Mentors at Marshall University

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Marshall University Mentor Listing According to Area of Research

Addiction: Egleton; Henderson: C. Risher; L. Risher

Cancer Research: Koc; Salisbury;

Cardiovascular Research: Arthur; Koc; Li; Liu; Pierre; Sodhi; Yan

Diabetes: Arthur; Cyphert; Kim; Koc

GI Research: Arthur; Haynes; Singh

Genetic Research: Kim

Informatics and Computational Biology: Cecchett; Denvir

Neuroscience/Sensory Research: Egleton; C. Risher; L. Risher

Obesity Research: Arthur; Borthakur, Cyphert; Kim; Koc; Singh; Sodhi

Renal Research: Liu; Sodhi; Yan

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Intestinal assimilation of Na and nutrients in the causation of cardiovascular diseases risk factors -- obesity, diabetes and hypertension.

Cardiovascular diseases dominate the health care disparities of West Virginia and Appalachia. Obesity, hypertension and diabetes are well known risk factors for a large spectrum of cardiovascular diseases. The intestinal assimilation of sodium, glucose, and other nutrients are a critical component in the causation and perpetuation of obesity, diabetes and hypertension. Thus, better understanding of the intestinal absorption of Na, glucose and other nutrients in the normal and pathophysiological intestine has been the focus of our NIH funding over the last 15 years. Specifically, regulation of transport processes responsible for the absorption of these substances by immune-inflammatory mediators, nitric oxide and by each other has been areas of investigation. The studies are largely translational utilizing in vitro, in vivo, animal and human intestine. We anticipate the student working closely with Dr. Subha Arthur, Assistant Professor of Clinical and Translational Sciences, and Dr. Uma Sundaram, Vice Dean for Research and Graduate Education in their laboratories at the Joan C. Edwards School of Medicine. It is anticipated that the student will work together with Drs. Arthur and Sundaram to develop a hypothetically driven project with a defined goal that can be accomplished in the 9-week period. The student will take advantage of all the necessary expertise, equipment and reagents available in the lab to accomplish the project. In the process, the student will learn appropriate techniques, more importantly, gain an appreciation for scientific thought, the conduct of research and critical analysis of existing literature.

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Role of gut microbiota in health and disease

My research interests broadly encompass the role of gut microbiota cross-talk with host intestinal epithelium and its relevance to the pathophysiology of inflammatory bowel disease (IBD) and obesity.

Project 1: Probiotic bacteria stimulate intestinal nutrient/ion absorption and counteract dysregulated ion transport in IBD and infectious diarrhea: Inhibition of electrolyte (NaCl) absorption is a hallmark of IBD and infectious diarrhea. Our studies delineated novel mechanisms underlying the beneficial effects of the probiotic *Lactobacillus acidophilus* in enhancing intestinal nutrient/ion absorption and counteract pathogen infection. We have partially characterized the *L. acidophilus*-secreted factors that stimulate intestinal Cl^- absorption and counteract *Citrobacter rodentium* infection-induced diarrhea. My NIH-funded current research utilizes crypt-derived human intestinal organoids to delineate the molecular pathophysiology of cryptosporidiosis, a widespread diarrheal disease caused by *Cryptosporidium* infection and an emerging global health problem. Utilizing this novel ex vivo model as well as in vivo mouse models, our studies, for the first time, have demonstrated that *Cryptosporidium* infection disrupts intestinal epithelial barrier function via downregulation of key tight junction proteins and inhibits Cl^- absorption by downregulating the expression of DRA (DownRegulated in Adenoma, SLC26A3), the apical membrane Cl^-/HCO_3^- exchanger protein responsible for Cl^- absorption. Our results implicate that dysregulated ion transport and impaired barrier function could be major contributing factors to cause cryptosporidiosis. Our subsequent studies will investigate the mechanisms of *Cryptosporidium* infection in immunocompromised hosts, such as HIV patients, in which the parasite is known to cause fatal diarrhea.

