MENTOR DIRECTORY

2017 SUMMER RESEARCH INTERNSHIP FOR MINORITY STUDENTS

to be held at

The Joan C. Edwards School of Medicine at Marshall University

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Mentor Listing According to Area of Research

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Cardiovascular Research: Arthur; Egleton; Liu; Pierre; Santanam; Yan

Diabetes: Arthur; Kim; Valentovic

Drug Action and Metabolism: Egleton; Henderson; Valentovic

GI Research: Arthur

Genetic Research: Georgel; Kim

Infectious Diseases: Yu

Molecular Biology: Georgel; Salisbury; Yu

Neuroscience/Sensory Research: Egleton; Grover

Obesity Research: Arthur; Kim; Koc; Santanam

Renal Research: Larre; Yan

Toxicology Research: Rankin; Valentovic

PROJECT DESCRIPTIONS

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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 10-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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The following projects are available in my laboratory:

1. **Anti-cancer activity of nicotinic antagonists in lung cancer:** Smoking bears a strong correlation to the development of a type of lung cancer called lung adenocarcinoma. In our laboratory we study the signaling pathways of how nicotine and NNK (components of cigarettes) promote the growth of lung cancer. Specifically, students working on this project will examine whether compounds which block the effect of nicotine can be useful for lung cancer therapy. Other techniques the students will learn are (i) to measure the effects of nicotine on the growth of human lung cancer cells (ii) the measure the anti- cancer activity of compounds (that inhibit the effects of nicotine) in human lung adenocarcinoma.

2. **Capsaicin and small cell lung cancer:** Capsaicin is the major active ingredient of chilli peppers.
Preliminary data in our laboratory shows that capsaicin can inhibit the growth of human small cell lung cancer cells. We are interested in investigating molecular pathways contribute to this process. If you are interested in this project, you will learn (i) to perform specific assays to determine whether capsaicin can cause cell death in human small cell lung cancer cells (ii) to examine the biochemical mechanisms underlying this growth-inhibitory activity of capsaicin

TECHNIQUES:

The techniques that are routinely performed in our laboratory:

1. Cell culture techniques
2. Preparation of lysates, nuclear, membrane and cytosolic fractions
3. Assays to study cell growth and cell cycle progression
4. Detection of proteins using Western Blotting
5. Measurement of tumor angiogenesis.
6. Animal studies: anti-cancer studies on nude mice models

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Inhibition of Wnt/ß-catenin signaling and induction of autophagy in melanoma.

The incidence of melanoma has increased to an alarming degree in recent years. While early melanoma is both preventable and treatable, later stage invasive disease has a very poor prognosis. The Wnt signaling pathway is known to play a central role in several cancers, however comprehensive study of the role of Wnt pathway components in melanoma is lacking. We are examining the effect of blocking Wnt/ß-catenin signaling in melanoma. Our data show that inhibiting the Wnt pathway reduces the migratory behavior of melanoma tumor cells, even in advanced lines that are resistant to other treatments. This suggests that inhibition of the Wnt pathway may be a productive route for developing new therapies. Through mathematical modeling we identified a unique signaling control node in a Wnt co-receptor protein, LRP6. The efforts of several student researchers have shown that one of the inhibitors we study induces the process of autophagy in human melanoma cells. This offers a unique way to induce melanoma cell death and we will be following up on these interesting data. The summer researcher would be invited to participate in experiments to continue examining the induction of autophagy in melanoma cells, using a number of experimental approaches. The likely techniques would include migration and invasion assays, subcellular fractionation, western blotting, fluorescent immunocytochemistry, RNA isolation, real-time PCR, siRNA transfection and reporter gene assays.

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My research focuses on the barrier systems that protect the brain and promote optimal neuronal function. Over the last decade research has shown that these barriers are modulated by diet, drugs and disease. My studies focus on investigating the mechanisms that regulate changes in barrier function.

Opioid regulation of brain endothelial cells
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 vasculature. This project will investigate the effects of opioid exposure on the functional and molecular regulation of brain endothelial cells. Changes in cerebral endothelial cell function can have a significant effect on brain development. Methods that will be used will include Western blot analysis, immunofluorescence microscopy, real-time PCR and transport studies.

