

# **MENTORS DIRECTORY**

## **2018 SUMMER RESEARCH INTERNSHIP AND FELLOWSHIP PROGRAM**

Offered by the

**West Virginia IDeA Network of Biomedical Research Excellence  
(WV-INBRE)**

to be held at

**The Robert C. Byrd Health Sciences Center  
Of West Virginia University**

**And**

**The Joan C. Edwards School of Medicine  
at Marshall University**

## Introduction

WV-INBRE is pleased to offer summer research internships to students from colleges and universities participating in the WV-INBRE program. In 2018 the internship period will be from May 29 through July 31, with the Summer Research Symposium to be held on July 31 in Morgantown, WV. Listed in this directory are faculty members at the West Virginia University Health Sciences Center and the Joan C. Edwards School of Medicine at Marshall University who have agreed to participate as mentors in the summer internship program. Each mentor has submitted a description of the project(s) that is (are) available to interns in his/her laboratory. Please review these carefully so that you are aware of what is available for summer projects.

A listing of mentors with a short description of their research and the general area of their research is presented on pages 3-5. Mentors and project descriptions begin on page 6. Listed for each mentor is an e-mail address, phone number and, where available, a web site address. The web sites will allow you to learn more about the mentors and their research programs.

Application forms are available on the WV-INBRE web site (<http://www.wv-inbre.net>) at a link under **2018 Summer Program**. Applications may be submitted by mail or e-mail; however, **direct electronic submission is available and its use is encouraged.**

For general questions about the summer internship and fellowship program please contact one of the following individuals who are serving as summer research program coordinators.

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WV-INBRE website: <http://www.wv-inbre.net>

**Directory of Mentors – Mentors are listed by their location; the first list contains mentors at the West Virginia University Health Sciences Center and the second list contains mentors at Marshall University**

**Mentors at the West Virginia University Health Sciences Center**

<u>Mentor</u>	<u>Description of Research</u>	<u>Page #</u>
Dr. Mariette Barbier	Characterization of <i>Pseudomonas aeruginosa</i> pathogenesis	6
Dr. Vagner Benedito	Regulation of the antimalarial medicine artemisinin biosynthesis in <i>Artemisia annua</i> L.: effects of salt stresses	7
Dr. Candice M. Brown	Brain-immune interactions in acute and chronic systemic inflammation	8
Dr. Paul Chantler	Cardiovascular responses to exercise	9
Dr. F. Heath Damron	Characterization of Pertussis and development of vaccines	10
Dr. Wei Du	1. Collaboration between DNA damage and immune responses in leukemic stem cell emergence and expansion 2. Hematopoietic stem cell polarity in bone marrow failure and leukemia	11
Dr. Werner J. Geldenhuys	1. Discovery of compounds to treat Parkinson's Disease. 2. Deliver of therapeutic proteins using nanoparticles	12
Dr. Robert Goodman	Are neurons that respond to kisspeptin for NKB critical for pulsatile LH secretion in ewes?	13
Dr. Lori Hazlehurst	Development of novel therapeutic strategies for tumors that reside or home to bone	13
Dr. Stan Hileman	Brain pathways underlying puberty onset and photoperiodic control of reproduction	14
Dr. Brad Hillgartner	Regulation of genes involved in fatty acid synthesis relative to obesity, diabetes and atherosclerosis	14
Dr. John Hollander	Proteins involved in protection against cardiac diseases	15
Dr. Alexey Ivanov	1. Breast cancer cell dissemination, dormancy and reactivation at the metastatic sites in mouse xenograft model. 2. Negative control of EMT by epithelial-specific transcription factors. 3. Role of the TGF-beta pathway in partial EMT and drug resistance of triple-negative breast cancer	16
Dr. Steven Kinsey	Cannabinoid system: 1. New mouse models of cannabis withdrawal. 2. Cannabinoid-based drugs to explore inflammation caused by arthritis	17
Dr. Roberta Leonardi	Regulation of CoA levels in diabetes	17
Dr. James Lewis	Mechanisms of multisensory and hearing perception, and spoken language processing	18
Dr. Bingyun Li	Stimulating host's immune response to reduce infection; Intra-cellular infection and antimicrobial peptides; Nanostructured materials and nanomedicine	19
Dr. Paul R. Lockman	Prevention of brain metastases in breast cancer	20
Dr. Ivan Martinez	Importance of Non-coding RNAs in Human Papillomavirus (HPV)-Related Cancers and Models of Cellular Growth Arrest	21

Dr. Junaith Mohamed	Understanding the mechanism of induction of post-stroke skeletal muscle morbidities	22
Dr. Mohammed A. Nayeem	Prevention of Cardiovascular Diseases with specific gene manipulation and pharmacology	23
Dr. Timothy Nurkiewicz	Airborne particles and systemic microvascular endothelial dysfunction	24
Dr. Mark Olfert	Microvessel and vascular responses to E-cigarettes, nicotine and/or environmental stress	25
Dr. Elena Pugacheva	Molecular mechanisms of breast cancer metastasis Molecular mechanisms of cell cycle driven disassembly of primary cilium in normal and cancer cells	25
Dr. Vazhaikkurichi M. Rajendran	Molecular Basis of Ulcerative Colitis; Approach to Cure and Prevent Ulcerative Colitis	26
Dr. Yon Rojanasakul	Cancer Cell Biology and Nanotechnology	26
Dr. Linda Vona-Davis	Tumor-associated adipocytes support breast cancer in obesity	27