Project 2: Gut microbes regulate energy homeostasis in obesity: Obesity commonly results from imbalance in the body's regulation of energy intake, expenditure, and storage. Gut hormones, more particularly glucagon-like peptide 1 (GLP1) and glucose-dependent insulinotropic peptide (GIP) secreted by enteroendocrine cells (EECs) of the intestinal epithelium in response to food intake regulate energy balance and glucose homeostasis by stimulating insulin secretion, regulating appetite, gut motility and gastric emptying. Generation of EECs from intestinal stem cells is controlled by the sequential expression of HATH1 and two other basic helix-loop-helix transcription factors, Neurogenin 3 (Ngn3) and NeuroD1, a process significantly decreased in obesity. This results in decreased secretion of GLP1/GIP that critically regulate appetite via gut-brain axis and blood glucose via stimulating insulin secretion. Our studies showed that the probiotic gut bacterium *Lactobacillus acidophilus* significantly increased EECs in the intestinal mucosa by increasing the transcription factors Math1 (mouse counterpart of Hath1) and Ngn3 in mouse intestine and mouse intestinal organoid model. Our studies unravel a novel facet of gut microbiota involvement in the pathogenesis of obesity via its effects on EEC differentiation and production of gut hormones that regulate glucose homeostasis and energy balance which will be investigated in detail.

Alfred Cecchetti, PhD, MSc, MSc IS

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We have developed an informatics model at Marshall that we think will be useful in clinical research. My interests are in the areas of data warehouse development, machine learning- especially using unstructured data to develop classification and predictive capabilities, interactive visual analytics using Tableau, algorithm evaluation. I am also interested in mobile programming especially using the SignalR library for ASP.NET, which introduces real-time web functionality and database interactivity using SQLDependency.

Summer program participants who have an interest in the technical side of clinical research can take part in the following:

1. Developing survey tools using REDCap, an NIH sponsored tool used for research projects
2. Text extraction and text mining using the R programming language
3. Classification and prediction using decision trees, SVM, and k-NN in a R programming environment.
4. Smart Phone (android and iPhone) to server programming using Xamarin and C# and exploring real-time web functionality
5. DataMart development

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Diabetes and obesity are truly epidemics in our society. Unfortunately, current therapeutics do not provide complete relief and are attached with devastating side effects. Bariatric surgery can relieve diabetes and insulin insensitivity mere days after surgery in most patients. Current research has focused on the molecular and physiological changes that occur between pre- and post- surgery as potential avenues of diabetes reversal for people unfit for surgery. Interestingly, bile acids, molecules normally involved in emulsifying fats and cholesterol metabolism, are dramatically altered, both in species and accumulation. My lab focuses on bile acids in the pancreas and how they affect the beta cell, the epicenter of diabetes. In addition, the gut microbiota is also researched in regards to how bile acids can alter the gut dynamics. Lastly, my lab also examines the role of FGF21, a novel anti-diabetic hormone, on pancreatic function.

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My research focuses on how opioids regulate various cells in the brain during development. I have projects that look at cells in tissue culture and also in whole animals. My studies focus on how opioids given in utero alter the development of the brain.

Opioid regulation of brain development
In West Virginia we have one of the highest levels of opioid abuse in the whole country. Unfortunately this also includes among pregnant women, with approximately 10% of all neonates having exposure to opioids during pregnancy. The long term consequences of this exposure are not currently known. Studies with other drugs of abuse have shown that there can be significant developmental issues for the child when given during pregnancy. Our lab investigates how opioids can regulate the development of the brain. This project will investigate the effects of opioid exposure on the regulation of oligodendrocytes and brain myelination. Changes in myelination can have a significant effect on brain development, and lead to long term developmental delay. Methods that will be used will include dissection, Western blot analysis, immunofluorescence microscopy, and real-time PCR.

