New Discovery of RV Pathological Changes in Mice using PAH and DM Models

Although Diabetes Mellitus (DM) is known to damage the left ventricular (LV) structure and function, far less is known about its effects on the right ventricle (RV), especially when it is combined with pulmonary arterial hypertension (PAH). In our experiment, we induce PAH by the combination of VEGFR inhibition with SU5416 and chronic hypoxia, aiming to investigate how PAH alters RV structure and function in mice. We then measure any changes in protein content and gene expression as well as its negative effects on cardiac structure and function using a non-invasive ultrasound (echocardiography) before further investigating the mechanisms by which RV structure and function are negatively impacted in transgenic mice. This approach will provide new information on how PAH, alone and combined with DM, changes RV structure and function over a period of time in order to identify the molecular pathways that could be blocked and reduce such negative effects.

PRI Academic Activities

Up-to-date Research Papers Published in 2018

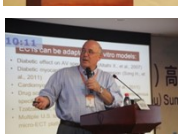
	G.B	J.C	L.C	P.N.E	E.G	Y.T
2018	7	4	29	2	1	7

PRI Work in Progress (WIP) Monthly Seminar

9/26/2018: Dr. Andrew Roberts presented his work in progress, "Roles of Oxidative Stress and Nitric Oxide Signaling in Causing Pulmonary Microvascular Dysfunction in Type-1 Diabetes".

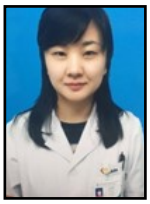
11/14/2018: Dr. Esma Yolcu presented her work in progress, "Targeting FAS Pathways for the Prevention and Treatment of Graft-vs– Host Disease".

PRI China Training Program



Drs. Lu Cai, Brad Keller, and Yi Tan along with Program Coordinator **Sallye Burns** traveled to China for student recruitment. They visited cooperating institutions in Changchun, Wenzhou, Beijing, Nanchang. More students and visiting scientists are expected to enter the program in the coming year. The team also participated the 9th US-China Diabetic Complication (Wenzhou) Summit Forum and gave talks at the summit forum.

Welcome Visiting Scholars and Students



Xiofeng Wang, MD, China-Japan, Union Hospital of Jilin University

Zhongxin Zhu, MD. School of Pharmacy, Wenzhou Medical University

Li Feng, MD. Ph.D. The Qianfoshan Hospital of Shandong Province

Shan Huang, the first hospital of Jilin University. Ph.D. candidate

Wenqian Zhou, MD, the first hospital of Jilin University

Hongbo Men, MD, the first hospital of Jilin University

Xiang Wang, MD. Ph.D. the first hospital of Jilin University.

Representative Papers Published

Ohja K, Gozal E, Fahnestock M, **Cai L**, **Cai J**, Freedman JH, Switala A, El-Baz A, **Barnes GN**. Neuroimmunologic and Neurotrophic Interactions in Autism Spectrum Disorders: Relationship to Neuroinflammation. Neuromolecular Med. **2018** Jun;20(2):161-173

Kang Y, Wang S, Huang J, **Cai L, Keller BB**. Right ventricular dysfunction and remodeling in diabetic cardiomyopathy. Am J Physiol Heart Circ Physiol. **2018** Nov 9. doi: 10.1152

Zhou S, Wang J, Yin X, Xin Y, Zhang Z, Cui T, **Cai J**, Zheng Y, Liu Q, **Cai L**. Nrf2 expression and function, but not MT expression, is indispensable for sulforaphane-mediated protection against intermittent hypoxia-induced cardiomyopathy in mice. Redox Biol. **2018** Oct;19:11-21.

Yu H, Ye F, Yuan F, **Cai L**, Ji H, **Keller BB**. Neonatal Murine Engineered Cardiac Tissue Toxicology Model: Impact of Metallothionein Overexpression on Cadmium-Induced Injury. Toxicol Sci. **2018** Oct 1;165(2):499-511.

Young JL, **Cai L**, States JC. Impact of prenatal arsenic exposure on chronic adult diseases. Syst Biol Reprod Med. **2018** Dec;64(6):469-483.