Instrumentation:
This projects may involve using fluorescent and UV plate readers, real-time PCR, microscopy, blood gas analyzers, lactometers, gel rigs, HPLC, centrifuges, balances and other standard lab equipment.

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My laboratory currently investigates the effects of emerging water pollutants, specifically opioids and endocrine disrupting chemicals, on the epigenome of organisms exposed to such pollutants. The project described below, in collaboration with Dr. Egleton (MUSOM, Department of Pharmacology, Physiology and Toxicology), focuses on *in utero* effects of opioids on Neonate Abstinence Syndrome (NAS). We investigate, using a cellular model system, the potential changes in gene expression mediated by exposure to doses of Buprenorphine similar to that experienced by embryos during gestation when the mother undergoes drug withdrawal treatment. using our model system, we have already identified several epigenetic markers which are affected by the presence of Buprenorphine (see Figure 1 below). These markers and associated proteins have been shown to be associated with different steps in the development of the brain, and are very likely to be associated with NAS in neonates.

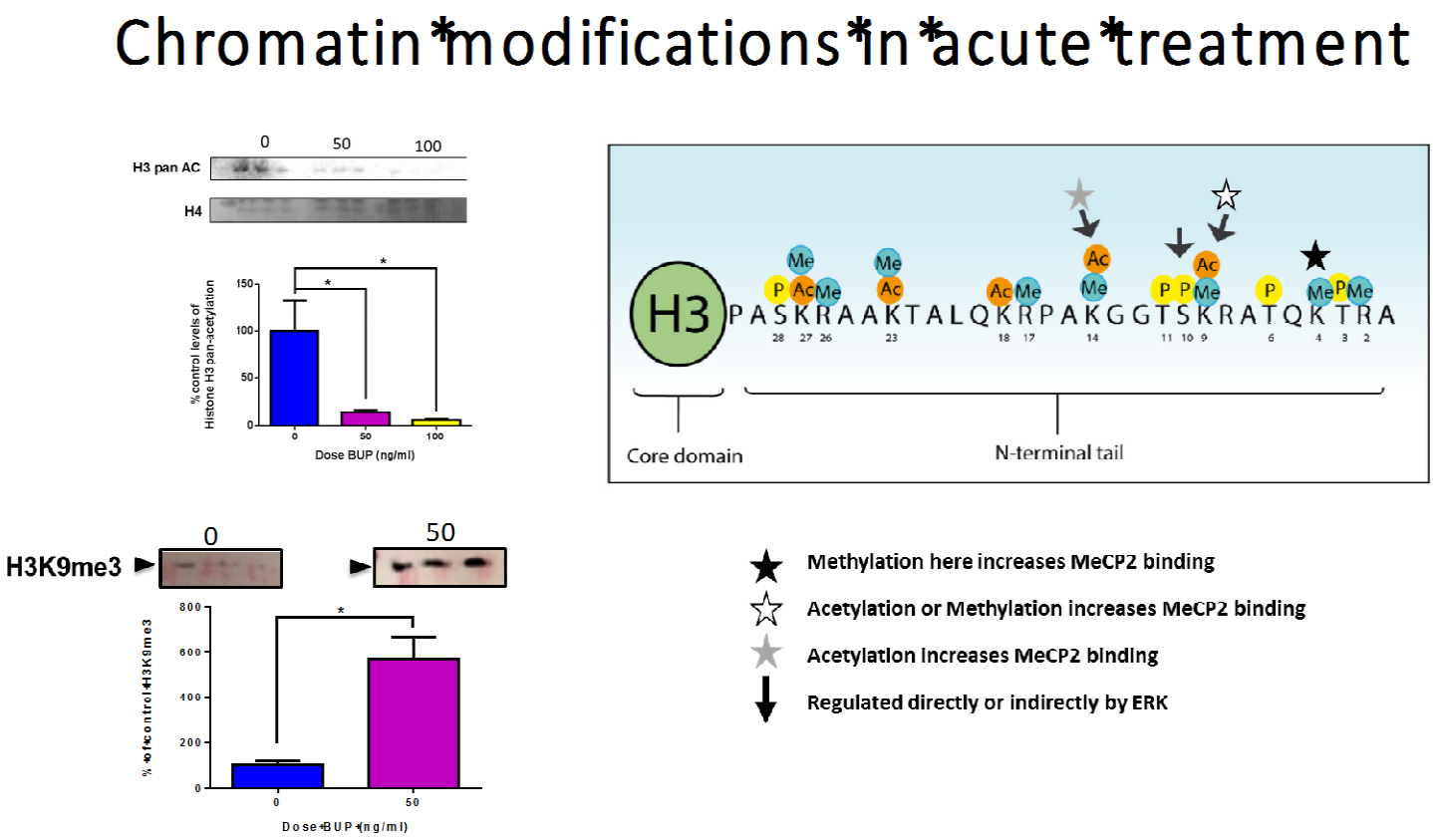

Figure 1: Epigenetic changes in response to Buprenorphine exposure

The summer project would involve various aspects of cell culture (using different cells as model system), proteins and mRNA purification, as well as western blotting analysis of purified proteins before and after Buprenorphine treatment. Depending on the state of our current research, we may also use quantitative Polymerase Chain Reaction (qPCR) as another mean to investigate changes in regulation of gene expression mediated by Buprenorphine exposure.

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Mechanisms of action of antidepressant medications. Mood disorders, including depression, are extremely common, affecting 5-10% of the population. A number of antidepressant medications are currently used to treat depression; however, many patients do not respond to medication. In addition, although the immediate effects of these medications are known (most alter serotonin and/or norepinephrine neurotransmission), therapeutic effects of these drugs occur with a delay of several weeks. While the reasons for this delayed effect are not known, current research hypotheses focus on changes in synapses function and structure (plasticity). In this project, we are examining synaptic plasticity, and the expression of plasticity related molecules in brain areas that are affected by depression and are targets for antidepressant medications. By increasing our understanding of how antidepressant medications affect brain function, we hope to contribute to improved therapies for depression.