Instrumentation: This project may involve using fluorescent and UV plate readers, real-time PCR, microscopy, gel rigs, centrifuges, balances and other standard lab equipment.

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My research is in analysis of data generated by next-generation sequencing. The majority of my research is conducted in collaboration with basic and clinical scientists and is focused on analyzing and interpreting very large data sets in order to extract biological information to answer questions posed by these collaborators.

Robust and Reproducible Data Analysis Methodologies A particular focus of our facility is in performing analyses in a fully-reproducible manner, so that the same analysis can be re-run on the same data set with a guarantee of producing the same results. While it may sound as though this would happen by default, these analyses rely on software tools developed by third parties and on external resources, such as reference genomes and gene annotations. Both of these are subject to changes as new versions of software and resources are released, and these changes can alter the outcome of an analysis. We borrow techniques from the software engineering industry, such as concurrent version control and containerization in order to create fully reproducible bioinformatic analysis pipelines.

Customized Data Investigation Tools for Investigators Clients of our core facility typically perform genome-scale sequencing analyses such as expression profiling by RNA-Seq, variant calling by whole exome or genome sequencing, and other similar assays. Primary and secondary analyses of these data can be performed by our facility in a collaborative manner with individual investigators, but further exploration of the data generated in order to form biological hypotheses is best carried out by the investigator with specialized biological knowledge of the problem at hand. We are therefore interested in building interactive web-based tools through which an investigator can explore their own data set in a flexible and intuitive manner.

Methods and instrumentation Students participating in these projects will either perform large-scale data analysis of sequencing data or will build web-based interfaces to interact with such data. These projects will be entirely computer-based. Students will work with Linux servers via a command-line interface and will use dedicated open-source tools developed by the bioinformatics community, develop scripts in bash or Python, and use the statistical programming language R. Some projects may involve web development and database development. Students should be (or be prepared to become) comfortable operating with a computer purely from the command line.

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Regulation of nutrient and electrolyte transporters in human primary intestinal epithelial cells

Inflammatory Bowel Disease (IBD) disrupts proper assimilation of nutrients, electrolytes and water, and is one of the five most prevalent gastrointestinal diseases in the United States. To treat IBD, it is necessary to determine its "broken" molecular mechanisms, such as the dysregulation of nutrient and electrolyte transporters. Currently, there are no satisfactory human cell culture-based models of the small intestine to study this. We have recently established a panel of long-term human small intestinal 3D organoid culture models, consisting of small intestine epithelial cell types that self-organize into tissue-like structures *in vitro*. However, the apical domain is on the interior of an organoid, and thus not easily accessible. We are currently generating 2D monolayer cultures, in which the apical domain is exposed to the medium. The development of this 3D organoid-derived 2D intestinal epithelial monolayer culture system will enable us to study alterations in transporter activity in the context of IBD.

The student will work closely with Dr. Jennifer Haynes, Research Assistant Professor in the Department of Clinical and Translational Sciences in the laboratory of Dr. Uma Sundaram, Vice Dean for Research and Graduate Education at the Joan C. Edwards School of Medicine. The student will participate in a project examining the regulation of transporters in human organoid-derived intestinal epithelial monolayer cultures. The experimental methods will likely include cell and organoid culture, immunocytochemistry, fluorescence microscopy, RNAi transfection, protein extraction, and western blot analysis. Participants will learn both the appropriate experimental techniques and also gain insight into the scientific method used to conduct biomedical research.

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Characterizing the effect of tobacco flavorants on nicotine addiction

Nicotine, the primary addictive component of tobacco products, is one of the most heavily used drugs of abuse in the United States. It is estimated that a third of the U.S. population uses cigarettes, cigars and or chewing tobacco products. This results in ~440,000 premature deaths each year and an annual cost of more than $75 billion in direct medical charges. Menthol is the only remaining legal cigarette flavorant; but smokers of menthol cigarettes have lower quit rates. This has suggested that menthol may enhance nicotine reward; but how this occurs is unknown. To compound this problem, electronic nicotine delivery systems (ENDS), which allow a multitude of flavors, are becoming increasingly popular. It is becoming increasingly important to study how flavors play a role in the addiction to nicotine.