### **WVU Mentor Listing According to Area of Research**

**Addiction:** Kinsey

**Cancer Research:** Du; Hazlehurst; Ivanov; Lockman; Martinez; Pugacheva; Rojanasakul; Vona-Davis

**Cardiovascular Research:** Brown; Chantler; Hillgartner; Hollander; Mohamed; Nayeem; Nurkiewicz; Olfert

**Diabetes:** Hillgartner; Leonardi

**Drug Development:** Benedito; Geldenhuys; Kinsey; Li

**GI Research:** Rajendran

**Inflammation:** Brown

**Infectious Disease:** Damron; Barbier; Li

**Muscle Research:** Mohamed

**Nanotechnology:** Geldenhuys; Li; Rojanasakul

**Neuroscience Research:** Brown; Geldenhuys; Hileman; Lewis

**Obesity Research:** Hillgartner; Vona-Davis

**Pharmacology Research:** Geldenhuys; Kinsey

**Pulmonary Research:** Nurkiewicz; Rojanasakul

**Reproductive Biology Research:** Goodman; Hileman

**Toxicology Research:** Li

## Mentors at Marshall University

<u>Mentor</u>	<u>Description of Research</u>	<u>Page #</u>
Dr. Subha Arthur	Intestinal assimilation of Na and nutrients in the causation of cardiovascular diseases risk factors -- obesity, diabetes and hypertension	28
Dr. Beverly Delidow	Inhibition of Wnt/ $\beta$ -catenin signaling and induction of autophagy in melanoma	29
Dr. Richard Egleton	Opioid regulation of brain endothelial cells	29
Dr. Philippe Georgel	<i>in utero</i> effects of opioids on Neonate Abstinence Syndrome	30
Dr. Lawrence Grover	Mechanisms of action of antidepressant medications	31
Dr. Brandon Henderson	Neurotrophic factors in neonatal abstinence syndrome Characterizing the effect of tobacco flavorants on nicotine addiction	32
Dr. Jung Han Kim	Genetics of obesity and type 2 diabetes	32
Dr. Emine C. Koc	Role of mitochondria in aging, heart disease, diabetes, neurodegenerative disorders, obesity, and cancer	33
Dr. Isabel Larre	Na/K-ATPase-mediated TJ regulation in renal epithelial cells	34
Dr. Wei Li	1. Examine the mechanistic role of thymidine phosphorylase (TYMP) in thrombosis 2. To examine the role of thymidine phosphorylase in development of atherosclerotic disease	36
Dr. Jiang Liu	Salt retention/salt-sensitive hypertension and heart/kidney function and remodeling	37
Dr. Sandrine V. Pierre	1. Cardioprotection by Na <sup>+</sup> /K <sup>+</sup> -ATPase ligands in acute myocardial infarction. 2. Role of $\alpha$ 1 Na/K-ATPase in adverse cardiac remodeling and heart failure	38
Dr. Gary Rankin	Kidney toxicology; Metabolism of methadone	39
Dr. Travis Salisbury	Environmental pollutants and breast cancer	39
Dr. Nalini Santanam	Obesity, behavior and appetite Epigenetics and ovarian cancer risk	40
Dr. Vincent Sollars	What are the processes that enable a normal cell to start misbehaving and become cancerous?	40
Dr. Monica Valentovic	1. Reducing serious cancer chemotherapy side effects 2. Identification of ways to reduce the liver damage of acetaminophen overdose 3. Mechanisms exploring the link between obesity and cancer 4. Examination of the mechanism of renal damage by an antiviral agent used in treating HIV and hepatitis	41
Dr. Yanling Yan	The role of reactive oxygen species, inflammation and cardiotonic steroids-mediated Na/K-ATPase signaling in kidney and cardiovascular disease	42
Dr. Hongwei Yu	Cystic Fibrosis Biofilms; Modeling Lung Infection; Novel Probiotics	43

### Marshall University Mentor Listing According to Area of Research

**Addiction:** Egleton; Georgel; Grover; Henderson; Rankin

**Cancer Research:** Delidow; Koc; Salisbury; Santanam; Sollars; Valentovic

**Cardiovascular Research:** Arthur; Egleton; Koc; Li; Liu; Pierre; Yan

**Diabetes:** Arthur; Kim; Koc

**Drug Action and Metabolism:** Egleton; Valentovic

**GI Research:** Arthur

**Genetic Research:** Georgel; Kim; Rankin

**Infectious Diseases:** Yu

**Neuroscience/Sensory Research:** Egleton; Grover

**Obesity Research:** Arthur; Kim; Koc; Santanam

**Renal Research:** Larre; Liu; Rankin; Valentovic; Yan

**Toxicology Research:** Rankin; Valentovic

# MENTORS FOR THE 2015 WV-INBRE SUMMER INTERNSHIP PROGRAM

## I. At The West Virginia University Health Sciences Center

### **Mariette Barbier, PhD**

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### **Characterization of *Pseudomonas aeruginosa* pathogenesis**

*Pseudomonas aeruginosa* is a major nosocomial pathogen and an important cause of respiratory, blood stream and soft tissue infections. The treatment of these infections is made difficult by the alarming rise in antibiotic resistance detected in the past few years in *P. aeruginosa*. Our laboratory characterizes the molecular factors involved in the infectious process and the pathogenesis of this bacterium in order to identify novel therapeutics for the treatment of these infections.

Our laboratory aims to understand the function of *P. aeruginosa* virulence factors by studying gene and protein expression during infection. We use both traditional molecular approaches as well as novel next generation sequencing technologies to understand how this bacterium interacts with the host and the immune response triggered by this interaction. By providing exciting research experience to INBRE students, we want to further our understanding of *P. aeruginosa* pathogenesis and advance towards the development of therapeutics. In particular, the INBRE student would be involved in studying heme and iron uptake in *P. aeruginosa* and the interaction of this pathogen with epithelial cells and macrophages. The student would also potentially be involved with team-based vaccine development studies focused on heme and iron acquisition.

**Vagner A. Benedito, Ph.D.**

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**Understanding the biosynthesis regulation of the antimalarial medicine artemisinin in *Artemisia annua* L.: effects of salt stresses**

**Introduction and rationale:** *Artemisia annua* L. (Asteraceae family) is a medicinal herb native to temperate Asia and the main commercial source of the *anti-malarial drug artemisinin*, which is a sesquiterpene lactone used in standard treatments. Given its complex chemical structure, artemisinin is difficult to synthesize *ex vivo*, which leads to great global shortage and high cost. Therefore, to improve artemisinin yield, it is essential to understand the physiology and genetic regulation *in planta*. **Research goal and objectives:** *The main goal of our research is to understand the effects of salt stress on artemisinin biosynthesis and the genetic regulation of this pathway.* At WVU, we have a unique germplasm collection of *A. annua* genotypes differing in yields of artemisinin and its immediate precursors. Abiotic stress has been linked to increased artemisinin yields, but the physiological mechanisms are unknown. *Our hypothesis is that artemisinin is a byproduct of oxidative stress as a result of oxidation of precursor metabolites.* Biochemical and physiological parameters are being analyzed along with expression levels of known terpenoid biosynthesis genes to understand how abiotic stress regulates artemisinin biosynthesis. We are assessing whether salt stress applied to the roots of clones with high precursor production will lead to higher yield of artemisinin. We are also evaluating whether clones with high DHAA or artemisinin are more tolerant to salt stress than clones with high levels of artemisinic acid.

## **Candice M. Brown PhD**

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### **Brain-immune interactions in acute and chronic systemic inflammation**

Brain-immune communication is essential in human health and disease. The blood-brain barrier (BBB) is a dynamic structure that mediates communication between the brain and periphery. Research in my laboratory is centered on brain-immune interactions that affect BBB integrity in acute and chronic systemic inflammation. Our current studies are focused on the role of tissue nonspecific alkaline phosphatase, an enzyme localized on brain endothelial cells, in the maintenance of BBB integrity. We integrate this research with the study of sex differences in order to better understand how male brains and female brains respond differently to acute and chronic systemic inflammation. To carry out our research, we employ a multidisciplinary approach that combines: *in vivo* mouse models of experimental sepsis, ischemic stroke and Alzheimer's disease (AD); *in vitro* and *ex vivo* cell and tissue culture models that mimic aspects of these disorders; and recruitment of sepsis patients from Ruby Memorial Hospital.

INBRE students will have the opportunity to engage in projects aimed at understanding short- and long-term peripheral immune responses in mouse models of ischemic stroke, sepsis, and AD. S/he will interact with graduate students, medical students, fellows, and other staff members to answer research questions. Studies will focus on comparisons between brain and peripheral organs such as liver, spleen, and small intestine. Skills and techniques learned during the internship may include: 1) handling and husbandry of transgenic mouse models to study sepsis, ischemic stroke, or AD; 2) animal behavior paradigms; 3) tissue sectioning, immunohistochemistry, and imaging; 4) DNA and RNA isolation, qPCR, and Western blotting; 5) bioinformatics analysis of gut microbiome next generation sequencing data.



**Dr. Paul Chantler**

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**Cardiovascular responses to exercise**

INBRE program participants will work in conjunction with laboratory personnel on current projects. Projects in the laboratory are focusing on cardiac and arterial structure and function, and includes exploring the age-associated changes in arterial structure and function, how they interact with aging, lifestyle, and various disease states, in particular the Metabolic Syndrome (MetS), and how they influence the structure and function of the heart. My lab also uses animal models of obesity/MetS to examine stroke related pathological insults on the cardiovascular system and how various forms of anti-oxidant compounds improve stroke outcome. Current research is examining how adipose tissue regulates stroke outcome via modifying cerebrovascular function and microvessel density. INBRE participants will interact with graduate students and staff members to answer research questions, using both invasive and non-invasive approaches to examining cardiovascular function. Training provided to the participants will include human and animal CV physiology, ultrasound, and applanation techniques, and biochemical analyses.

