.5 would alter integral endothelial barrier proteins as well as inflammatory mediators in a dose and temporal dependent manner, subsequently exacerbating the impact of acute ischemic-like injury. Primary adult male human brain microvascular endothelial cells (HBMEC) were preconditioned with PM2.5 (300, 75, or 15 μg/m3; 12, 24, or 36h) or vehicle, then exposed to normoxia (21% O2) or ischemic-like injury, hypoxia plus glucose deprivation (HGD; 1% O2), for 3h. HBMEC levels or expression of barrier markers (Claudin-5, Occludin, ZO-1), adhesion molecules (ICAM-1 and PECAM-1), inflammatory proteins (iNOS, COX-2, LOX-1, TNF-α, IL-1β), and autophagic protein (Beclin-1) were examined using qRT-PCR, in cell western, and standard immunoblotting techniques. PM2.5 (300 and 75ug) induced a concomitant temporal and dose dependent decrease in claudin-5 and increase in iNOS as well as TNF-α levels. Additionally, PM2.5 (75ug) increased protein levels of Beclin-1 and LOX-1 like that of HGD alone; however, combination of PM2.5 (75ug) and HGD decreased levels of Beclin-1 and LOX-1. HGD alone or in combination with PM2.5 decreased levels of PECAM-1, but PM2.5 (75ug) alone did not alter PECAM-1. PM2.5 (75ug) in the presence or absence of HGD induced differential alteration in claudin-5 isoform protein levels. Intriguingly, PM2.5 (75ug) decreased claudin-5 mRNA levels like that observed in HBMECs exposed to HGD alone. PM2.5 (75ug) plus HGD exposure significantly increased mRNA levels of both ICAM-1 and IL-1β. In conclusion, PM2.5 mediated inflammatory and vascular pathogenesis involves a potential complex intracellular molecular framework associated with the brain endothelium which is compounded by ischemic like injury. These findings have revealed detrimental effects of PM2.5 on the brain vascular endothelium which will help to identify targets in the endothelium to restore or preserve cerebrovascular homeostasis.

Presenting authors: **Trevor Wendt** and **D. Macias**, trevorwendt@arizona.edu

Funding: University of Arizona Valley Research Partnership Grant VRP37 P2 (RJG), American Heart Association 19AIREA34480018 (RJG), UA VRP Grant VRP55 P1a (TSW)

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Graduate/Professional Student

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P22: OxLDL/LOX-1 Mediated Sex, Age, and Endothelial Dependent Alterations in Vascular Reactivity in Murine Thoracic Aortic Rings

Wendt TS and Gonzales RJ

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Elevated oxidized low-density lipoprotein (oxLDL) is a risk factor and component that worsens cardiovascular disease states. OxLDL can elicit its detrimental action, via lectin-like oxLDL receptor 1 (LOX-1) and has been shown to disrupt endothelial dependent relaxation in aortic rings (Mehta et al, 2007). The impact of oxLDL on age and sex in terms of vascular reactivity and wall stiffness has not been investigated. Therefore, in this study, we determined whether oxLDL, via LOX-1, alters contraction to phenylephrine (PE) and relaxation to acetylcholine (ACh) as well as stiffness and remodeling in isolated murine aortic rings across age and sex. Thoracic aortic endothelium-intact or -denuded ring segments from intact C57BL/6J female and male mice were preincubated with oxLDL ex vivo (50ug/dL; 2h). Using wire myography, cumulative concentration-response curves to PE were generated to determine contractile responses. From these curves, the EC50 was determined and used to contract rings to assess endothelial ACh dependent relaxation. Additionally, calculated aortic stiffness and remodeling, as well as mRNA expression of vasoactive and pro-inflammatory mediators were assessed. The selective LOX-1 inhibitor, BI-0115 (10µM;), was used to determine LOX-1 dependence. We observed differential sex and age dependent alterations to the efficacy of PE-induced contractile responses and ACh-mediated vasorelaxation following oxLDL exposure. These responses were LOX-1 dependent. Additionally, we observed a distinct sex and age effect on thoracic aortic stiffness following exposure to oxLDL. There was also a sex effect on calculated vessel diameter, as well as an age effect on oxLDL-mediated inward remodeling that was LOX-1 dependent. Interestingly, endothelial removal abolished the effects of oxLDL on the observed responses to vasoreactivity as well as vessel wall stiffness in our mouse aortic ring preparation. Thus, LOX-1 inhibition and the resulting attenuation of oxLDL/endothelial-mediated alterations in aortic function suggests that there are differential sex differences in the role of oxLDL/LOX-1 in the thoracic aorta of male and female mice. This study reveals potential complex interactions in oxLDL/LOX-1-mediated vascular responses that could serve as potential therapeutic intervention for vascular diseases such as atherosclerosis in both men and women.