Our work has found that menthol enhances nicotine reward-related behavior (addiction) in mice. Our current and future work will focus on studying how tobacco flavorants, such as menthol, alter cellular mechanisms that are involved with addictive behavior. Summer students will receive training in general cell culture methods, quantitative microscopy, tissue sectioning, and immunohistochemistry. Depending on time and student preference, experiments with mouse models is an option as well. Our goal is to give students adequate experience in common biomedical techniques that will provide an excellent foundation for a future biomedical scientist. For more information please visit the Henderson lab website: https://www.hendersonlab.org

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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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SUMMER RESEARCH PROJECTS

The role of mitochondria in aging, heart disease, diabetes, neurodegenerative disorders, obesity, and cancer is becoming more apparent due to their central role in energy metabolism. In mammals, mitochondria are responsible for providing over 90% of the energy in the form of ATP, which is generated by the process of oxidative phosphorylation. They have their own 16.5 kb circular genome and translation machinery/ribosomes essential for the synthesis of 13 essential proteins of the oxidative phosphorylation complexes. The mammalian mitochondrial ribosome (55S) is composed of ~80 mitochondrial ribosomal proteins (MRPs), accumulating data suggest that alterations in expression levels, mutations, and post-translational modifications of MRPs affect disease states, apoptosis and cancer. Our multidisciplinary research takes advantage of biochemical, molecular and biological, and mass spectrometry (MS)-based proteomics technologies in a "systems biology" approach. The following studies will be aimed at understanding the role of mitochondrial translation in 1) cancer and 2) neurodegenerative diseases.

Project 1: Role of MRP expression defects in cancer. Apoptosis is an essential process for normal development, tissue maintenance and aging. Two pro-apoptotic proteins, DAP3 (Death Associated Protein 3) and PDCD9 (Programmed Cell Death Protein 9), were identified in our proteomics analysis of the mitochondrial ribosome as MRPS29 and MRPS30, respectively. We have recently characterized a DAP3 splice variant with an upstream open reading frame (uORF) that is involved in regulation of its expression in different cell lines. Alterations in MRPS29 and MRPS30 transcript levels are also observed in tumors; however, regulation of their expressions and contributions to tumor formation is not yet understood. Expression of pro-apoptotic MRPs will be screened at the transcript and protein levels by quantitative RT-PCR and immunoblotting analyses in various tumors.

Project 2: Regulation of protein synthesis by Fyn kinase. Investigation of the specific roles for phosphorylated MRPs on protein synthesis is underway in my laboratory. Using the state-of-the-art MS-based technologies, we identified several candidate kinases associated with the mitochondrial ribosome including Fyn and Pten-induced kinase 1 (PINK1). Fyn kinase is one of the targets in Alzheimer's disease and PINK1 is a Ser/Thr kinase related to Parkinson's disease (PD) and regulates mitochondrial biogenesis by mitophagy. To investigate the roles of Fyn and PINK1 in regulation of mitochondrial translation and biogenesis further, *in vivo* and *in vitro* translation assays will be performed.

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Project 1. Examine the mechanistic role of thymidine phosphorylase (TYMP) in thrombosis.

We recently demonstrated that TYMP, a platelet cytoplasmic protein, plays important mechanistic roles in facilitating multiple agonist-induced platelet activation. We found TYMP haploinsufficiency significantly inhibits arterial thrombosis without disturbing systemic hemostasis (Li et al. Circ Res. 2014). These exciting findings indicate that modulation of TYMP activity can potentially become a novel and systemically safe anti-platelet therapy. For this, it is first necessary to elucidate the detailed mechanistic pathways of TYMP in platelet activation and thrombosis. Therefore, based on these findings, we will test the hypothesis 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, among others. The intern will participate in platelet isolation, stimulation, cell lysate preparation, measurement of protein concentration and perform Western blot assays for this project.