## **F. Heath Damron, PhD**

Assistant Professor

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### **Characterization of Pertussis and development of vaccines**

*Bordetella pertussis* is a respiratory pathogen and the primary causative agent of Pertussis, also known as whooping cough. Despite the currently used acellular vaccines (DTaP/Tdap), an alarming increase of whooping cough cases has occurred in the past two decades. Today in the US, we have the same number of cases as back in 1953 just after the whole cell vaccines were first introduced. Not enough is known about the biology of infections with *B. pertussis* and it is clear that the current acellular vaccines need some refinements/additions to improve the efficacy and duration of the protection. In addition, it is vital to better understand the progression of respiratory infections caused by this pathogen. The objective of the Damron laboratory is to develop next generation pertussis vaccines. We are currently evaluating an intranasal formulation of a DTaP vaccine that would serve as a booster to enhance protection in school age children. While the antigens we currently use are effective we hypothesize that adding additional antigens can expand the range of protection. For example there are other Bordetellae that cause whooping cough and not all of them express the antigens that are in DTaP/Tdap. We have developed methodology to perform *in vivo* gene expression analysis using RNAseq. In that study, we have obtained a snapshot of the gene expression profile of *B. pertussis* in the mouse lung. With this method, we will continue to characterize the expression profiles of *B. pertussis* and other Bordetellae in the murine airway. In parallel studies, we will be performing RNAseq on Bordetellae growing in human sputum. When genes are commonly expressed in both the mouse and human sputum, as well as meet our antigenicity criteria, we will select them for further antigen development. The INBRE student will be involved in cloning the promoter and ribosomal binding sites of identified antigens into a dual fluorescent protein reporter vector. This vector expresses GFP constitutively and the far red protein, E2Crimson. E2Crimson will be controlled by the promoter that was selected. Enhanced red to green signal will indicate the relative expression of the gene of interest. We can then study the promoter activity *in vitro* in laboratory conditions with various clinical strains in both synthetic growth medium and human sputum. Next, the Bordetellae containing the reporter can be used to challenge mice to study the *in vivo* expression of the gene, respective to the upper, middle, and lower airways. Bacteria will be isolated by filtration and then analyzed by flow cytometry and other confirmatory analyses. These studies will be essential to identifying highly expressed antigens and will contribute to our efforts to develop new vaccines. The INBRE student would receive training on the following: general bacteriology culture methods, cell culture, quantitative gene and protein expression, molecular cloning, as well as receive experience in bioinformatics and next generation sequencing. These studies are currently funded by the Vaccine Development center at WVU Health Sciences where the student will also learn about other vaccine development projects during their internship. Our goal will be to provide the student with an exciting research experience, training, and work towards our goals of understand *B. pertussis* infection to develop the next-generation of safe and effective pertussis vaccines.

**Dr. Wei Du**

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**Collaboration between DNA damage and immune responses in leukemic stem cell emergence and expansion**

Acute Myeloid Leukemia (AML) has a 5-year survival rate of 25%. Thus, clinical evidence continues to support the need to identify novel targets and therapeutics for the treatment of this deadly disease. Experimental evidence has clearly shown that interaction of the leukemic cell with the tumor microenvironment (TME) contributes to *de novo* drug resistance and likely failure to eliminate minimal residual disease (MRD). It is currently less clear what the impact of TME-induced expansion of regulatory T cells (Tregs) in mediating MRD following standard of care treatment and bone marrow (BM) transplant. We will utilize a model of Fanconi anemia (FA), a cancer-prone disease with extremely high incidence of myelodysplastic syndrome (MDS) and AML, to determine the role of the TME in the expansion of the Treg population, relapse and progression of AML.

**Hematopoietic stem cell polarity in bone marrow failure and leukemia**

Stem cell and gene therapies through hematopoietic stem cell transplantation (HSCT) is the only definite treatment for various hematological malignancies, including FA. However, three major hurdles have been hampering scientific and clinical advance in the blood cancer HSCT field: 1) ineffective mobilization of patient stem cells; 2) hypersensitivity of recipient patients to pre-conditioning regimens; and 3) inefficient delivery of donor stem cells to the BM of cancer patients. Therefore, there is a great need to develop novel pre-conditioning agents that can optimize homing and entry of HSCs into recipient BM niche with minimal toxicity. The project will examine the mechanistic link between stem cell polarity, and HSC renewal and engraftment defects. Further, an innovative xenotransplant model will be employed to determine the potential of targeting stem-niche interaction in stem cell and gene therapies.

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**Discovery of compounds to treat Parkinson's disease**

Parkinson's disease is an age-related neurodegenerative disease which affects the motor skills of patients. Unfortunately no drugs are currently available to slow down the disease progression, and there is a great need to discover these types of compounds. In this study we will be screening a library of compounds which consist of FDA approved and novel compounds identified through computer aided drug design techniques in several enzyme and *C. elegans* models. Once the compounds are identified which show promise, we will test them for neuroprotective activity. During the period of the study, students will learn how to screen compounds for biological activity in a high throughput manner as well as how to utilize models of Parkinson's disease to screen for phenotypic improvement afforded by the compounds. The student will learn more about the drug discovery process and how new drugs are found and characterized.

**Deliver of therapeutic proteins using nanoparticles**

Parkinson's disease is an age-related neurodegenerative disease which affects the motor skills of patients. Unfortunately no drugs are currently available to slow down the disease progression, and there is a great need to discover these types of compounds. In Parkinson's disease there are some mitochondrial proteins which we have found can be used to restore the damaged mitochondria seen in the disease. In this project we will work on developing a nanoparticle drug delivery system to deliver a therapeutic protein to the brain using several cell culture models. This project will introduce the student to the art of nanoparticle drug delivery formulation using biological therapeutic proteins as disease modifiers.

### **Dr. Robert Goodman**

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The following project is available in my laboratory:

#### **Are neurons that respond to kisspeptin for NKB critical for pulsatile LH secretion in ewes?**

Kisspeptin and neurokinin-B (NKB) are neurotransmitters found in the same set of neurons and are critical for normal reproductive function in humans because mutations in receptors for each produce infertility due to abnormally low release of gonadotropin-releasing hormone (GnRH). GnRH stimulates secretion of LH and FSH from the anterior pituitary and is the primary means by which the brain controls reproductive function. One important feature of GnRH release is that it occurs in episodes, not continuously. Kisspeptin and NKB stimulate GnRH secretion in several species and both are essential for this episodic pattern of GnRH secretion. However, receptors for these two peptides are found on different neurons indicating that they act via different intermediaries to control GnRH pulses. We plan to lesion neurons containing receptors for either kisspeptin or NKB in a specific region of the brain and determine the effects of these lesions on episodic GnRH secretion, using LH as an index of GnRH release. The student or faculty member will have the opportunity to assist with this study, work on other ongoing experiments, and learn the following techniques: 1) surgical removal of the ovaries and neurosurgical procedures for implanting chronic guide tubes into specific areas of the brain, 2) injection of substances into the brain, 2) blood collection and processing, 3) radioimmunoassay procedures for measuring hormone levels in the blood, 4) and immunocytochemical procedures for identifying proteins (e.g., receptors for NKB) in tissue slices.

### **Dr. Lori Hazlehurst**

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Co-Leader Osborn program MBRCC

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#### **Development of novel therapeutic strategies for tumors that reside or home to bone**

**Background:** It is clear that tumors that reside in the bone marrow such as multiple myeloma or tumors that metastasize to the bone such as lung, breast and prostate are difficult to treat with standard of care chemotherapeutics agents. We propose this is due in part to the identification of targets using unicellular models which do not account for the cross talk between the tumor and the tumor microenvironment in mediating disease progression and drug sensitivity. Our laboratory previously showed that tumor cell lines and primary patient specimens adhered to fibronectin are resistant to multiple structural and mechanistically diverse anti-cancer agents which we coined CAM-DR or cell adhesion mediated drug resistance. Moreover, tumors cells co-cultured with bone marrow stroma show increased resistance to standard of care agents. The goal of our laboratory is to define novel targets in the context of the bone marrow microenvironment and pursue the development of inhibitors that will either reverse CAM-DR or take advantage of vulnerabilities that occur due to cross talk between the tumor and bone marrow microenvironment.