Neurotrophic factors in neonatal abstinence syndrome. Neonatal abstinence syndrome (NAS) occurs as a consequence of fetal exposure to opiate drugs due to maternal drug use during pregnancy, and drug withdrawal after birth. Immediate symptoms of NAS are variable and may include hyperexcitability, high- pitched cry, tremor, diarrhea, vomiting, sweating, rapid breathing, feeding and sleep problems, and seizures. These immediate symptoms of NAS reflect disturbances in the nervous system as a consequence of opiate exposure. Infants exposed prenatally to opiates also have a long-term risk for neurobehavioral problems lasting at least through childhood. The mechanisms through which prenatal opiate exposure produces these adverse consequences are still poorly understood. We are investigating the hypothesis that neurtophic factors, which play critical roles in development and plasticity of the nervous system, are altered by prenatal opiate exposure leading to both immediate symptoms of NAS and longer term alterations in the nervous system and behavior.

Methods and instrumentation. Students participating in these projects will have the opportunity to learn animal handling, techniques for *in vitro* analysis of synapse function (preparation of brain tissue slices, electrophysiological measurement of synaptic responses), techniques for measuring protein expression (Western blotting, enzyme-linked immunosorbent assay or ELISA), techniques for working with human tissue (umbilical cord blood) samples, and techniques for analysis of emotional and cognitive behaviors in laboratory animals. For tissue preparation and analysis of synapse function, we use a vibrating microtome, brain slice chambers, micromanipulators, amplifiers, stimulators, and oscilloscopes; data is collected and analyzed using software running on personal computers. For Western blotting and ELISA we use gel electrophoresis equipment, chemiluminescence, a digital imager, and a plate reader. Animal behavior is recorded and analyzed using a computer-based animal tracking and measurement system. Students will use standard lab equipment (scales, pH meter, osmometer, pipetters, sonicator, centrifuge, etc.) for preparing solutions, reagents and samples.