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Funding: University of Arizona Valley Research Partnership Grant VRP37 P2 (RJG), American Heart Association 19AIREA34480018 (RJG), UA VRP Grant VRP55 P1a (TSW)

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Graduate/Professional Student

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P23: OxLDL preconditioning temporally intensifies ischemic-like injury mediated alterations in human male brain endothelial cell tight junction protein levels and proinflammatory mediators

Wendt TS and Gonzales RJ

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Acute ischemic stroke (AIS) triggers endothelial activation and induces cerebrovascular inflammation which can result in vascular function and integrity loss leading to worsened stroke outcome. A clinically correlated risk factor for stroke shown to mediate vascular dysfunction and injury is elevated levels of oxidized low-density lipoprotein (oxLDL). We have previously shown that oxLDL and hypoxia plus glucose deprivation (HGD; in vitro ischemic like injury) independently increase inflammatory mediator expression in human brain endothelial cells. Therefore, we hypothesized that oxLDL would exacerbate HGD-mediated alterations of endothelial inflammatory mediator and integral barrier protein levels and this response would be dose and time dependent. Primary adult male human brain microvascular endothelial cells (HBMEC) were preconditioned with human oxLDL (50 or 100µg/dL; 6, 12, 24, or 36h) or vehicle. HBMECs were then exposed to normoxia (21% O2) or HGD, (1% O2), for 3 or 6h. HBMEC barrier markers (claudin-5, occludin, ZO-1), adhesion molecules (VCAM-1, ICAM-1, PECAM-1), and inflammatory proteins (iNOS, COX-2, TNF-α, IL-1β) were examined using qRT-PCR, in cell western, and FIJI mediated immunocytochemical analysis. Secondary analysis was performed on RNA sequencing of adult male aortic endothelial cells (HAoECs) exposed to oxLDL (50µg/mL; 3, 6, 12, 24h) obtained from GEO dataset GSE13139. HGD exposure concomitantly decreased mRNA and protein levels of claudin-5 as well as protein levels of both occludin and ZO-1. HGD also increased mRNA and protein levels of IL-1β, as well as increased iNOS and TNF-α protein. Similarly, HGD exposure increased mRNA of ICAM-1 as well as VCAM-1 protein. Additionally, LOX-1 mRNA expression and protein levels were increased following HGD. Pre-conditioning to oxLDL prior to HGD exposure exacerbated TNF-α protein levels in a dose and time dependent manner. Similarly, oxLDL increased protein expression of the inflammatory mediator, IL-1β. Intriguingly, there was an increase in claudin-5 and ZO-1 oxLDL and HGD. Contrary to HBMECs, expression of HAoEC barrier, adhesion, and inflammatory mediator mRNA expression were not altered by oxLDL. In conclusion, these data suggest that the human brain microvasculature phenotype may be more sensitive to increased plasma levels of oxLDL potentially resulting in increased local inflammation as compared to the aorta. Further elucidation of the detrimental effects of oxLDL on the vascular endothelium not only in the brain, but across organ systems may shed light on the differential and specific responses of endothelial cell phenotypes to oxLDL-mediated injury.

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Funding: University of Arizona Valley Research Partnership Grant VRP37 P2 (RJG), American Heart Association 19AIREA34480018 (RJG), UA VRP Grant VRP55 P1a (TSW)

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Undergraduate

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P19: Inconsistent Sleep Decreases Urinary and Salivary PERK Levels

Shah AL, Ravia JJ and Teske JA

University of Arizona, AZ.

High noise exposure is positively associated with stress and negatively associated with sleep.The integrated stress response is a stress-adaptive intracellular signaling network activated by four protein kinases, one of which includes RNA-like endoplasmic reticulum kinase (PERK). Sleep affects cognitive function and protein levels, resulting in a bidirectional relationship between sleep and protein production. The purpose was to determine if inconsistent sleep time affected PERK protein levels and if the consistency of sleep affected the relationship between sleep time and noise exposure in different environments among undergraduate students. To test this, undergraduate college students [N=21, 18-22 years old, (mean/stdev: 20.5/1.3), 28.6% male, 66.7% female, 4.8% non-binary/gender variant/non-conforming] enrolled in a course-based undergraduate research experience (CURE) at the University of Arizona in 2022 and 2023 provided urine and saliva samples. Students also completed a self-reported questionnaire to assess sleep quality, recorded noise exposure in 4 different environments, and objectively measured sleep time and physical activity (Actiwatch, Phillips, Respironics) for four 24h periods. Urinary and Salivary PERK protein levels were measured by ELISA. Inconsistent sleepers had significantly a greater standard deviation (stdev) for sleep time across 4 days compared to consistent sleepers ($P < 0.0001$). Inconsistent sleepers had lower urinary and salivary PERK/GAPDH compared to consistent sleepers, which was significant for urinary PERK ($P = 0.04$ and $P = 0.1$, respectively). For consistent sleepers, noise exposure while walking was negatively associated with the stdev of sleep time ($R2 = 0.48$, $P = 0.02$) while there was no association for inconsistent sleepers. There is a negative association between noise during class and stdev of sleep time for consistent sleepers ($R2 = 0.12$, $P = 0.29$). Yet, there was a positive association between noise while sleeping and stdev of sleep time for inconsistent sleepers ($R2 = 0.17$, $P = 0.36$). There was no association between the stdev of sleep time and noise during eating for both consistent and inconsistent sleepers. Inconsistent sleep time affects PERK in multiple biofluids and stratifying students based on the consistency of the stdev of sleep time affected the relationship between sleep time and noise exposure in different environments.