**Project:** The incoming INBRE student would work with other students and post-docs in the laboratory and focus on determining whether: MTI-101 which targets a CD44/Alpha 4 intergin-IP3R-SOC signaling circuit is a viable strategy for inducing calcium overload and necrotic cell death in tumor cells residing in the bone marrow.

Students that joined are laboratory will learn cell culture, calcium flux measurement, standard genetic and pharmacological approaches for inhibiting mediators of calcium flux as well as exposure to analyzing microarray data, high throughput screening and in vivo drug testing.

**Dr. Stan Hileman**

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The process of puberty can be defined as the process whereby an individual gains the capacity for reproduction. This process is dependent upon changes in the release of gonadotropin releasing-hormone (GnRH) from the hypothalamus of the brain. Prior to puberty, GnRH release is minimal and the reproductive system is largely quiescent. As the time of puberty approaches, GnRH secretion increases, eliciting a corresponding increase in the release of luteinizing hormone (LH) and follicle stimulating hormone from the anterior pituitary gland that causes follicular maturation and, eventually, the first ovulation. The neural mechanisms underlying the pubertal increase in GnRH secretion are not completely understood, but may involve a set of neurons in the arcuate nucleus of the hypothalamus that coexpress kisspeptin, neurokinin B, and dynorphin, thus termed KNDy neurons. Kisspeptin and neurokinin B are critical for puberty onset in humans and have been shown to stimulate LH secretion in a number of species. The aim of our current project is to define the role of the KNDy peptides in puberty using female sheep as the model animal. One experiment is aimed at determining the expression of the KNDy peptides during the pubertal process. Another is to determine if involvement of neurokinin B in regulating pubertal GnRH/LH release is dependent upon kisspeptin and where neurokinin B may be acting within the hypothalamus to stimulate GnRH/LH release. A third aim is to determine if dynorphin is responsible for the inhibition of GnRH/LH secretion observed during the prepubertal period.

**Dr. Brad Hillgartner**

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<http://wvuhealthcare.com/wvuh/Content/Media/News-Releases/2008/10/08-190>

Work in my laboratory focuses on the regulation of genes involved in the development of obesity, diabetes and atherosclerosis. We are currently investigating how nutritional and hormonal factors regulate the expression of genes controlling fatty acid synthesis and fatty acid oxidation. One specific project is to characterize the molecular mechanisms controlling the expression of fibroblast growth factor-21, a novel hormone that reverses obesity and diabetes in experimental animals. A student intern or fellow participating in these studies would gain experience in a variety of cell and molecular biological techniques, including cell culture, transfection, DNA and RNA analyses, and Western analysis.

**Dr. John Hollander**

Associate Professor

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**Cardiovascular Research** (This project is appropriate for faculty and/or students)

INBRE program participants will work in conjunction with laboratory personnel on projects examining metabolic aspects of cardiac diseases. Projects in the laboratory focus specifically on understanding the role played by proteins thought to be protective against the development of heart failure during diabetes mellitus as well as the genetic regulation of these proteins. Our studies have a tremendous impact on Appalachia. The goal of these studies is to provide insight into the mechanism of action of these proteins and genes, with the goal of designing therapeutics to treat cardiac disease states. Our experimentation involves both basic research and analyses in patient populations.

INBRE participants will interact with graduate students and staff members to answer research questions, using a multidisciplinary approach that includes genetic modification of the heart in both cell and animal models as well as analyses in patient samples. Training will be provided to the participants, which includes molecular cloning, whole heart physiology, RNA, DNA, and protein manipulation, bioinformatics as well as biochemical analyses.

## Alexey Ivanov, Ph.D.

### Research Assistant Professor

Department of Biochemistry and Mary Babb Randolph Cancer Center,  
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### Description of Research

Vast majority of human tumors are of epithelial origin, e.g. they derive from cells normally highly organized in specialized epithelial layers. At the same time, most cancer-related deaths occur due to tumor recurrence and spread to distant organs (metastasis), which are tightly linked to acquisition by cancer cells of mesenchymal properties such as increased motility, invasion and resistance to chemotherapy. The metastasis stage of cancer is associated with epithelial-to-mesenchymal transition (EMT). Normally acting only during early embryonic development, the EMT program is hijacked by cancer cells during evolution of individual tumors. EMT is activated by a handful of transcription factors referred to as the EMT master regulators, such as Snail and ZEB.

The goals of our research are to identify transcriptional network involved in activation of EMT during cancer metastasis. This knowledge will help to develop future therapeutic approaches in treating cancer and prevention of metastasis.

#### Available projects:

##### 1. Breast cancer cell dissemination, dormancy

###### and reactivation at the metastatic sites in mouse xenograft model.

Cancer cell dissemination can occur before primary breast tumor diagnosis. Most disseminated cells stay dormant for years and are resistant to therapy. Tumor recurrence from these reactivated cells accounts for metastatic outgrowth and subsequent patient death. The goal of this project is to understand the mechanisms of tumor cell dormancy using a mouse xenograft model.

##### 2. Negative control of EMT by epithelial-specific transcription factors.

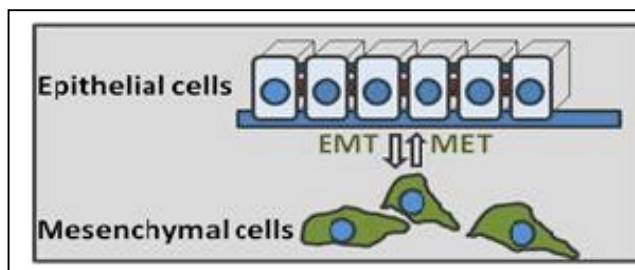
EMT promotes cancer cell invasion, metastasis and drug resistance. Primary breast tumors largely maintain inherent epithelial status. However, cancer cells on the tumor periphery are believed to undergo partial EMT and disseminate to distant organs. The goal of this project is to define the roles of several transcription factors responsible for the maintenance of the epithelial state in suppression of EMT.

##### 3. Role of the TGF-beta pathway in partial EMT and drug resistance of triple-negative breast cancer.

Transforming growth factor beta (TGF-beta) acts as a tumor suppressor at the early stages of cancer development. Cancer cells evolve various mechanisms to overcome TGF-beta inhibitory effects, including silencing and mutation of TGF-beta receptors or silencing and deletion of TGF-beta target genes involved in growth suppression. The latter mechanism is often observed in triple-negative breast cancer (TNBC). TNBC cells show increased TGF-beta signaling leading to partial EMT and resistance to certain drug therapies. The goal of this project is to investigate if pharmacological inhibition of the TGF-beta pathway combined with standard cancer therapy will improve drug response in vitro.

#### Former WV-INBRE summer research interns in the lab

<u>Year</u>	<u>Name &amp; college</u>	<u>Current position</u>
2015	Brandon Trinh, Bethany College	
2013	Morgan Johnson, Shepherd University	WVU medical student
2012	Anna Alappat, Shepherd University	WVU medical student
2009	Icel Cavis, Shepherd University	FBI Forensics Lab, Quantico, VA





**Steven Kinsey, PhD**

Associate Professor, Department of Psychology, WVU  
sgkinsey@mail.wvu.edu

The Kinsey lab studies the cannabinoid system, which is responsible for the effects of cannabis on the brain and other parts of the body. This summer, our lab will be working on at least two major projects involving cannabinoids, using mice. The first will investigate new mouse models of cannabis withdrawal. Although not as big a problem in our region as opioids, cannabis is an addictive drug that can be difficult for some people to quit. The goal of these studies is to develop pharmacological treatments for cannabis withdrawal that could be used in people. The second project is about rheumatoid arthritis. We are using cannabinoid-based drugs to explore inflammation caused by arthritis. An intern working in our lab would have the opportunity to work on one or both projects and will gain experience using behavioral, immunological, and pharmacological techniques.