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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. Our goal is to give students adequate experience in common biomedical techniques that will provide an excellent foundation for a future biomedical scientist.

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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. 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. 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 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, and StepOne Real-Time PCR 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) Parkinson's disease, 2) cancer, and 3) aging and obesity.

Project 1: Regulation of protein synthesis by ribosome associated PINK1. 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 Pten-induced kinase 1 (PINK1). PINK1 is a Ser/Thr kinase related to Parkinson's disease (PD) and regulates mitochondrial biogenesis by mitophagy. To investigate the role of PINK1 in regulation of mitochondrial translation and biogenesis further, *in vivo* and *in vitro* translation assays will be performed.

Project 2: 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 3. Role of caloric restriction and various flavonoids on regulation of mitochondrial protein synthesis.
Recent studies suggest that reduced expression of proteins related to protein synthesis by caloric restriction promotes longevity in animals. There is limited information available on contribution of mitochondrial translation components in this process. We will perform quantitative MS-based techniques to identify and quantify changes in the components of the mitochondrial translation machinery in human cell lines grown at varying nutrition conditions and in the presence of several natural flavonoids known to mimic caloric restriction.

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The exchange of substances between metazoans and the environment takes place across transporting epithelia that have two fundamentally differentiated features: tight junctions (TJ) and apical/basolateral polarity. Tight junctions are the intercellular junctions primarily responsible for barrier formation; they form paracellular diffusion barriers that regulate the flow of ions and solutes along the paracellular space. Structurally, they are composed of a large number of transmembrane proteins including claudins, occludin and junctional adhesion molecules, peripherally associated cytoplasmic proteins and proteins involved in signal transduction. These proteins interact to form a continuous and regulated paracellular barrier. Claudins are the primary proteins involved in developing the selectivity of the barrier. There are at least 25 annotated claudin isoforms with molecular mass of 20-23 kDa, 12 of which are differentially expressed within the kidney.

The three major renal tubular segments are the proximal tubule, the thick ascending limb of Henle's loop and the distal nephron, including the collecting duct. TJ permeability, as measured by transepithelial electrical resistance (TER), increases from proximal tube to the collecting duct. The TER, for instance, varies from 5-8 $\Omega.cm^2$ in the proximal tubule to as high as 2000 $\Omega.cm^2$ in the collecting duct. These changes in permeability have been linked to segment-specific expression of claudin isoforms. *Therefore, revealing the molecular mechanism involved in the regulation of claudin isoform expression in kidney is not only important for advancing our knowledge of epithelial biology and renal physiology, but is also relevant to various human diseases.*

In a previous report, my colleagues and I have demonstrated that ouabain regulates TJ function by activating the NKA-mediated signal transduction in renal epithelial cells. Those results suggest that the Na/K-ATPase plays a critical role on TJ permeability. We found that a specific mutation on alpha 1 Na/K-ATPase sequence regulates the degree of tightness of TJ. We are interested in studying ***Na/K- ATPase-mediated TJ regulation, and determining the molecular mechanism by which Na/K- ATPase exerts such regulation in renal epithelial cells phenotype***. Our long-term goal is to establish both cellular and animal platforms that will allow us to develop new tools for *in vivo* investigation of the role of Na/K-ATPase-mediated TJ regulation of renal tubular structure and function.

Students working in my lab will be exposed to molecular, cell biology and transgenic animal techniques and other approaches that are currently available to perform integrated renal physiology research.

Project 1: **We will test the hypothesis that Na/K-ATPase differentially regulates the expression and trafficking of claudin isoforms.**

Rationale: Since our preliminary data demonstrated an increase in TER in cells expressing Na/K-ATPase mutants, we propose that such changes in TER are due to altered expression of claudins. To test our hypothesis, we will first analyze cellular expression of different isoforms of claudins, and the role of Na/K-ATPase specific mutation on claudin expression. We will then reveal the molecular mechanisms by which Na/K-ATPase regulates the expression of claudin isoforms.