Presenting author: **Ananya Shah**, als6@arizona.edu

Funding: University of Arizona

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Undergraduate

Talk: Friday October 27th, 11:30 AM

S2.3: Sex Differences in Redox Balance: Effects of Aging and Exercise

Condes A, **Policastro E**, Rodriguez D, Ostrom EL and Traustadóttir T

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Advanced age increases the risk for a host of diseases including CVD, Alzheimer's disease, and cancer, and this increased risk is tied to dysfunction of pathways that respond to cellular stress. One potential reason for this dysfunction is a gradual shift in the redox state toward a more oxidized cellular environment potentially disrupting cell-signaling. Nrf2 is an important player in the protection through controlling expression of a host of genes involved in cellular detoxification and antioxidant defenses. Nrf2 is translocated into the nucleus under stimulated conditions and therefore nuclear levels should be low under basal conditions. The purpose of this study was to investigate sex differences in basal redox balance, (nuclear levels of Nrf2), across young and older groups. Additionally, changes in basal redox balance in response to an 8-week exercise intervention was investigated across sex and age groups. Study participants were 21 young (18-28y, 10 men and 11 women) and 19 older (≥60y, 10 men and 9 women) inactive adults. The subjects were randomly assigned to an 8-week aerobic exercise training (ET; 3 d/wk, 45 min/d, n=21) or a non-exercise control group (CON, n=19). Basal nuclear Nrf2 levels were measured in nuclear extracts from PBMCs, using Western blotting and Lamin as an internal control. As expected, the older group had significantly higher basal Nrf2 levels compared to the young ($p<0.001$). There were no sex differences when analyzed with the age groups combined. When parsed out by age and sex, the higher basal redox balance with age was primarily driven by women and there was a trend for age-by-sex interaction ($p=0.09$). The exercise intervention improved aerobic capacity in ET while CON did not change ($p<0.01$). ET lowered basal nuclear Nrf2 levels in young and older ($p<0.05$) and there was a trend for greater lowering in women compared to men ($p<0.05$).When analyzing the groups further by age, sex, and intervention, despite very low n's (4-6 subjects per group), there was a significant three-way interaction ($p<0.05$) where the older women in ET had the biggest improvement in basal redox balance, while the older women CON got worse over the 8-week period. Together these data demonstrate sex differences in the age-related increase in basal redox, with a greater effect in women. The group with the highest basal redox balance, older women, had the strongest response to the exercise intervention. These results demonstrate that regular exercise can improve basal redox balance, particularly in older inactive women which could improve their adaptive cell signaling response. Conversely, older men may need adjunctive therapies to enhance the effects of exercise.

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Funding: NIH/NIA R15 AG055077

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Undergraduate

Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P9: Impact of Aging After Traumatic Brain Injury: Evaluation of neuropathology, axonal injury, neuroinflammation, autophagy, and pTau pathology in the dentate gyrus at 6-months post-injury

Bhavik Rajaboina[1,2,3], Gokul Krishna[1,2], Erum Mian[1,2], Zackary Sabetta[1,2], Caitlin E Bromberg[1,2,3], Jim Baun[4], Cody Zurhellen[4], P. David Adelson[1,2,3] and Theresa Currier Thomas[1,2,3,5]

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Traumatic brain injury (TBI)-induced Wallerian degeneration and secondary injury sequelae are associated with persisting neuroinflammation hypothesized to increase risk of cognitive decline and neurodegenerative diseases, but long-term impact on pathology and potential sex-specific differences are underexplored. We evaluated markers of neuropathology, neuroinflammation, astrogliosis, axonal injury, phospho-tau, and amyloid pathology in the dentate gyrus (DG) of the hippocampus in adolescent male and female Sprague Dawley rats 7 and 168 days after experimental diffuse axonal injury (DPI) in comparison to age- and sex-matched controls. Neuropathology differed as a function of TBI, Sex, TBIxDPI, and TBIxDPIxSex, with distinct differences in neuropathology distribution at 168DPI. At 168DPI, evidence of neuroinflammation was present in all groups compared to 7-day shams. Astrogliosis was greater in 7DPI rats but was significantly reduced in TBI rats compared to sham at 168DPI. Axonal pathology was sparsely identified in sham and injured rats at 168DPI. A 45% increase in neutral red staining was present in TBI rats at 168DPI ($p<0.05$), where red staining co-localized with neuropathology. No pathological tau or amyloid staining was observed. These findings underscore the need for more comprehensive investigations into long-term consequences of TBI in adolescents.