Liang X, Zheng S, Cui J, Yu D, Yang G, Zhou L, Wang B, **Cai L**, Li W. Alterations of MicroRNA Expression in the Liver, Heart, and Testis of Mice Upon Exposure to Repeated Low-Dose Radiation. Dose Response. **2018** Sep 24;16(3).

Congratulations, Qian Lin!

Qian Lin, the first Ph.D. Student of Dr. Yi Tan successfully performed her Ph.D. defense and received her degree in August of 2018. During her Ph.D. training, Qian immersed herself in her project of an engineered fibroblast growth factor 1 (FGF1) partial agonist, carrying triple mutations (FGF1HBS) on nonalcoholic fatty liver disease (NAFLD), which is strongly associated with type 2 diabetes (T2D). Her findings indicate that, in addition to its potent glucose-lowering and insulin-sensitizing effects, the novel non-mitogenic variant FGF1HBS has preventive and therapeutic effects on NAFLD in T2D by effectively inhibiting oxidative stress and improving lipid metabolism, which allows great potential to replace the use of FGF1WT to treat NAFLD in diabetes. More importantly, the study provides new insight into the mechanisms by which FGF1HBS prevents hepatic oxidative stress and steatosis in T2D. AMPK, which activates Nrf2-mediated anti-oxidative pathways and inhibits SREBP-1- mediated lipid metabolic pathways, is a critical target for FGF1 protection against NAFLD in T2D. From her perspective, a full understanding of the FGF1 function in metabolic disorders requires further investigation of the multiple roles and aspects of AMPK or other molecular targets in these pathophysiological processes. This project provides fundamental evidence for FGF1 as a novel therapeutic approach to the prevention of NAFLD by activating hepatic AMPK and is ready for submission in Hematology. During her Ph.D. training period, Qian won numerous awards in various international conferences and co-authored several papers in several journals including Cell Rep, Kidney Int., and Diabetes and Int. J Pharm. Now, she is a post-doctorate fellow in Dr. Lu Cai's lab.

PRI Awards

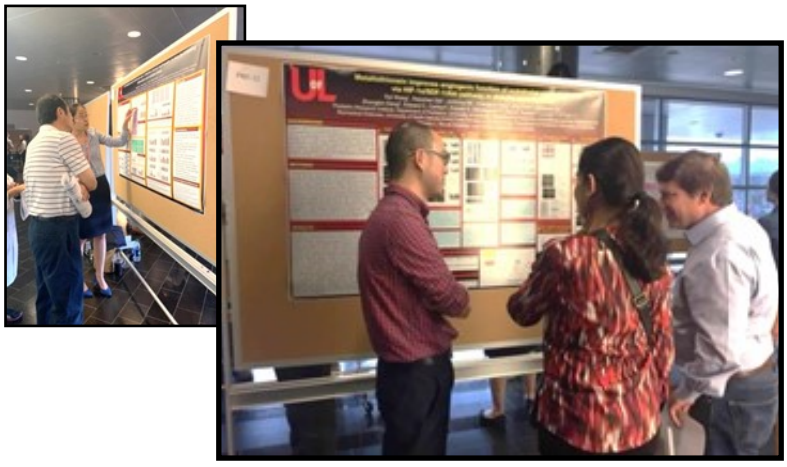
Jamie Young
won the "Travel Award" at the 10th Conference on Metal Toxicity and Carcinogenesis on October 28-31, 2018 in Albuquerque, New Mexico.


Certificate of Appreciation

Dr. Qian Lin received a Certificate of Appreciation in the 2nd International Conference on Diabetes and its Complications (JCDC2018) on October 22-24, 2018 in Houston, Texas for her talk on "a Novel Fibroblast Growth Factor I Variant Reverses Nonalcoholic Fatty Liver Disease via Activating AMPK in Type 2 Diabetes".

Research! Louisville

PRI had more than 10 individuals including faculty, staff, and students present their research posters at **Research! Louisville**.



Community Support

PRI faculty, staff, and students joined the UofL Department of Pediatrics' Team at the American Heart Association's annual Heart Walk held on September 22, 2018.