Method: To assess the mechanism of Na/K-ATPase-mediated claudins regulation, students will be exposed to cellular methodology like western blot and confocal immunostaining and immunoprecipitation.

Project 2: Development of *in vivo* study to assess human relevance of TJ regulation by Na/K- ATPase.

Rationale: Since cell lines approaches have limitations, it will be necessary to develop new strategies to corroborate our previous finding.

Method: To assess the human relevance of our new findings from cell culture and animal models, we will make an effort to develop a CRISPR-based approach and generate human kidney organoids from iPS cells in which the endogenous Na/K-ATPase is replaced by an A420P mutant. We consider this an important study because it not only allows us to verify the physiological relevance of our findings, but also generates a new technology platform that will enable us to generate other NKA mutants in human iPS cells that could differentiate into various cell types.

Students working in this project will learn and get involve with CRISPR techniques and organoids culture.

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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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The Pierre lab studies specific intracellular pathways involved in the integrated response of the myocardium to ischemia-reperfusion injury and metabolic disturbances. Our goal is to develop new paradigms to therapeutically address cardiomyocyte dysfunction following myocardial infarction. 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, tail-cuff measurement of blood pressure, cardiac and vascular catheterization). Hence, the student will be exposed to the key techniques and approaches that are currently available to integrated cardiac and vascular physiologists and pharmacologists.

Project. Cardioprotection by Na^+/K^+-ATPase ligands

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: Interns will learn the isolated Landendorff-perfused mouse heart preparation and will submit it to our standardized ischemia-reperfusion protocol with or without addition of novel compounds targeting the Na^+/K^+- ATPase cardioprotective signaling pathway. The intern will learn how to analyze contractile function in real time, measure cardiac enzyme release and determine infarct size.

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The following projects are available in my laboratory:

Project #1: Chloroanilines are commonly used chemical intermediates in the manufacture of dyes, drugs, agricultural herbicides and fungicides and thousands of other products. Exposure to a chloroaniline can result in a number of toxicities including toxicity to the blood, liver and kidney. This project seeks to determine the chemical species (parent compound or metabolite) responsible for liver and kidney damage and the mechanism by which nephrotoxicity occurs.

Project #2: Methadone is a drug used to reduce the dependence of heroin addicts on heroin. However, some methadone users die unexpectedly when using normal doses of methadone. Preliminary studies have suggested that there may be a defect in the inactivation of methadone in the liver in these individuals who die unexpectedly. The purpose of this study is to determine if genetic polymorphisms are responsible for these deaths.

Assays and Instrumentation: Projects that will investigate nephrotoxicity will use in vitro assays that involve isolation of rat kidney cells, measurement of enzyme release from treated and control cells, and potentially, the measurement of cellular ATP levels. Toxicogenomic studies involve isolation techniques for obtaining genetic material from treated and control rat kidneys. Additional techniques may involve Western blotting, quantifying urinary contents (protein, glucose), measuring blood urea nitrogen and glucose levels, and real time PCR techniques. Instrumentation will primarily involve the use of balances, centrifuges and UV-visible spectrophotometers. High pressure liquid chromatography and thermocycler use is also possible.

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The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that mediates the effects of environmental pollutants, as well as, endogenous cellular growth. We have discovered that AHR antagonists inhibit adipocyte-breast cancer cell interactions by interfering with IGF1 signaling. Current efforts my laboratory is to test the molecular mechanism(s) by which AHR antagonists inhibit IGF1 signaling in breast cancer cells by studying signal transduction and gene expression. 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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The following projects are available in my laboratory:

Project 1: Exercise, antioxidants and obesity: Obesity is an imbalance between energy intake and energy expenditure. We are interested in studying the effects of exercise on appetite regulation in novel mouse models of obesity. In this project we will measure changes in genes that regulate appetite in the brain and fat tissue obtained from mice that exercise (treadmill) versus sedentary group.