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Funding: NIH(R01NS100793),PCH Leadership Circle Grant, PCH Mission Support

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Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P13: Levels of dietary carbohydrate, sleep, and noise exposure affect PERK protein levels in biofluids

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Background: The integrated stress response is a stress-adaptive intracellular signaling network activated by four protein kinases, including RNA-like endoplasmic reticulum kinase (PERK). Poor sleep, elevated noise exposure, and inadequate consumption of dietary carbohydrate (CHO) are physiological stressors that have been linked to adverse mental and physiological outcomes. The relationship between sleep duration, noise exposure, CHO, and PERK levels in multiple biofluids in adults is unclear. Purpose: To examine if the amount of CHO intake, sleep, and noise exposure affected the relationship between these variables and salivary and urinary PERK protein levels. Methods: Undergraduate college students [N=21, 18-22y (mean/stdev: 20.5/1.3), 28.6% male, 66.7% female, 4.8% non-binary] enrolled in a course-based undergraduate research experience (CURE) at the University of Arizona in 2022 and 2023 provided urine and saliva samples. Students completed a 4d food diary, 24h dietary recall, self-reported questionnaire to assess sleep quality), recorded noise exposure in 4 environments, and objectively measured sleep duration and physical activity (Actiwatch, Phillips, Respironics) for 4d. Salivary and urinary PERK protein levels were measured by ELISA. Results: For students in the CURE, 57% consumed less dietary CHO than the acceptable amount (<45%), 24% slept less than recommended (7h), and 27% were exposed to harmful noise levels (>70 dB). For only the students with adequate CHO intake, the %CHO was positively associated with urinary and salivary PERK/GAPDH levels (R2= 0.59, P = 0.01 and R2 = 0.47, P = 0.04, respectively). There were no associations when all students or those with low CHO intake were included in the analysis. For students exposed to high noise levels, noise was negatively associated with urinary and salivary PERK/GAPDH protein levels (R2 = 0.45, P = 0.0460 and R2 = 0.24, P = 0.18, respectively). Yet, for students exposed to normal noise, noise was positively associated with urinary and salivary PERK (R2 = 0.30, P = 0.13 and R2 = 0.30, P = 0.12, respectively). Sleep duration was not associated with urinary or salivary PERK/GAPDH regardless of how the students were stratified. Yet, among students with inadequate sleep, sleep duration trended towards being negatively associated with urinary and salivary PERK (P = 0.11 and P = 0.25, respectively). Conclusions: The amount of dietary CHO, sleep and noise exposure affected the relationship to PERK regardless of whether PERK was measured in urine or saliva. The lack of association between sleep and PERK may be related to sample size during stratification of the data.

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Funding: University of Arizona

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Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P43: Efficacy of Rapamycin for Increasing Female Reproductive Longevity in Old Rhesus Macaques

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More women are delaying parenthood until later in their lifetime. However, the chances of successful conception at later ages are significantly less due to the gradual decline in follicle counts and oocyte viability in ovaries. Before puberty, primate ovarian follicles are arrested in a quiescent state. At the onset of puberty, ovarian follicles progress through distinct phases ranging from primordials (earliest stage) to antral follicles (pre-ovulatory stage) before ovulation. The phosphatidylinositol 3-kinase/AKT serine/threonine kinase/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway triggers a signal transduction cascade in mammalian ovaries that causes primordial follicle activation. Rapamycin (RAPA) inhibits the mTOR pathway and has the potential to arrest primordial follicle loss, and is therefore a promising therapeutic to slow ovarian aging by allowing a greater pool of oocytes for successive pregnancies. However, its effect on primate ovaries is unknown. The purpose of our research is to investigate the feasibility of RAPA to preserve the ovarian reserve in older macaques to shed light on the efficacy of RAPA for increasing female reproductive longevity. We analyzed ovaries from aged old (n=2, 18-22 yr) female rhesus macaques, reproductively similar to women, to investigate the impact of RAPA on the ovarian follicular reserve. One ovary from each macaque was removed prior to RAPA treatment (baseline), and the second ovary was removed after 11 months of RAPA treatment (treated). Ovaries were fixed, serial sections were prepared, and stained with hematoxylin and eosin. Three spatially distributed sections per ovary per animal for each group (baseline and treated) were scanned via Olympus cellSens ™ imaging software. We counted and analyzed follicles in different developmental stages from both groups. In total, 12 histology slides were digitized and 12 were annotated with follicle identifications (2 donors, 2 ovaries per donor, 3 histology sections per ovary). Comparisons were made between baseline and treated total follicle counts of all major follicle types; for each type of follicle the sum over all three slides serves as an estimate of the total number of follicles in the ovary. Of the total number of follicles counted, we observed similar percentages between the baseline and treatment groups, respectively, of primordial (23 vs 28%), transitional primordial (37 vs 34), primary (5 vs. 7), transitional primary (13 vs 9), secondary (7 vs 6), multilayer (11 vs 11) and antral follicles (5 vs 6). Our preliminary results suggest that RAPA maintained the follicular pool, thereby having the potential as an intervention to increase reproductive longevity.