Project 2. To examine the role of thymidine phosphorylase in development of atherosclerotic disease.

There is a large body of evidence demonstrating that platelets are central actors in the inflammatory reactions, which underlie chronic disease states. Accumulating experimental and clinical data suggest that platelets play important roles in the process of atherogenesis, a chronic inflammatory disease. Various chemokines, such as CXCL4 and CCL5, released by activated platelets trigger atherosclerotic monocyte recruitment and uptake of oxLDL, and possess multiple atherogenic activities. Our studies have demonstrated that TYMP plays a key role in platelet activation. This suggests that a TYMP inhibition mediated anti-platelet effect may diminish the vessel wall inflammation and thus prevent monocytes recruitment, uptaking of oxLDL by macrophage and VSMC, and VSMC proliferation, and thus promote an anti-atherosclerotic effect. We are currently testing the *hypothesis that deletion of TYMP or systemic inhibition of TYMP prevents the development of atherothrombotic vascular diseases.*

In addition to the basic laboratory techniques mentioned in project 1, this project will need a large amount of work on preparation of aortic tree and ring for oil-red O staining to evaluate the atherosclerotic lesion. The intern will participate in dissection of the aortic tree, histological examination and quantification of the lesion areas.

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The major research interest is renal physiology, focusing on understanding the molecular mechanism of cardiotonic steroids (CTS)/Na/K-ATPase-mediated signal transduction in the regulation of renal sodium handling. The long-term goals are to understand the role of endogenous CTS and the Na/K-ATPase signaling in salt retention/salt-sensitive hypertension as well as heart/kidney function and remodeling.

Our current project is to understand the intrinsic relationship between the receptor Na/K-ATPase/Src complex and ROS generation/signaling, and the molecular basis of ROS/Na/K-ATPase interaction and its role in renal salt handling and organ remodeling. Specific projects that we are currently working on are:

1. The involvement of ROS/carbonylation in the Na/K-ATPase signaling.
2. The structure determinant(s) and effect of carbonylation of the Na/K-ATPase in Na/K-ATPase signaling.
3. The role of Na/K-ATPase signaling and salt sensitivity.
4. Animal (mouse) models of renal insufficiency mediated heart/kidney fibrosis

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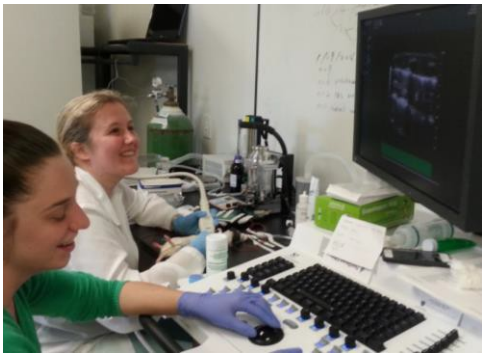

Echocardiographic assessment of rodent cardiac function by Dr. P. Marck and undergraduate fellow A. Bryant.

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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Recently, much progress has been made towards understanding how neurons, the cells responsible for the processing and transfer of information in the central nervous system (CNS), interact with non-neuronal brain cells. However, we have still only begun to scratch the surface about how non-neuronal cells contribute to the structural and functional maturation of the neuronal junctions known as synapses. Our work focuses on identifying and elaborating the genes, molecules, and signaling pathways that are crucial for linking non-neuronal cells with the synaptic structures that have been shown to be severely disrupted in nearly all known neurodevelopmental and psychiatric disorders. The long-term goal of our research is to contribute to novel therapeutic strategies to prevent or repair the impaired synaptic connectivity that occurs during abnormal brain development and following CNS injury or insult.