**Roberta Leonardi, Ph.D.**

Assistant Professor  
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Coenzyme A (CoA) is an essential and universally distributed cofactor that acts as the major acyl group carrier in the cell. Free CoA and acyl-CoAs are involved in hundreds of metabolic reactions, and are among a selected number of small molecules that have the ability to act as global regulators of cellular metabolism. Consistent with this key function, CoA levels are at the same time tightly regulated and flexible, so that the available supply is sufficiently adaptive to metabolic challenges such as fasting or a high fat diet. Regulation of CoA levels occurs through coordination of synthesis and degradation. In the liver, modulation of the amount of CoA contributes to the metabolic flexibility of this organ and to its ability to maintain glucose homeostasis during a fast. Conversely, in diabetic mice, hepatic CoA levels are abnormally high and unresponsive to changes in the nutritional state.

Not much is known about CoA degradation. The goal of our research is to establish the importance of two recently discovered CoA-degrading enzymes, Nudt7 and Nudt19, in the regulation of CoA levels and glucose homeostasis. In particular, we are interested in studying these enzymes in the context of diabetes and other metabolic diseases using a combination of biochemistry, animal studies and metabolomics.

**James W. Lewis, Ph.D.**

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**Description of Research (2017-2018):** Neuroimaging of sensory perception and cognition in the human brain.

**Lewis laboratory activities:**

Our lab studies mechanisms of multisensory and hearing perception, and spoken language processing, using either evoked response potential (ERP) methods or 3 Tesla functional magnetic resonance imaging (fMRI). This includes studying aspects of human auditory system function ranging from processing of low-level features of sound (acoustic signal processing principles) to intermediate- and high-level perceptual features of action sounds and speech processing (cognitive processing), which together mediate our sense of recognition of the every day sounds we hear. By understanding basic mechanisms for how acoustic information is processed and how these relate to language systems, we seek to advance cognitive models of knowledge representations. This basic science is designed to further develop diagnostic tools for early screening of children with central sensory processing disorders, and develop interventional therapies for individuals recovering cognitive abilities following brain injury. We primarily use computational approaches and methods for studying brain function, and thus applicants with a solid background in neuroscience or computer scripting are preferred.

Potential projects include:

- (1) Identifying differences in functional (fMRI) and anatomical circuits for multisensory processing in individuals with versus without autism spectrum disorder.
- (2) FMRI study of brain networks for processing natural sounds and spoken language in English and Chinese.

**Bingyun Li, Ph.D.**

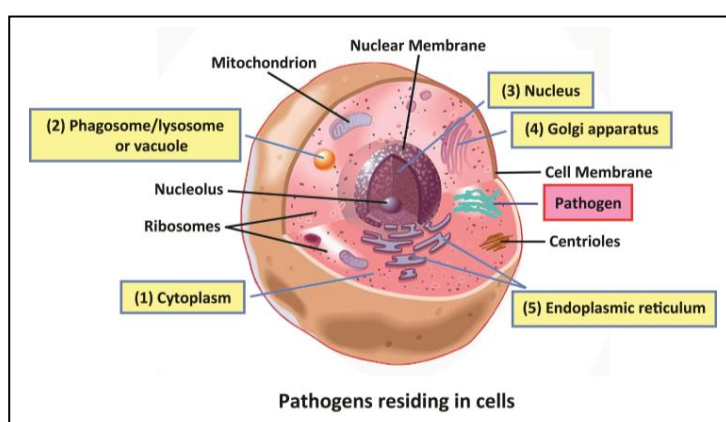
**Professor, Department of Orthopaedics  
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**Research Interests:** Nanomedicine, nanotoxicity, drug development and delivery, and intracellular disease pathogenesis.

### **Description of Research**

Diseases such as tuberculosis, hepatitis, and HIV/AIDS are caused by intracellular pathogens. Pathogens reside within cell compartments are often difficult to treat using conventional approaches. Professor Li's research focuses on drug development and delivery as well as nanotechnology-based therapies to prevent or treat infection, cancer, and intracellular diseases, and determination of related nanotoxicity and immune responses. A multidisciplinary research approach including nanotechnology, microbiology, immunology, cell biology, and surgery is applied.



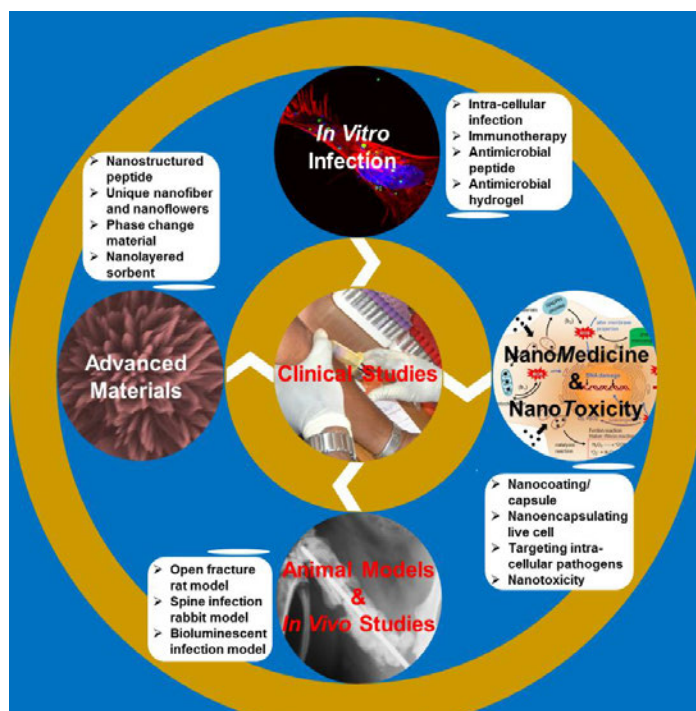
**Figure.** Pathogens may reside in various locations, including: the cytosol, phagosome, lysosome or vacuole compartments, the nucleus, and some may associate with the golgi apparatus or endoplasmic reticulum.

### **Potential project examples**

Projects may include (see right figure):

- Antimicrobial peptides and proteins
- Controlled drug delivery
- Innovative biomaterials and biomimetics
- Microbiology and infection
- Microsurgery and animal models
- Nanotechnology, nanomedicine, nanotoxicity
- Pharmaceutical drug development
- Stimulating immune responses
- Technology development
- Tissue engineering

**Note:** Professor Li has trained > 80 students including INBRE, MD, and PhD students, and published > 80 papers. Some INBRE students in the past have been *co-authors* of journal papers and/or national presentations. Participants will gain experience in *microbiology, immunology, cell biology, pharmaceutical science, microsurgery, or nanotechnology*.



**Dr. Paul R. Lockman**

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**Significance and Translational Relevance**

Brain metastases pose a life threatening problem for women with advanced metastatic breast cancer. Of women who have been diagnosed with disseminated breast cancer, ~10-16% will develop symptomatic brain metastases and at least 20-30% will have micrometastatic lesions present at autopsy. Once lesions are established in the central nervous system, only one in five women survive one year. We have recently shown that chemotherapeutics do not reach effective concentrations in ~90% of CNS metastases. Therefore, our lab is working on ways to prevent the formation of metastases in brain.

**Project Information**

Our lab uses cutting edge microscopy to identify single breast cancer cells that can invade into brain tissue. Once the cells are found we have techniques that can remove the individual cancer cell. Once the cell is collected the goal of the project is to identify if there is a DNA signature that allows the cancer cell to get into brain (>99% of breast cancer cells do not enter into brain tissue). Once that signature is identified it is hoped we will find a molecular target that can be blocked by a drug, which should reduce penetration of the cancer cells into brain. It is hoped this project will be a first step in the prevention of brain metastases of breast cancer.