Project 2: Epigenetics and ovarian cancer risk: Ovarian cancer is the third leading cancer in women. Obesity and endometriosis increases risk to ovarian cancer. Epigenetics, which are heritable changes that are not caused by alterations to DNA, is studied by changes in DNA methylation, histone methylation or acetylation and microRNAs. Our laboratory is interested in determining the role of epigenetics in the risk to ovarian cancer in obese patients with endometriosis.

Project 3: Obesity and cardiac muscle function: Obesity increases risk to cardiovascular disease. Our laboratory is interested in studying the role of the fat that surrounds the heart on cardiac function. In this project we will study changes in human cardiomyocyte (cardiac muscle cells) function when exposed to cardiac fat derived factors from patients with and without coronary artery disease.

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

1. Animal studies: mouse exercise and diet studies
2. Cell culture techniques, isolation of fat cells (adipocytes) and adipose derived stem cells
3. Isolation and quantification of RNA (including miRNA) and DNA from fat tissue, brain tissue and cardiac muscle cells
4. Detection of genes using quantitative PCR/Real time PCR and Western Blotting
5. Detection of Epigenetic markers: DNA and histone markers using Western blotting and microarrays, microRNAs arrays (Next generation sequencing for small RNA or total RNA sequencing)
6. Detection of biomarkers using Luminex technology

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The Question: *"What are the processes that enable a normal cell to start misbehaving and become cancerous?"* The process that cells in our bodies undergo to become cancer cells all end up producing a cell that ceases to listen and cooperate with its neighbors, which is necessary for the complex mixture of cell our bodies are. This grant will investigate a process known as "canalization", which much like a canal for water directs the flow of water, directs a cell as it matures to the necessary type of cell the body requires. Disrupting this "canalization" process can cause a cell to change and lose its direction, potentially pushing it down paths that lead to cancer.

Research Goals: The research will use both cells grown in the laboratory and animal models of human leukemia, along with advanced scientific methods to test the role of canalization in the process of maturing cells and cancer development. The research will allow students at Marshall University the opportunity to participate in cutting edge research in preparation for careers in science.

Specific Project: A cell culture model for hematopoietic stem cells is used in our laboratory. This project will involve the differentiation of these cells and the study of the effects of inhibition of canalization during this maturation of the resulting cells. Techniques involved will be flow cytometry and mammalian cell culture.

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Our laboratory is focused on exploring new interventions that will reduce the adverse effects of drugs. We have recently focused on examining ways to reduce the toxicities of cancer chemotherapy agents. Projects available in my lab:

Projects #1 Reducing serious cancer chemotherapy side effects. This is an ongoing project that has been funded by a federal grant from NIH. Our laboratory is evaluating new compounds that may reduce the adverse effects experienced by individuals treated with cancer chemotherapy drugs. In addition, another goal of this project is to come up with methods to improve the effectiveness of the cancer chemotherapeutic agents while lessening the side effects. This project has clear clinical relevance and is translational. An individual involved in this project will investigate cellular changes in toxicity, specifically we want to explore changes in the mitochondria as well as post-translational modifications of proteins caused by exposure to two cancer chemotherapy drugs, doxorubicin or cisplatin.

Projects #2 Identification of ways to reduce the liver damage of acetaminophen overdose. Acetaminophen (APAP) is a common ingredient in nonprescription pain, fever and flu remedies. APAP can cause liver damage when used in excess and is the #1 cause of drug induced liver failure. The purpose is to investigate new ways to lower the severe liver failure associated with acetaminophen overdose. Acetaminophen is an over the counter agent for pain and fever that is very safe but when taken in excess can damage the liver and kidney. Once this damage occurs a liver transplant may be the only alternative. This project is examining how a nutraceutical, S-adenosylmethionine (SAMe) reduces acetaminophen mediated liver damage.

Project #3 Mechanisms to reduce diabetic renal complications. Diabetes mellitus afflicts 1 in 50 Americans. Diabetes is the major cause of kidney failure and why people must go on dialysis in the United States. The long-term goal is to examine what makes the diabetic more susceptible to kidney failure. These results may then be applied to develop new treatments for diabetics. Individuals (students or faculty) involved with this project will participate in examining cellular changes that may increase cellular stress in the diabetic kidney.