Two primary projects are currently ongoing in the Risher lab:

1) Astrocytes, the primary glial cell type in the brain, secrete a variety of factors that promote synaptogenesis during development and after injury. One family of synaptogenic proteins, the thrombospondins (TSPs), acts through a neuronal receptor, calcium channel subunit α2δ-1, which is known to be altered in some patients with epilepsy, intellectual disability, and autism. Our recent work showed that the interaction between TSP and α2δ-1 promotes downstream signaling via the actin cytoskeleton-regulating protein, Rac1, to facilitate synapse growth and maturation. In transgenic mice lacking α2δ-1 throughout the body, the dendritic spine structures that commonly receive synaptic input in the brain are severely disrupted, showing reduced density and structural maturity. We are currently investigating whether these brain abnormalities are present in a cortex-specific α2δ-1 knockout mouse line, as well as determine the mechanism by which TSP/α2δ-1 triggers Rac1 activation.

2) Neonatal abstinence syndrome (NAS) is a devastating consequence of the national opioid epidemic that is showing striking incidence rates in West Virginia and Central Appalachia. NAS infants are essentially born with an addiction to opiates, and they enter an intense state of withdrawal after being cut off from the mother's nutrient supply. The babies require constant supervision and, approximately 50% of the time, pharmacological intervention before being able to be discharged from the NICU. The long-effects of NAS on cognition and behavior are predicted to be numerous, but there is currently not much known about how prenatal opioid exposure affects brain development. Recently, at Cabell Huntington Hospital, a subset of NAS infants have been described with a particularly harsh form of the condition; these infants were born to mothers who co-abused opioids and the drug gabapentin. Gabapentin is a ligand for the synaptogenic receptor α2δ-1 which prevents the binding of TSP and subsequent synapse-promoting effects. We are now conducting experiments to try to understand the mechanism by which gabapentin and opioids interact to affect the formation and maturation of synaptic circuitry in animal and human models of NAS.

In the Risher lab, students will be exposed to a variety of cellular, molecular, genetic, and imaging techniques. Commonly used methods include animal handling (mouse/rat), primary cell culture, organotypic brain slice culture, Western blotting, immunohistochemistry, plasmid DNA transformation and transfection, confocal microscopy, electron microscopy, 3D reconstruction-based image analysis, genotyping, and viral vectors including CRISPR/Cas9. Students will have the opportunity to meet regularly with Dr. Risher as well as in a group setting such as our biweekly lab meetings/journal clubs.

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Our laboratory is interested in understanding how adolescent binge drinking influences brain function and contributes to the development of alcohol use disorder. Using a rodent model of adolescent binge drinking, our laboratory and others have demonstrated that there are acute and long-term changes to neuronal structure, function, and behavior across multiple cognitive domains.

Over the last few decades it has become apparent that non-neuronal cells called astrocytes which outnumber neurons and ensheathe many neuronal connections, play an important role in synapse formation, synapse maintenance across the life-span, and synaptic recovery following injury. However, how astrocytes contribute to neuronal and synaptic remodeling following ethanol exposure is not fully understood. Understanding how astrocytes contribute to the long-term effects of adolescent binge drinking in a rodent model is crucial for understanding the impact that underage alcohol exposure can have on the adult brain and how early onset drinking may contribute to the development of alcohol dependence later in life.

We have three ongoing projects: 1. Investigating the acute and long-term effects of binge drinking on astrocyte function. 2. Investigating the role of astrocytes in the development of addiction. 3. Investigating how changes in astrocyte function following adolescent binge drinking influence recovery from secondary injury later in life, e.g., following stroke and/or traumatic brain injury. Techniques used to answer these questions include: intracranial survival surgery, immunohistochemistry, Western blot, qPCR, organotypic slice culture, confocal microscopy, 3D morphometric analysis of astrocytes, and a battery of behavioral paradigms including conditioned place preference, open field, social interaction, and plus maze.