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Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P38: Cytotoxicity effects of Cyanidin Chloride and Withaferin-A on SHSY-5Y and CHLA-03 cell growths using MTT assay

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Many people turn to dietary vegetables, medicinal herbs, and plant extracts to prevent or treat cancer due to natural compounds' antioxidant properties and health benefits. Ayurvedic plants are used in Indian medicine to target cancer cells and their macromolecules. Cyanidin chloride (CYC) and Withaferin A (WFA) are natural compounds found in pigmented and rooted plants in many retail stores. CYC and WFA were tested against Temozolomide (TMZ) for their cytotoxicity and cell growth effects on brain cancer cells using the MTT assay. The materials and methods used vary between the 48-hour culture and the five-day culture. The SHSY-5Y cells (standard cell line cloned from neuroblastoma) and CHLA-03 cells (pediatric astrocytoma cell line) were cultured for both 48 hours and five days. The passage cells were at a concentration of 2 x 105 cells/200µls in a culture medium. 10µg/µl (2µls per well) and 50µg/µl (10µls per well) of WFA, CYC, and TMZ were added to separate sets of wells along with untreated control cells into microplates, divided equally into two 10µM, 50µM, and controls. The cell cultures were incubated for 48 hours and five days at +37°C and 5% CO2. After incubation, 10µl of the MTT labeling reagent (final concentration 0.5 mg/ml) was added to each well. The microplate was incubated for 4 hours in a humidified atmosphere. 100 µl of the Solubilization solution was added to each well. They were incubated overnight in a humidified atmosphere, and the quantity of formazan of viable cells was measured in the ELISA reader at an absorbance between 550 nm and 600 nm. Both SHSY-5Y and CHLA-03 cells had decreased CYC and WFA after 48 hours. Purple crystals were found in all wells. CHLA-03 cells saw increased viability at both 10µM and 50µM CYC concentrations. WFA had similar results to TMZ. After five days, all three chemicals increased cell viability for SHSY-5Y and CHLA-03 cells at 10µM and 50µM concentrations. Natural compounds like WFA and TMZ show cytotoxic properties that may be promising for treating pediatric brain cancer. CYC has low cytotoxicity in CHLA-03 cells due to increased viable cells. This study provides insight into the correlation between CYC, WFA, and TMZ's cytotoxicity properties in cancer cell lines.

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Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P20: Sex-Specific Regulation of Catecholamine Signaling in Rats Exposed to Dexamethasone In Utero and Angiotensin in Adulthood

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Pregnant women who are at risk of pre-term delivery are given the synthetic glucocorticoid dexamethasone (DEX) to stimulate fetal lung development as it is not degraded by 11ß-hydroxysteroid dehydrogenase, enabling DEX to freely cross through the placenta and act on the developing fetus. Our lab has previously found that in-utero DEX exposure increases stress-induced blood pressure and heart rate responses in female, as well as autonomic dysregulation in the adult offspring. Angiotensin II (Ang II) induces hypertension and cardiac remodeling in part through activation of the sympathetic nervous system. Given these prior findings, this project explores whether prenatal DEX exposure alters the response of Ang II on cardiac sympathetic nervous system regulation. Pregnant rats were administered either vehicle (20% w/v 2-hydroxypropyl ß-cyclodextran) or the glucocorticoid DEX (0.4 mg/kg body weight, i.p) on gestation days 18-21. When offspring reached ~15 weeks of age, groups were administered either subcutaneous AngII (200 ng/kg per min) as a cardiovascular challenge or saline as experimental control for four weeks. To measure local sympathetic signaling, tyrosine hydroxylase (TH) was analyzed as it serves as the rate limiting step of catecholamine synthesis while catechol-O-methyltransferase (COMT) was selected as it catalyzes catecholamine breakdown. Gene expression of adrenoreceptor ß1 (Adrb1) was measured to assess receptor availability for sympathetic activity. Data were analyzed by 3-way ANOVA with sex, prenatal treatment (i.e., DEX vs. Vehicle), and postnatal treatment (i.e., saline vs. AngII) as the variables. There was an overall main effect of prenatal treatment to reduce TH expression in the LV ($p=0.018$), although this effect was more pronounced in males. COMT expression was found to be significantly impacted by sex, prenatal treatment, and post-natal treatment (3-way interaction, $p=0.016$). Thus, the degree to which DEX and Ang II impacted COMT expression differed by sex. There was a sex x postnatal treatment interaction ($p=0.013$) on ADRB1 expression whereby expression was increased by Ang II only in female hearts. Although prior studies have shown that Ang II can increase local sympathetic activity in the heart, the present data suggest that prenatal treatments disrupt this response in a sex-specific manner. Moreover, sex and prenatal treatment were greater drivers of local sympathetic regulation than Ang II.

