MENTORS DIRECTORY

2022 AMERICAN HEART ASSOCIATION UNDERGRADUATE SUMMER INTERNSHIP RESEARCH PROGRAM

to be held at

The Joan C. Edwards School of Medicine

at Marshall University

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The Bihl lab studies the role of extracellular exosomes (EXs), stem cell therapy, and the renin-angiotensin system in ischemic stroke, hemorrhagic stroke, and diabetic vascular complications. Our goal is to develop new therapeutical avenues addressing cerebrovascular diseases based on stem cells and their-released exosomes. The research approaches include transgenic mouse models in combination with animal surgeries, such as telemetric probe implantation for recording blood pressure and heart rate, minipump/microinjection for chronic/acute drug administration, and animal modeling for MCAO-induced ischemic stroke and brain injection for hemorrhage stroke.

Project 1. The role of exosomes in strokes and diabetes.

These studies emphasize the protective effects of EXs derived from endothelial progenitor cells (EPC-EXs) on vascular cells and neurons. During the summer program, the student could perform the *in vitro* studies to test the effects of EPC-EXs on vascular cells (endothelial cells and smooth muscle cells) and neuronal cells (neurons and astrocytes) under hypoxia/reoxygenation condition or oxHb stimulation. Moreover, we have human blood samples from stroke and diabetes patients. The students could use these samples to identify the biomarker for the outcome of these diseases.

Project 2. The protective role of ACE2/Ang-(1-7)/Mas in strokes and ageing by counteracting the effects of ACE/Ang II/AT1.

The studies in this project will verify the protective effects of ACE2 on hypertension, strokes and ageing models. During the summer program, the student could use *in vitro* cell culture to study the effects of ACE2 on ageing cells induced by Ang-II. For the *in vivo* model, we have the Renin-transgenic hypertensive mice and ageing mice samples. The students could measure the levels of ACE2 and angiotensin II in the brain or other organs from hypertensive and ageing mice.

Project 3. The role of exercise in vascular diseases by modulating the concentration and contents of exosomes.

Studies will focus on the effects of exercise on different organs, such as adipose tissue, vessels, and the brain through the communication of EXs. The students could measure the levels of EPC-EXs and ACE2 in the plasma, adipose tissue, blood vessels and brain samples from different animal models after exercise.

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Genetics of Obesity, Type 2 Diabetes, and Hyperlipidemia

My research interest is in understanding the etiology and pathogenic mechanisms underlying type 2 diabetes, obesity, and hyperlipidemia, which have strong implications for cardiovascular diseases (CVD). Type 2 diabetes is the most common form of human diabetes, accounting for over 90% of cases and obesity at such epidemic proportions creates serious public health problems. The prevalence of atherogenic dyslipidemia including hypercholesterolemia has increased considerably. Atherogenic dyslipidemia is causally linked to the development and progression of atherosclerotic CVD. There is substantial evidence demonstrating that genetic factors are strongly involved in the development of type 2 diabetes, obesity, and hyperlipidemia, and I have focused my attention on the link between gene dysfunction and these diseases and its interaction with diets. As an internship project in our laboratory for the AHA Summer Research Program, I propose to study candidate genes for diabetes, obesity, and hyperlipidemia loci identified in a genetic mouse model and their interactions with diets. This study will ultimately provide ready targets for the disease therapies in humans. Experimental methods involved in this internship research will include enzyme-linked immunosorbent assay, colorimetric assay, polymerase chain reaction (PCR), western blot analysis, and real-time quantitative PCR. DNA, RNA and protein will need to be isolated from mouse tissues. Instruments involved in this project include gel electrophoresis, western blotting apparatus, microplate readers, spectrophotometer, imaging system, thermal cyclers, EchoMRI, and comprehensive lab animal monitoring system.

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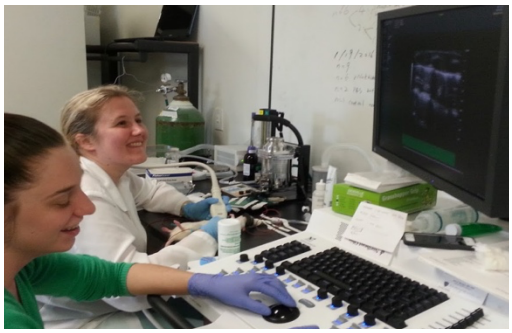

Echocardiographic assessment of rodent cardiac function by Dr. P. Marck and Undergraduate fellow A. Bryant.