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The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that binds environmental toxicants, pharmaceutical drugs and endogenous ligands. We have and others have discovered that the AHR promotes or inhibits breast cancer depending on the ligand that it binds. We hypothesize that the AHR modulates breast cancer progression by regulating the activity of embryonic pathways that have become oncogenic in breast cancer cells. We hypothesize that a better understanding of the mechanisms by which AHR regulates signaling in breast cancer cells will lead to novel therapies to treat this disease. Students in my lab would have the opportunity to study these questions in several lines of human breast cancer cells. Our methods are largely molecular biology based; therefore, students would have the opportunity to use real time PCR machines, electrophoresis equipment, and laminar flow tissue culture hoods. Students will also have a choice as to what technique they would like to learn during their intern. Techniques in lab will include, but are not limited to, real-time PCR, western blot, chromatin immunoprecipitation analysis, interfering RNA approaches to gene knockdown and proliferation assays.

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Regulation of Na-glutamine cotransport in physiological and pathophysiological conditions

West Virginia ranks first in adult obesity in the whole country. Obesity is characterized by numerous physiological changes that may directly or indirectly influence the metabolism of intestinal epithelial cells. Adipose-derived secretome (ADS) factors that are termed as adipokines have been suggested to play an important role in the modulation of physiological function and inflammatory processes. In intestinal epithelial cells, glutamine is the primary nutrient and is assimilated by Na-dependent glutamine co-transport (B0AT1/ SLC6A19) on the brush border membrane (BBM) of villus cells. We have shown that enhanced uptake of glutamine via B0AT1 occurs in obesity. Therefore, we hypothesized that the ADS might regulate B0AT1 in intestinal epithelial cells. Students will have the opportunity to work cell culture, siRNA transfection, biochemical assayses, western blot, and qPCR.

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Dr. Sodhi is a faculty member in the Department of Surgery at Marshall University Joan C. Edwards School of Medicine. Dr. Sodhi's principle research focus is to investigate contributions of chronic oxidative stress and metabolic imbalance as it pertains to development of obesity and diabetes with associated long-term complications. Her research further focused on physiological and molecular aspects of dysregulation of the cellular antioxidant defense system. Recently, Dr. Sodhi has extensively published data demonstrating the role of Na/K-ATPase oxidant amplification loop in exacerbating ROS generation and aggravating subsequent oxidative stress in several clinical conditions. The students' active participation and involvement in this important learning opportunity, they will be able to expand their focus and develop skills in formulating much advanced innovative research strategies. This program will further allow them to nourish their skills as a research scientist and to have better insightful approach to their future projects and proposals. Students will also be able to enhance their positive outlook of their work and aim to maximize their strengths and combat weaknesses to improve the overall quality of their future projects.

Summer Project 1: Developing a panel of serum biomarkers in patients with nonalcoholic fatty liver disease (NAFLD) in West Virginia
Non-alcoholic fatty liver disease (NAFLD) is characterized by a steatosis of the liver that may progress to more serious pathological conditions including: nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. NAFLD is related to and shares common serum biomarkers with cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), obesity, and metabolic syndrome (MetS). West Virginia (WV) is a state with some of the highest rates of cardiovascular disease, obesity and diabetes mellitus. As nonalcoholic fatty liver disease (NAFLD) is closely related to these diseases, it is of particular interest in WV. Currently

there is no cost-effective, standardized method used clinically to detect NAFLD prior to the onset of reversible complications. At this time, the diagnosis of NAFLD is made with costly radiologic studies and invasive biopsy. These studies are only diagnostic once changes to hepatic tissue have occurred. Creating and implementing a biomarker panel for the early detection and attenuation of NAFLD, prior to the onset of irreversible complication, would provide maximum benefit and decrease the disease burden on the patients and healthcare system of WV. In order to create a method of early intervention, we plan to study serum biomarkers known to be associated with NASH. With this data, we hypothesize we could develop a panel of serum biomarkers, for the screening of early liver disease. This method would be cost effective, accessible and a minimally invasive way to recognize the early onset of NASH, prior to the development of current markers.