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Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P49: Novel Nanoparticle Drug Delivery System Improves Brain Endothelial Cell Barrier Properties Following Acute Ischemia Reperfusion-like Injury

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Acute ischemic stroke triggers endothelial activation and induces cerebrovascular inflammation which can result in blood-brain barrier (BBB) loss leading to worsened stroke outcome. Physiologically, the BBB serves as a protective barrier which can pose an obstacle for drug delivery into the injured brain following a stroke. The human serum albumin (HSA) nanoparticle is a novel drug delivery method currently being investigated. In this study we investigated whether ApoE ligated HSA nanoparticles loaded with or without the BDNF mimetic peptide (GSB-106) affects barrier integrity proteins and inflammatory mediators in human cerebrovascular endothelial cells (HBMEC) after an ischemic like injury in vitro. Primary HBMECs were exposed to normoxia (21% O2) or hypoxia plus glucose deprivation (HGD; 1% O2). Following HGD 3h or normoxia, HBMECs were subjected to simulated reperfusion (HGD/R, 21% O2) for 12h. Immediately following the onset of reperfusion HBMECs were treated with either vehicle, blank HSA nanoparticles (10-7 or 10-6 M), GSB-106 (10-7 or 10-6 M), or HSA nanoparticles containing GSB-106 (10-7 or 10-6 M). HBMEC expression of barrier markers (claudin-5, occludin, ZO-1, PECAM-1), pluripotent intracellular signaling molecule (Akt), and inflammatory protein (IL-1β) were examined using qRT-PCR, in cell western, and immunoblotting techniques. HGD/R exposure increased IL-1β mRNA and PECAM-1 protein expression and exposure to blank HSA nanoparticles, GSB-106, or HSA nanoparticles containing GSB-106 did not have an effect. HGD/R exposure also decreased claudin-5 mRNA and treatment with HSA nanoparticles containing GSB-106 attenuated this HGD/R mediated decrease. HGD/R exposure decreased occludin mRNA expression; however, intriguingly we observed a concomitant increase in occludin protein expression. Furthermore, treatment with the HSA nanoparticles containing GSB-106 attenuated increased occludin protein expression in cells exposed to HGD/R. Protein levels of the activated p-Akt relative to Akt was decreased following HGD/R exposure. However, expression of p-Akt was not altered by treatment with either blank HSA nanoparticles, GSB-106, or HSA nanoparticles containing GSB-106. In conclusion, these data suggest that HGD/R injury decreases integral barrier properties and increased inflammation, potentially via decreased activation of Akt. Further elucidation of the pluripotent effects of the biomimetic peptide as well as nanoparticle carriers on the vascular endothelium and the ability to improve barrier integrity following an acute ischemic reperfusion-like injury may shed light on its potential as a therapeutic delivery system.

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Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P47: Development of Novel Drugs to Combat Alzheimer's Disease

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Alzheimer's disease (AD) is a neurodegenerative disorder that is the most common cause of cognitive decline in elderly individuals. AD is pathologically defined by an accumulation of amyloid-ß (Aß) plaques, neurofibrillary tangles (NFTs), neuronal and synaptic loss, brain atrophy, and inflammation. There is currently no effective cure for AD neuropathology. Thus, most treatments are implemented with the goal of slowing the accumulation of the pathological identifiers of AD, such as Aß plaques. Retinoids are structural derivatives of vitamin A which promote activation of transcription factors that regulate the expression of gene activity involved in tumor suppression and other functions. Retinoids can be broken down into two specific classes: retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Bexarotene is a "rexinoid" due to being selective for RXR binding, and it is also an FDA approved drug primarily used to treat cutaneous T-cell lymphomas (CTCLs) and other cancers by regulating gene expression of anti-cancer genes. Bexarotene has also been reported to reduce brain Aß levels and improve cognitive function in mouse models of AD. The putative mechanism for this effect involves heterodimerization of RXR and liver X receptor (LXR). The RXR-LXR heterodimer then binds to LXREs in the ApoE gene promoter to induce the expression of ApoE in brain cells which promotes Aß clearance. While bexarotene is an effective treatment against CTCL and could be used as a possible treatment against AD, it has significant side effects of hyperlipidemia and hypothyroidism. In the current study, we have evaluated multiple generations of novel bexarotene analogs for their potential to bind and activate the RXR-LXR heterodimer via cell culture techniques in human embryonic kidney and brain cells by employing the mammalian 2-hybrid (M2H) luciferase assay to determine the degree of transcriptional activation induced by each analog. Current results suggest that these new compounds may possess similar or even enhanced therapeutic potential since several of our novel rexinoids display augmented RXR activation as high as 117% of the bexarotene control in embryonic cells and 123% of control in human brain cells. This work broadens our understanding of RXR-ligand relationships and allows us to study the effects of utilizing bexarotene analogs to develop efficacious pharmaceutical drugs that target AD. Our current results reveal that modifications of RXR agonists can yield agents with enriched biological selectivity and potency when compared to the parent bexarotene compound, potentially leading to the development of drugs that could combat AD and improve patient outcomes.