**Skills and or Experiences the student will be exposed to**

1. Cell culture of human and mouse cells
2. Fluorescent microscopy – to potentially include multi-photon imaging
3. Bioluminescence imaging of cancer cells in living animals.
4. Laser micro-dissection of cells in tissue
5. RNA amplification
6. Microarray data

**Dr. Ivan Martinez**

Assistant Professor  
Department of Microbiology / Cancer Center  
School of Medicine  
West Virginia University

Description of Research

**Importance of Non-coding RNAs in Human Papillomavirus (HPV)-Related Cancers and Models of Cellular Growth Arrest**

The recent discovery of different classes of non-coding RNAs and their importance in almost every cellular process has opened a new frontier in understanding the regulation of gene expression. The main interest in my laboratory is to study the importance of non-coding RNAs, such as microRNAs (miRNAs) and large intergenic non-coding RNAs (lincRNAs) during the process of carcinogenesis in cells infected by human papillomaviruses (HPVs). miRNAs are double-stranded ~22 nt RNAs that can base-pair with specific messenger RNA (mRNA) targets and regulate their expression by translational repression or mRNA degradation. Many different miRNAs have been implicated in human cancers, either as oncogenic miRNAs or tumor suppressor miRNAs. In addition, viruses have been associated with 15-20% of all cancers and previous studies have shown that the expression of HPV oncogenes can regulate host miRNAs (such as miR-218) and influence the transcriptional profile of the infected cells.

Another class of non-coding RNAs recently discovered is known as lincRNAs. This type of large non-coding RNAs have the ability to regulate gene expression by directly interacting with chromatin-modifying proteins and helping them target specific genomic regions at distant loci. By using global lincRNA expression assays, reporter constructs, mutational and biochemical analyses, as well as functional assays, my lab also wants to explore the importance of lincRNAs in HPV-related cancers.

We are also interested in the importance of non-coding RNAs in different types of cellular growth arrest. Interestingly, the repression of the HPV viral oncogenes in cervical carcinoma cell lines reactivates the expression of the tumor suppressor proteins p53 and Rb that leads to a rapid induction of senescence (a form of irreversible growth arrest and a major tumor suppressor mechanism). Thus, we are also interested in studying the differences in miRNA expression and processing pathways during senescence and other types of growth arrest important in carcinogenesis such as quiescence (a form of reversible growth arrest important for tissue homeostasis and stem cell self-renewal).

There are several options for undergraduate students to participate in our research. Our laboratory offers to the participants the opportunity to learn different techniques in molecular genetics such as Real Time Reverse Transcription-Polymerase Chain Reaction (qRT-PCR), Western Blot, molecular cloning and mutational analysis, manipulation of gene expression by infection or transfection of exogenous genes and small interfering RNAs (siRNAs), etc.

**Junaith Mohamed, Ph.D.**

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The following project is available in my lab:

**Understanding the mechanism of induction of post-stroke skeletal muscle morbidities**

Skeletal muscle is the primary target organ of stroke after the brain. Stroke causes serious long-term disability in adult life. Even with optimal acute therapy, most of the patients remain in a state of insufficient recovery after stroke. Studies have shown that the loss of function of spinal alpha motor neurons after stroke initiates skeletal muscle atrophy and weakness. However, the molecular mechanism through which the loss of alpha motor neurons causes post-stroke muscle morbidities yet to be identified. We and others have shown that the NAD<sup>+</sup> dependent protein deacetylase Sirtuin1 (SirT1) plays a significant role in almost every main aspect of skeletal muscle biology. For example, SirT1 prevents muscle atrophy and promotes muscle growth, metabolism, resistance to muscle fatigue, and regeneration and repair. SirT1 also controls or mimics many of the exercise-regulated muscle pathways. SirT1 can turn genes on and off due to its spectrum of deacetylase activity on histone and a variety of non-histone proteins. We have recently identified that cerebral ischemic stroke down regulates SirT1 protein levels and activity in skeletal muscles, suggesting that the loss of the epigenetic role of SirT1 may be responsible for, in part, post-stroke muscle morbidities. The goal of above project is to 1) investigate the mechanism by which stroke causes loss of muscle mass and function, and 2) establish the role of SirT1 in the regulation of post-stroke muscle mass and function.

In this project, we will use a mouse model of transient cerebral ischemic stroke, skeletal muscle-specific SirT1 knockout and overexpressing mice, and various cell and molecular techniques. In our lab, INBRE participants will interact with graduate students and staff members to answer research questions, using a multidisciplinary approach that includes how the epigenetic modifications by SirT1 would protect skeletal muscle against stroke. The following types of training would be provided to the participants: 1) working with wild-type, transgenic, and stroke mice; 2) method of induction of stroke in mouse; 3) methods of isolating different types of muscles; 4) tissue sectioning, staining, and imaging techniques; 5) isolation of RNA, DNA, and protein from muscles; 6) next-generation sequencing technology; 7) analyzing sequencing data using bioinformatics software; 8) measuring global gene expression; 9) determining individual gene expression by real-time PCR and western blot; 10) rodent muscle fatigability measurement and exercise training techniques.

**Mohammed A. Nayeem, MSc, PhD.**

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<http://www.ncbi.nlm.nih.gov/sites/myncbi/mohammed.nayeem.1/bibliography/45750663/public/?sort=date&direction=ascending>

<https://scholar.google.ru/citations?user=SYQwJY0AAAAJ&hl=ru>

**Prevention of Cardiovascular Diseases with specific gene manipulation and pharmacology**

INBRE program participants will work with our laboratory staff (postdoctoral fellows, graduate student & technician) on projects including NIH funded project to understand the mechanisms involve in cardiovascular diseases in humans having genetic variations (genetic polymorphisms in humans) in cyp2j2, sEH, cyp4a A<sub>2A</sub>AR, PPARs genes. The cardiovascular diseases including pre-hypertension, hypertension, salt-sensitive hypertension, coronary artery disease, heart failure, cardiac arrest, cardiac death, heart attack, etc., may possibly occur due to the defect in genes (cyp2j2, sEH, cyp4a A<sub>2A</sub>AR, PPARs), where the enzymes and receptors of heart and blood vessels work abnormally in individuals, then these individuals are prone to have high risk cardiovascular diseases. We will explore the mechanism and drug development for those individuals who has the risk of cardiovascular diseases. We have started to identify some of the possible factors (enzymes and receptors) involved in vascular dilations and vascular contractions. For instance, we work with mice that have been genetically engineered so that they are missing or over-expressing specific enzymes or/and receptors (cyp2j2, sEH, cyp4a A<sub>2A</sub>AR, PPARs) that interfere in natural processes involved in vascular dilations and vascular contractions. These genetically engineered mice may possible mimic the same way as the human individuals who have specific genetic variants (genetic polymorphism) in their body with a risk of coronary, heart and vascular diseases. Our long-term goal is to identify the possible targets leading to the development of novel drugs to treat clinical problems of cardiovascular diseases including pre-hypertension, hypertension, salt-sensitive hypertension, coronary artery disease, heart failure, cardiac arrest, cardiac death, heart attack, etc., associated with the defect in the enzymes and receptors (cyp2j2, sEH, cyp4a A<sub>2A</sub>AR, PPARs) in humans who have genetic variants that may possibly act similar to our genetically engineered mice. INBRE participants will interact with our lab staff (postdoctoral fellows, graduate student & technician) and learn the techniques to measure the cardiovascular response in in vitro and in in vivo.

