MENTORS DIRECTORY

2021 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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Genetics of Obesity and Type 2 Diabetes

My research interest is in understanding the etiology and pathogenic mechanisms underlying type 2 diabetes and obesity, concomitantly related diseases. 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. There is substantial evidence demonstrating that genetic factors are strongly involved in the development of type 2 diabetes and obesity, 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 WV-INBRE Summer Research Program, I propose to study candidate genes for diabetes and obesity loci identified in a genetic mouse model of obesity and type 2 diabetes and their interactions with diets. This study will ultimately provide ready targets for diabetes and obesity 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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Project 1. Examine the mechanistic role of thymidine phosphorylase in thrombosis.

Our recent study revealed, for the first time, that thymidine phosphorylase (TYMP), an enzyme in the DNA salvage pathway, plays important, mechanistic roles in facilitating platelet activation and thrombosis (Li et al. Circ Res. 2014). Thrombosis, namely, clot formation in the vascular system, is a fatal complication for many diseases, which causes myocardial infarction, stroke, or pulmonary embolism. Various anti-platelet and anti-thrombotic drugs have been developed; however, in addition to that they cause severe side effects, such as bleeding, some patients do not respond to those drug. Therefore, developing novel mechanism-mediated anti-platelet and anti-thrombotic therapy is a top priority. We believe that TYMP is a promising target because TYMP deficiency significantly inhibits arterial thrombosis but does not disturb systemic hemostasis. Furthermore, TYMP inhibitor has been approved by the FDA for clinical use, which makes it possible to be repositioned as a novel and systemically safe anti-platelet drug. For this, it is first necessary to elucidate the detailed mechanistic pathways of TYMP in platelet activation and thrombosis. Our hypothesis is that *TYMP plays an important mechanistic role in platelet activation via signaling pathways involving platelet glycoprotein VI (GPVI) and G-protein coupled receptors (GPCRs)*.

In this project, we will use basic laboratory techniques including cell lysate preparation, protein concentration quantification, Western blot and immunohistochemistry, as well as platelet aggregation assay, flow chamber assay, among others. The intern will participate in platelet isolation, stimulation, cell lysate preparation, measurement of protein concentration and perform Western blot assays etc.

Project 2. Examine the mechanistic role of thymidine phosphorylase in obesity and atherogenesis.

Dysregulated lipid metabolism and chronic inflammation have been recognized as key contributors to the development of obesity and atherogenesis. All of these are risk factors for causing thrombosis, which leads to myocardial infarction and stroke. TYMP is an enzyme in the pyrimidine salvage pathway. Our recent study revealed, for the first time, that TYMP possesses signaling functions and is essential for platelet activation and thrombosis, suggesting a novel function of TYMP in the cardiovascular system. TYMP is present in the lipid rich core of human atherosclerotic lesions, yet its function remains unknown. By searching Gene Expression Omnibus, we have found that TYMP is potentially correlated with the development of obesity. We thus hypothesize that TYMP participates in lipid metabolism and is essential for obesity and atherogenesis.
In addition to the basic laboratory techniques mentioned in project 1, this project will include preparation of aortic tree and aortic root for evaluation of atherosclerotic lesion. The intern will participate in dissection of the aortic tree, histological examination and quantification of the lesion areas as well as evaluation of leukocyte adhesion and rolling assay etc.

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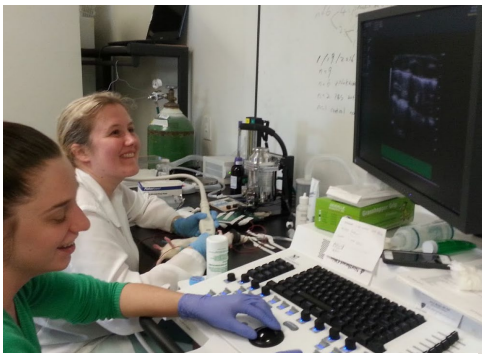

Echocardiographic assessment of rodent cardiac function by Dr. P. Marck and undergraduate fellow A. Bryant.

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 ligands in 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 on the Ischemic Heart

My laboratory studies the effect of methamphetamine on the ischemic heart. We have found that prenatal exposure to methamphetamine causes female rats (but not their male littermates) to become hypersensitive to myocardial ischemic injury when they become adults. Likewise, exposure to methamphetamine during early adulthood also selectively hypersensitizes the female (but not male) heart to ischemic injury. Importantly, this cardiac effect of methamphetamine persists even after exposure to the drug has been discontinued, providing evidence that methamphetamine induces cardiac changes that are long lasting and potentially irreversible. Our data suggest that women who have heart attacks may experience more extensive cardiac injury if they have a history of methamphetamine exposure during the prenatal or early adult periods. We are currently trying to understand the mechanism by which methamphetamine sensitizes the female heart to ischemic injury. We are also investigating methamphetamine-induced changes in cardiac gene expression that may underlie cardiomyopathy and other methamphetamine-induced cardiac problems.

Undergraduate students 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), learn how to quantify myocardial ischemic injury in a Langendorff isolated heart model, and conduct tissue bath experiments with blood vessels or other isolated tissues. Students will also have the opportunity to interact with other investigators (faculty, graduate students, postdoctoral fellows and graduate / undergraduate students), assess scientific literature, and learn to present their data to a scientific audience.

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My laboratory is interested in studying how various organs (gut-brain-adipose) cross-talk in reducing risk to cardiometabolic diseases in all age groups. We are interested in studying lifestyle changes (diet and exercise) on metabolic outcomes.

The following projects are available in my laboratory:

Project 1: Aging, Gut microbiome and risk to cardiometabolic diseases: The microbes that live within the gut play an important role in metabolism. These microbes can release factors that affect the host's metabolic function. In our laboratory we are studying changes in gut microbiome after exercise or dietary modifications and its effect on cardiometabolic function.

Project 2: Behavior and appetite regulation: Energy balance is key to maintaining body weight. Hypothalamic regulation of appetite maintains energy balance. Stress, anxiety and depression may lead to changes in appetite. Our laboratory is interested in studying the interplay between behavioral stress (such as anxiety or depression) and appetite regulation. We are investigating the effect of dietary modification or exercise on behavioral changes in rodent models.