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Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P46: Synergism of Novel Rexinoids and Vitamin D for the Potential Treatment of Human Diseases

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The active form of vitamin D, 1,25-dihydroxyvitamin D (1,25D), binds to the vitamin D receptor (VDR) as a heterodimer with RXR and associates with vitamin D response elements (VDREs) to regulate the transcription of over 1,000 target genes. Bexarotene (Bex) is an RXR ligand developed to treat cutaneous T-cell lymphoma and may also be a putative therapeutic for Alzheimer's disease and for other human cancers. We postulate that VDR and RXR ligands can "synergize" to "super-activate" the VDR-RXR heterodimer. The purpose of the study is to determine if this receptor "cross-talk" could allow disorders that are normally treated with high-dose Bex therapy (leading to significant patient adverse side-effects) to instead be treated using both low-dose Bex and vitamin D. We designed experiments to examine the effect of both VDR ligands (1,25D) and RXR ligands (Bex/analogs), alone and in combination, to activate VDR-RXR-mediated transcriptional activation. The assay system was composed of human kidney cells that were transfected with a VDRE-luciferase reporter gene. The conditions of this assay were varied to include different VDREs, ligands, as well as increasing the amounts of expressed VDR protein to determine if select RXR-specific ligands (rexinoids) can synergize with vitamin D to produce amplified RXR-VDR heterodimer activity. Our results indicate that the direct repeat VDRE (XDR3) possessed much higher synergism than the everted repeated VDRE (PER6) when cells were treated with 1,25D and/or Bex. Moreover, in the presence of the XDR3 VDRE, the endogenous VDR produced much higher synergism between 1,25D and Bex when compared to cells transfected with extra human VDR cDNA. No major differences were observed in PER6 activation when endogenous versus extra VDR was assessed. In addition to Bex, we also evaluated several structurally diverse Bex analogs, and the results of these assays revealed that one analog (A30) displayed the highest synergism, even greater than the positive control Bex parent compound in the XDR3 assay. Taken together, these results suggest that VDR and RXR ligands may "cooperate" to drive enhanced RXR-VDR heterodimer activation, and that 1) the nature of the VDRE, 2) the concentration of VDR, and 3) the chemical nature of the RXR ligand (analog) can all impact this synergistic activation. Thus, a number of diseases that respond to treatment with either vitamin D, or with rexinoids, may be amenable to enhanced therapeutic potential by employing multi-ligand dosing via combinatorial therapy.

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Funding: New College Undergraduate Inquiry and Research Experiences (NCUIRE); NIH R15 CA249617

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Talk: Friday October 27th, 4:15 PM

S3.5: The impact of dietary tryptophan levels on energy in glucose homeostasis in LFD and HFD-fed mice

Connell NT, Wachsmuth HR and Duca FA

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The gut microbiota is a salient contributor to host energy and glucose homeostasis and is readily modified by diet. The gut microbiota alters ingested nutrients, generating metabolites that can act as signaling molecules to regulate host physiology. For example, dietary tryptophan is metabolized by gut bacteria into indoles, which are known to regulate host inflammation. Systemic inflammation is a hallmark characteristic of obesity and type 2 diabetes, and reducing inflammatory signaling improves metabolic parameters. Our lab has demonstrated that diet-induced obese rodents have reduced indole production compared to chow-fed, healthy controls despite identical tryptophan intake. However, how dietary tryptophan and gut microbiota indole production impacts host metabolism is not well characterized. Therefore, we investigated how dietary tryptophan levels impact energy and glucose homeostasis in mice via 1) tryptophan depletion and 2) tryptophan supplementation. For the first study, mice were placed on a low-fat diet (LFD) or a high-fat diet (HFD) with or without tryptophan in the diet. For the second study, mice were placed on a LFD or HFD with normal tryptophan levels or with 3 times the amount of normal tryptophan in the diet. Energy homeostasis was measured via weekly body weight, adiposity, and food intake measurements and acute and chronic effects of the diets were measured via indirect calorimetry. Additionally, acute and chronic effects of the dietary intervention on glucose homeostasis were assessed via glucose tolerance tests and insulin tolerance tests. We found that tryptophan depletion resulted in a significant decrease in body weight and adiposity in LFD and HFD feeding, and decreased food intake during HFD feeding, with no effect of tryptophan depletion on glucose homeostasis during LFD or HFD feeding. Surprisingly, tryptophan supplementation had no effect on body weight, adiposity, or glucose homeostasis in either the LFD or HFD groups. In conclusion, our studies indicate that dietary tryptophan is necessary to maintain body weight and that tryptophan supplementation has no impact on metabolic parameters. However, indole production remains to be assessed in these studies. Therefore, future studies will assess how altering dietary tryptophan levels impacts indole production and whether direct indole supplementation affects metabolic homeostasis.