**Dr. Timothy R. Nurkiewicz**

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**Airborne Particles and Systemic Microvascular Endothelial Dysfunction**

Evidence indicates that acute exposure to airborne pollutants such as particulate matter (PM) and nanoparticles increases the risk of pulmonary and cardiovascular morbidity and mortality. This implies that PM affects extra-pulmonary tissues, as evidenced by the occurrence of cardiovascular dysfunction on high pollution days. However, the biological mechanisms by which PM evokes systemic effects remain to be defined. Despite its obvious importance in regulating the delivery of cells and molecules to all tissues, and in the etiology of most cardiovascular diseases, no research has investigated how systemic microvascular function is affected by pulmonary PM exposure. Our preliminary observations in the rat spinotrapezius muscle indicate that endothelium-dependent arteriolar dilation is significantly impaired after pulmonary particle exposure, and this impairment is associated with microvascular oxidative stress. Interestingly, this systemic microvascular effect can occur independent of pulmonary inflammation. My central hypothesis is that acute particle exposure affects peripheral microvascular function, and this effect is achieved by local reactive oxygen species production and/or altered neurogenic input to the systemic microcirculation. A fundamental understanding of these mechanisms is vital in preventing and treating the life-threatening events associated with air pollution. Our studies are further applied to the rapidly growing field of nanotoxicology. Wherein, it is acknowledged that nanotechnology has become a regular component of most every aspect of our daily lives, yet the toxicity of exposure to specific nanoparticles remains to be determined. Exposure to these nanoparticles carries just as much, if not more potential for generating profound effects on microvascular function. The student or faculty member will have the opportunity to develop surgical and experimental techniques associated with animal studies and isolated microvessels, as well as assist in exposing animals to various particle aerosols. These techniques include: inhalation exposure, animal surgery, microsurgery, intravital microscopy, in vivo measurement of oxidative stress and various micropipette-based techniques.



**Dr. Mark Olfert**

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**Title: Microvessel and vascular responses to E-cigarettes, nicotine and/or environmental stress**

INBRE program participants will work in conjunction with laboratory personnel on projects examining blood vessel responses to varied conditions, such as E-cigarettes, inhaled nicotine and/or other conditions (hypoxia, chronic disease states, etc.). Projects in the laboratory focus specifically on understanding the proteins and cell signaling responsible for regulating the function and formation of blood vessels in response to environment stress (e.g. inhaled toxicants, electronic cigarettes), biological stresses (e.g. exercise), and/or the loss of blood vessels in disease (e.g. obesity, heart failure, lung disease, diabetes, etc.). The goal of these studies is to provide insight into the mechanism(s) involved with the ultimate goal of designing therapeutics to treat abnormal vascular pathology. INBRE participants will interact with graduate students and staff members to answer research questions, using a multidisciplinary approach that includes genetic modification, whole animal clinical and metabolic testing, and bench top tools for DNA, RNA and protein analyses. Training provided to the participants will include whole animal physiology, basic surgical and microscopy techniques, along with molecular and biochemical analyses.

**Dr. Elena N. Pugacheva**

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**Molecular mechanisms of breast cancer metastasis**

While significant progress has been made in the treatment of breast cancer, there remain substantial problems in metastasis treatment. Tumor cells not successfully eliminated by treatment often remain dormant, and later begin to grow and contribute to relapse of disease after cessation of treatment. Relapsed tumors are often more challenging to treat than that presented initially, and have a much less promising prognosis. This project will include using a model system of cultured breast cancer cells to investigate the effects of small molecule inhibitors against AURKA kinase on tumor metastasis and evaluate therapeutic benefits. Students will learn to do tissue culture, Western blot analysis of proteins, mouse tumor modeling, flow cytometry, and confocal microscopy during this investigation.

**Decipher the molecular mechanisms of cell cycle driven disassembly of primary cilium in normal and cancer cells.**

Cilium is a microtubule-based structure present on each cell in our body except lymphocytes. We have previously shown that activity of AURKA kinase is crucial to disassemble primary cilium, but the exact mechanism and mainly substrates of AURKA are unknown. We have identified several motor proteins as direct substrates of AURKA kinase and currently testing using live imaging techniques the impact of phospho-dead mutants on the trafficking along the cilia and ciliary disassembly. The main goal is to define the components of the signaling machinery that governs the ciliary disassembly in response to AURKA activation. Students will work in extending the current studies on the driving force of ciliary disassembly in brain cancer progression using patient derived models.

## **Dr. Vazhaikkurichi M. Rajendran**

Professor

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Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis. Crohn's disease affects any part of the intestine (small and large intestine). Ulcerative colitis affects only the large intestine/colon. Both Crohn's disease and ulcerative colitis are chronic inflammatory diseases. Ulcerative colitis that affects young adults is most prevalent in developed countries. This laboratory focuses on identifying the cause of the disease and on developing drugs for its prevention and cure.

### **Molecular Basis of Ulcerative Colitis**

Ulcerative colitis occurs as a result of inflammation of the mucosal cells that line the inner surface of the colon. This mucosal inflammation results in a reduced rate of nutrient, electrolyte and water absorption, leading to diarrhea. In addition, inflammation also reduces nutrient metabolism that produces energy needed to maintain healthy mucosal cells. An overactive immune system is one of the major reasons for mucosal inflammation in ulcerative colitis. The overactive immune reaction constantly produces free radicals (reactive oxygen species) that inhibit water absorptive processes and damage the mucosal cells.

### **Approach to Cure and Prevent Ulcerative Colitis**

To prevent ulcerative colitis, simultaneous reduction of the overactive immune system and improvement of mucosal cell health are essential. Overactive immune reactions could be controlled by supplying antioxidants. Mucosal health could be improved by supplying butyrate (a short chain fatty acid), which is the major nutrient of colonic mucosal cells. Butyrate is not present in food, but is produced from non-absorbed carbohydrates by bacteria present in the colon. Therefore, this laboratory is designing non-digestible carbohydrate (resistant starch) and free radical scavenger derivatives that, upon fermentation, deliver butyrate and an antioxidant right on target at the colon.

## **Dr. Yon Rojanasakul**

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### **Cancer Cell Biology and Nanotechnology**

Major research interest is in the area of cancer development and chemotherapy. Our laboratory is particularly interested in the carcinogenic effects of engineered nanomaterials and environmental agents. We also investigate drug resistance mechanisms and new therapeutic strategies for cancer treatment. The student will learn research techniques for 1) growing and manipulating cells in culture, 2) assessing cellular responses to carcinogenic and anticancer agents, 3) identifying biomarkers and drug targets for lung cancer using various molecular biology techniques.

**Linda Vona-Davis, Ph.D.**

Director of the Master of Science in Health Sciences Program

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**Tumor-associated adipocytes support breast cancer in obesity**

Given the high rates of obesity and breast cancer mortality in our Appalachian population, a systematic approach is urgently needed to identify key underlying molecular signals to reduce the burden of breast cancer. It is proposed that obesity-related biomarkers promote the dysregulation of pathways upon which cell growth, angiogenesis, and tumor invasion converge. Therefore, the objective of this summer project is to define the proinvasive nature of breast tumor cells cultured with cancer-associated adipocytes isolated from obese patients. The *rationale for the project* is that adipocytes and/or their conditioned media create a proinvasive microenvironment for tumors. Inflammatory and metabolic mediators secreted from adipocytes may be involved, however, it is not known whether these tumor-promoting properties are amplified in obese patients with breast cancer. We propose to define the key drivers of adipocyte-driven invasion in tumor cells cultivated either alone or with adipocytes from lean and obese cancer patients. In addition, the mRNA expression of adipocyte factors or inducible factors in tumor cells will identify key adipose tissue and/or breast epithelial-derived mediators linking obesity and breast cancer.

## **II. Mentors at Marshall University**

### **Dr. Subha Arthur**

Assistant Professor  
Department of Clinical and Translational Science  
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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.

**Dr. Beverly Delidow**

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**Inhibition of Wnt/ $\beta$ -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/ $\beta$ -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.

**Dr. Richard D. Egleton**

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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.