Summer Project 2: Left atrial strain, left ventricular strain and fibrosis biomarkers as predictors of atrial fibrillation recurrence after cardioversion.

Atrial fibrillation (AF) is a very detrimental cardiac arrhythmia characterized by patients having increased rates of strokes, other thromboembolic events, left ventricular dysfunction and heart failure, low quality of life, and death. While antiarrhythmic drugs are commonly used to treat AF, they can lead to increased risk for sudden cardiac death from torsades de pointe, peripheral neuropathies, pulmonary fibrosis, and lupus-like syndromes among many other side effects. Also, long-term usage can be contraindicated in patients with prior structural and ischemic heart disease. Left atrial strain has been a new indicator of interest in regard to AF recurrence. Studies have shown that while catheter ablation is effective in restoring sinus rhythm in AF patients, recurrence of AF is still a major problem. There is evidence; to support that left atrial strain could possibly be used clinically to predict AF recurrence. Through measurement of left atrial strain and identification of fibrous biomarkers, new screening protocols and targeted therapies can be developed in order to reduce AF recurrence rates and also increase predictability of subsequent AF events in patients post-cardioversion and in higher risk patients. These new forms of treatment could improve therapeutic guidance and provide AF patients with a better quality of life. This study should provide important insights into the role of left atrial and left ventricular strain as a predictor of atrial fibrillation recurrence after cardioversion. Also we expect to estimate the level of correlation between the fibrosis biomarkers and the recurrence of atrial fibrillation.

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My primary research interest is **the molecular mechanisms of renal sodium (Na) handling and blood pressure regulation**, focusing on **the role of reactive oxygen species (ROS), inflammation and cardiotonic steroids-mediated Na/K-ATPase signaling in kidney and cardiovascular disease**. Our long-term goal is to open up the possibility of translational clinical research and develop personalized patient management.

Obesity and hypertension (HTN) are leading risk factors for cardiovascular disease, the major cause of death around the world. However, the underlying mechanisms of obesity-associated are not fully understood.

The kidney plays a critical role in blood pressure regulation. The compelling evidence is as follows. Normotensive recipients of a renal graft from a genetically hypertensive donor developed post-transplantation hypertension. Furthermore, in genetically hypertensive rat bilateral nephrectomy together with transplantation of a kidney from a normotensive donor has been shown to be associated with a decrease in blood pressure.

Our lab has reported a novel mechanism by which cardiotonic steroids (CTS) mediated-Na/K-ATPase/Src/reactive oxygen species (ROS) signaling in the renal proximal tubules regulates renal sodium handling and blood pressure. We have documented this mechanism in the Sprague Dawley rat, and Dahl salt-resistant (R) rat fed a high-salt diet. However, this process is impaired in the Dahl salt-sensitive (S) rat and obese TALLYHo/JngJ mouse.

With the support of NIH COBRE grant, we focus on the role of ROS, and Na/K-ATPase signaling-mediated renal sodium handling in obesity-associated HTN. The novel findings could allow for the identification of new targets for interventions in the clinical treatment of obesity-related HTN.

INBRE program participants will join an active laboratory and work with medical students, graduate students, post-doctoral fellows, and faculty to contribute to ongoing biomedical research.

Summer program participants will have the opportunity to learn:

1. Animal handling and diet studies, as well as metabolic cage studies
2. Cell culture techniques
3. Preparation of lysates, including tissue and cell lysates
4. Subcellular fractionation – isolation of endosome
5. Western Blotting for detection of protein
6. qRT-PCR for mRNA measurement
7. Fluorescent microscopy techniques
8. Standard lab equipment (scales, pH meter, pipettors, sonicator, centrifuge, etc.) for preparing solutions, reagents, and samples.