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Funding: Department of Defense PRMRP

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Talk: Friday October 27th, 10:30 AM
Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

S1.3/P50: The Multifaceted Nature of Cardiovascular Disease and Why Race Matters

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It is no secret that health disparities exist in the healthcare field but why they exist is a hot topic. Many factors may contribute to health disparities among different ethnic racial groups. Currently, there is a lack of literature examining the potential link between various contributors, including racism, family history, genetics, and epigenetics. Here, we attempt to bring together findings related to these different contributors, specifically in the field of cardiovascular health and disease, in order to understand the effects of these factors on each other and on the existing cardiovascular health disparities. We find that race and ethnicity significantly contribute to cardiovascular health issues of minority groups. Moreover, race, ethnicity, and social determinants such as education, economic stability, and environment play a large part in the development of cardiovascular disease, in part through epigenetic regulation of gene expression, and should be seriously considered in the diagnosis of patients. Likewise, genetics, while not as significant as the aforementioned, should be considered but does not explain disparities in cardiovascular disease in minority groups. Implications of current disparities in cardiovascular outcomes may be a result of a combination of a lack of knowledge, discrimination, and level of care shown to minority groups within the healthcare system. The goal should be to create a mindset change among researchers, physicians, and public figures presenting health care information to take race, ethnicity and social determinants of health into consideration when discussing, diagnosing, and treating cardiovascular disease and similar ailments.

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Funding: N/A

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Poster Session 1: Friday October 27th, 7:00 PM - 9:00 PM

P14: Glycodeoxycholic Acid Impacts Metabolic Homeostasis in High Fat Fed Mice

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The purpose of this study is to quantify bile acid levels in chow-fed, obese high fat diet (HFD)-fed, and HFD-fed rats supplemented with the prebiotic fiber oligofructose (OFS), and to determine the impact of the secondary bile acid glycodeoxycholic acid (GDCA) on glucose and energy homeostasis during high fat feeding. We first quantified bile acid levels in the portal vein and liver of healthy chow, HFD-fed obese, and HFD-fed rats supplemented with oligofructose, and found that GDCA was decreased in high fat-fed mice, and increased with OFS supplementation. We then treated mice on HFD with a daily oral gavage of either saline (control) or GDCA to determine if this bile acid could be mediating the beneficial effects of OFS supplementation on body weight and glucose homeostasis. We also measured factors of energy homeostasis using a metabolic cage system and performed real time quantitative PCR to determine the signaling mechanism mediating the impact of GDCA treatment. We found that GDCA decreases body weight and adiposity and improves glucose and insulin tolerance. We also found that GDCA increases energy expenditure and locomotor activity in HFD-fed mice. GDCA-treated mice displayed increases in bile acid receptor signaling, specifically FXR and TGR5. From this we conclude that GDCA improves body weight, adiposity, and glucose homeostasis, likely due to increases in locomotor activity and energy expenditure. Further studies will determine if this increase in energy expenditure is due to voluntary or involuntary activity. GDCA may be acting on the intestinal bile acid receptors, FXR or TGR5, although future studies are necessary to better understand this mechanism and how it mediates changes in energy expenditure with GDCA treatment.

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Poster Session 2: Saturday October 28th, 11:30 AM - 1:30 PM

P33: Age- and Aging-with-Injury: Temporal Microglial Morphological Profiles Indicate Unique Pathological Processes in Behaviorally Relevant Circuit Relays

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Traumatic brain injury (TBI)-induced chronic neuroinflammation is implicated in the development of persisting neurological morbidities. A chronic time course of microglial activation in a behaviorally relevant circuit in both sexes is needed to accurately and comprehensively assess the benefits and consequences of neuroinflammation. Age-matched adolescent male and female Sprague-Dawley rats underwent midline fluid percussion injury (FPI) or sham surgery (n=5-6/group;total=64). At 7-, 56-, and 168-days post-injury (DPI), Iba-1 stained morphologies and morphological characteristics were quantified in the cortex and thalamus. Microglia had shorter branches and fewer endpoints, indicative of neuroinflammation, as a function of FPI ($p<0.05$), DPI ($p<0.05$), and FPI* DPI ($p<0.05$), where FPI-induced activation decreased and age-related activation (shams) increased over time. Cortical rod microglia were highest at 7DPI ($p<0.05$) and present through 168DPI (FPI* DPI interaction; $p<0.05$). FPI* DPI* Sex interaction for thalamic cell counts ($p<0.05$) indicated a greater FPI response in 7DPI males versus females ($p<0.05$). Chronic TBI-induced neuroinflammation has a distinct regional and sex-dependent temporal profile compared to age-related neuroinflammation, providing a template for more comprehensive interpretation of interventions' impact on specific pathological processes associated with aging- and aging-with-injury-related morbidities.

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