## Chromatin modifications in acute treatment

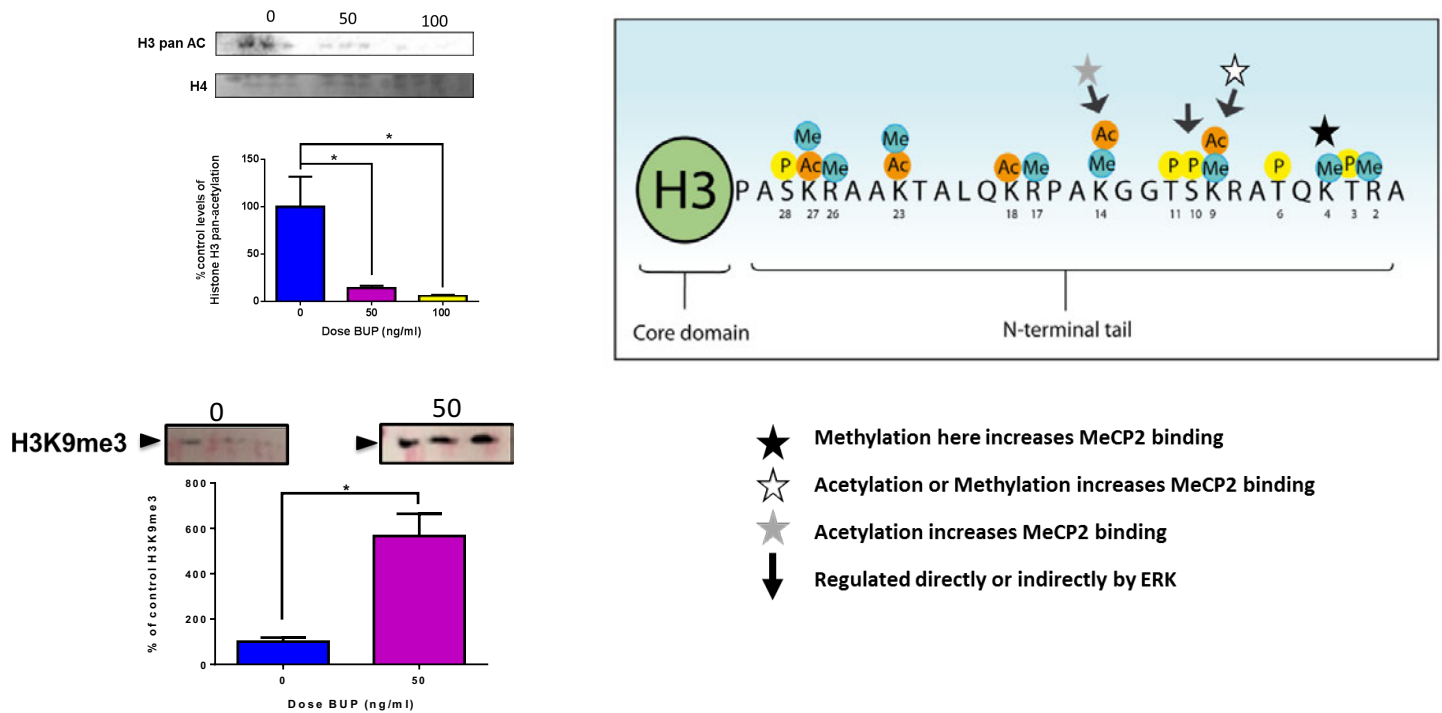


Figure 1: Epigenetic changes in response to Buprenorphine exposure

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 neurotrophic 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. 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. 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, and thermal cyclers.



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**WV-INBRE 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.

## Isabel Larre, Ph.D.

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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  $\Omega\cdot\text{cm}^2$  in the proximal tubule to as high as 2000  $\Omega\cdot\text{cm}^2$  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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Email: [liwe@marshall.edu](mailto:liwe@marshall.edu)<https://jcesom.marshall.edu/research/office-of-research-and-graduate-education/research-faculty/biomedical-sciences/wei-li/>**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, uptake 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

## Dr. Sandrine V. Pierre

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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 cardiomyocyte dysfunction based on the Na<sup>+</sup>/K<sup>+</sup>-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<sup>+</sup>/K<sup>+</sup>-ATPase ligands in acute myocardial infarction

**Rationale:** In addition to pumping ions, Na<sup>+</sup>/K<sup>+</sup>-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<sup>+</sup>/K<sup>+</sup>-ATPase receptor function will lead to novel interventions for the treatment and prevention of ischemia and reperfusion injury.

**Method:** Interns will learn the isolated Langendorff-perfused mouse heart preparation and expose it to novel compounds targeting the Na<sup>+</sup>/K<sup>+</sup>-ATPase cardioprotective signaling pathway. The intern will learn how to analyze contractile function in real time and assess activation of the Na<sup>+</sup>/K<sup>+</sup>-ATPase cardioprotective pathway biochemically. The effectiveness of promising compounds will be further tested *in vivo* following experimentally-induced acute myocardial infarction (AMI). C57BL6 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 intern 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 $\alpha$ 1 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<sup>+</sup>/K<sup>+</sup>-ATPase receptor function may lead to novel interventions

**Method:** Using our newly developed model of cardiac-specific KO of Na<sup>+</sup>/K<sup>+</sup>-ATPase  $\alpha$ 1, we will assess the role of Na<sup>+</sup>/K<sup>+</sup>-ATPase  $\alpha$ 1 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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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 binds environmental toxicants, pharmaceutical drugs and endogenous ligands. We 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.

## **Nalini Santanam, PhD, MPH, FAHA**

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The following projects are available in my laboratory:

**Project 1: Obesity, behavior and appetite:** Obesity is associated with changes in appetite. Our laboratory is interested in studying the interplay between behavioral stress (such as anxiety or depression) and obesity. We plan to study the effect of diet induced obesity on behavior modification.

**Project 2: Epigenetics and ovarian cancer risk:** Ovarian cancer is the third leading cancer in women. 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.

### **TECHNIQUES:**

Techniques that will be used in the above projects are:

1. Animal studies: mouse models of diet induced obesity; analysis of rodent behavior
2. Isolation and quantification of RNA (including miRNA) and DNA from fat tissue, brain tissue
3. Detection of genes using quantitative PCR/Real time PCR and Western Blotting
4. Detection of Epigenetic markers: DNA and histone markers using Western blotting and microarrays, microRNAs arrays

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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:

**Project #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. The drugs we are exploring are used in controlling breast, lung, ovarian cancer and leukemia. 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 cancer chemotherapy drugs including doxorubicin, cisplatin camptothecin or irinotecan.

**Project #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 exploring the link between obesity and cancer.** Obesity is associated with an increased risk of breast cancer. In this project we are examining surgical tissue from humans for increased free radical damage. In addition, we are culturing breast cancer cell lines with different medias containing lipids to evaluate their impact on the mitochondria. This has direct application to humans and is clinically relevant. Individuals (students or faculty) involved with this project will participate in examining cellular changes that may increase cellular stress in normal and cancer tissue or cells.

**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, 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 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  $\alpha 1$  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.

Hypertension (HTN) is a common and morbid complication of obesity. Moreover, obesity and HTN have additive effects in increasing the risk for cardiovascular disease, a leading cause of death around the world. Our recent research is to focus on the role of ROS, inflammation and Na/K-ATPase signaling-mediated renal sodium handling in obesity associated hypertension.

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. 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, pipettors, sonicator, centrifuge, etc) for preparing solutions, reagents and samples.

## **Dr. Hongwei David Yu**

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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 a bacterium called *Pseudomonas aeruginosa*. During the infection in CF, this bacterium forms a capsule (biofilms) by producing a polysaccharide called alginate. 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 alginate is regulated in CF. Elucidation of the alginate pathways will lead to better understand the pathogenesis, and development of novel therapeutics for treatment in 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<sub>17</sub>) cells. TH<sub>17</sub> 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.