The Pierre lab studies specific intracellular pathways involved in the integrated response of the myocardium to hemodynamic and metabolic disturbances. Our goal is to develop new paradigms to therapeutically address cardiovascular diseases based on the Na/K-ATPase signaling complex. We examine these issues by combining techniques of molecular and cell biology with *ex-vivo* (biochemistry and cell physiology, isolated heart perfusion, primary cardiac cell cultures, histology) and *in-vivo* assessments of cardiac function in genetically altered mice (echocardiography, measurement of blood pressure by tail-cuff and telemetry, cardiac and vascular catheterization). In the interdisciplinary environment provided by MIIR, interns are exposed to the pre-clinical models and key techniques that are currently available to cardiac and vascular physiologists and pharmacologists.

Project 1. Cardioprotection by Na/K-ATPase ligandsin acute myocardial infarction
Rationale: In addition to pumping ions, Na/K-ATPase interacts with neighboring membrane proteins and takes part in signaling complexes to send messages to various intracellular organelles. We believe that understanding these pathways and targeting the Na/K-ATPase receptor function will lead to novel interventions for the treatment and prevention of ischemia and reperfusion injury.
Method: the INBRE fellow will learn the isolated Landendorff-perfused mouse heart preparation and expose it to novel compounds targeting the Na/K-ATPase cardioprotective signaling pathway. This includes analysis of contractile function in real time and assessments of activation of the Na/K-ATPase cardioprotective pathway biochemically. The effectiveness of promising compounds will be further tested *in vivo* following experimentally-induced acute myocardial infarction (AMI). Mice will be subjected to an acute occlusion of the left descending anterior artery (LAD) for 30 min, and cardiac function and remodeling will be monitored after 1 and 2 weeks of reperfusion. In addition to functional echocardiographic assessments, the fellow will conduct morphometric and histological studies as well as biochemical (western blot) and qPCR evaluation of fibrosis, inflammation, and hypertrophy markers.

Project 2. Role of α1 Na/K-ATPase in adverse cardiac remodeling and heart failure
Rationale: Heart failure (HF), a chronic incurable illness, is the common end-stage of heart diseases caused by an array of highly prevalent conditions such as hypertension and coronary heart diseases. A greater and broader protection must be achieved to face the unmanageably high HF morbidity and mortality rates amidst the exploding incidence and prevalence of the condition worldwide. Targeting the Na^+/K^+-ATPase receptor function may lead to novel interventions
Method: Using our newly developed model of cardiac-specific KO of Na^+/K^+-ATPase α1, we will assess the role of Na^+/K^+-ATPase α1 in the development of hypertrophy, fibrosis and heart failure in mice subjected to Angiotensin II infusion by osmotic minipumps. In addition to functional echocardiographic assessments, the students will conduct morphometric and histological studies as well as biochemical (western blot) and qPCR evaluation of fibrosis, inflammation, and hypertrophy markers.

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Impact of Methamphetamine use during pregnancy on the cardiovascular function of adult offspring

My laboratory studies the impact of methamphetamine use during pregnancy on cardiovascular outcomes in adult offspring. We have found that prenatal exposure to methamphetamine leads to myocardial hypersensitivity to ischemic injury, induces long-lasting changes in cardiac gene expression, and alters vascular function in adult offspring. Importantly, some of these effects are sex-dependent. Our data suggest that individuals that were prenatally exposed to methamphetamine may be at increased risk of developing cardiovascular diseases. We are currently trying to understand the mechanisms by which prenatal exposure to methamphetamine induces these cardiovascular changes.

INBRE participants will have the opportunity to participate in the identification of methamphetamine-induced changes in cardiac gene expression (analysis of RNA sequencing data, real time PCR, western blotting), conduct experiments with isolated tissues (hearts and blood vessels), interact with other investigators in the department (faculty, graduate students, postdoctoral fellows, and undergraduate students), assess scientific literature, and learn to present their data to a scientific audience.

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The following projects are available in my laboratory:

Project 1: Adolescent vaping and behavior: Vaping (e-Cigarettes) is highly rampant among adolescents. This study will use mouse models to assess behavior changes due to vaping. My laboratory is interested in studying effects of vaping on cardiometabolic (obesity and heart disease) end points.

Project 2: Heart fat and heart function: Fat that surrounds the heart is different from fat that is present in rest of the body. My laboratory is interested in studying the function of this heart fat and its effects on heart. In this study the heart fat from patients with heart disease will be collected and used for studies.

TECHNIQUES:
Techniques that will be used in the above projects are:

1. Animal studies: rodent models of vaping
2. Behavior (anxious and depression) assessments
3. Isolating fat cells
4. Isolation and quantification of RNA (including miRNA) and DNA
5. Detection of genes using quantitative PCR/Real time PCR and Western Blotting
6. Detection of cardiometabolic endpoints