Project #4 Examination of the mechanism of renal damage by an antiviral agent used in in treating HIV and hepatitis. Patients with HIV or hepatitis B must take antiviral agents to slow the progression of heir disease for very long periods of time. Side effects often occur after someone takes an antiviral agent for over 1 year. We are examining the mechanism of damage to the kidney by a commonly used antiviral agent. We are using a normal human proximal tubular epithelial cell culture model for this study.

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My major research interest is **the role of reactive oxygen species and cardiotonic steroids-mediated Na/K-ATPase signaling in kidney and cardiovascular disease**. Our long-term goal is to open up the possibility of a translational clinical research and develop personalized patient management.
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. What is the key role of kidney in this case? Why does hypertension travel with the kidney?
Our lab has reported a novel mechanism by which cardiotonic steroids (CTS) mediated- Na/K- ATPase/Src/reactive oxygen species (ROS) signaling regulates renal sodium handling and blood pressure. Specifically, CTS mediate Na/K-ATPase/Src/reactive oxygen species (ROS) signaling and induce the redistribution of Na/K-ATPase α1 and sodium proton exchanger 3 (NHE3, responsible for Na and water reabsorption) in the renal proximal tubule (PT), resulting in a net increase in urinary Na excretion. 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.
Obesity and hypertension (HTN) have additive effects in increasing the risk for cardiovascular disease, a leading cause of death around the world. Our current research is to focus on the role of ROS and impaired renal sodium excretion in obesity-hypertension in terms of Na/K-ATPase signaling.
Summer 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. Cell culture techniques
2. Preparation of lysates, including tissue and cell lysates
3. Western Blotting for detection of protein
4. Fluorescent microscopy techniques
4. Subcellular fractionation – isolation of endosome
5. Animal handling and diet studies
6. Standard lab equipment (scales, pH meter, pipetters, sonicator, centrifuge, etc) for preparing solutions, reagents and samples.

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My research focuses on bacterial biofilms, lung infections and gut microbiota. Three projects are ongoing in the Yu lab.

Project #1: Cystic Fibrosis Biofilms. Individuals afflicted with cystic fibrosis (CF) are susceptible to recurrent lung infections with bacteria enclosed in a capsule (biofilms). *Pseudomonas aeruginosa* is a ubiquitous bacterium that readily forms a biofilm by producing a polysaccharide called alginate. The overproduction of alginate is a virulence factor that allows greater adhesion to lung epithelial cells, as well as protection from antibiotics and the host's immune system. We study how biofilm formation occurs through alginate regulation and production in CF lungs. Elucidation of the alginate pathways will lead to better understand the pathogenesis, and development of novel therapeutics to improve the quality of life for individuals with CF.

Project #2: Modeling Lung Infection. Most of bacterial lung infections starts with the colonization of upper respiratory tract. Aspiration of oropharyngeal secretions containing colonizing bacteria deep into the lung allows for the establishment of lower respiratory tract infections. We are using an inhalation exposure system to introduce the bacterial pathogens into the distal airways of the mouse lungs, causing the development of lung infection and pneumonia. This model is being utilized to test the safety and efficacy of novel antimicrobials against the multiple drug-resistant (MDR) lung infection. The goal of this project is to develop novel therapeutics against the MDR Lung infections and pneumonia.

Project #3: Novel Probiotics. Gut microbiota, a bacterial community made up of 1,000 different species, are important to human health. Among all the species, there is a morphologically-distinct symbiotic member known as segmented filamentous bacteria (SFB). The SFB belongs to a group of clostridia bacteria, which cannot be grown *in vitro*. However, the SFB play a vital role in the development of the immune system in mice. More specifically, SFB have been shown to attach to the apical epithelium of the small intestine to induce the interleukin-17-producing T helper (TH_{17}) cells. TH_{17} cells are important for the protection against intestinal pathogens as well as in maintaining gut homeostasis. In this project, we will examine possibilities of how to develop the SFB into a novel probiotic to prevent and control the gastrointestinal diseases in children.