

MENTORS DIRECTORY

2012 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

The WV-INBRE is pleased to offer summer research internships to students from colleges and universities participating in the WV-INBRE program. In 2012 the internship period will be from May 29 through July 27, with the Summer Research Symposium to be held on July 26 at West Virginia University. 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. Some descriptions are more comprehensive than others; therefore, you may want to contact certain mentors for more detail or to ask for clarifications about the opportunities in their labs. In any case, it is a good idea to speak with potential mentors to be sure you understand what will be expected if you work in his/her lab for the summer.

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 home-page address. The home-page addresses 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 **2012 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, or if you have difficulty reaching a mentor, 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

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Dr. John Hollander	Proteins involved in protection against cardiac diseases	18
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Dr. S. Jamal Mustafa	Nitric oxide production in coronary endothelial cells	22
Dr. Rajesh Naz	Development of a vaccine targeting sperm for contraception in humans; Immun contraceptives	23
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Dr. William Petros	Influence of tobacco on anti-cancer drug pharmacology in humans	26
Dr. Yon Rojanasakul	Nanotechnology and Cancer Research	26
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Dr. Peter Stoilov	Targeting alternative splicing in cancer therapy	29
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Dr. William Wonderlin	Permeability of the endoplasmic reticulum to small molecules	32
Dr. Zhongxin Wu	Environmental tobacco smoke-induced asthma	33
Dr. HanGang Yu	Mechanisms of cardiac bradycardia	34
Dr. Hanting Zhang	Long-QT in obesity induced insulin resistance Neuropsychopharmacology of Alzheimer’s disease	35

WVU Mentor Listing According to Area of Research

Cancer Research: Callery; Gibson; Ivanov; Liu; Petros; Rojanasakul; Stoilov; Thomas; Vona-Davis
Cardiovascular Research: Barr; Brock; Chantler; Dick; J Frisbee; S Frisbee; Hollander; Huber; Liu; Mustafa; Nurkiewicz; Olfert; Yu
Cell & Molecular Biology/Genetics: Gunther; Hillgartner; Salati; Schaller; Wenger; Wonderlin
Chemistry/Nanotechnology: Gannett
Chromosomal Biology: Wenger
Drug Action and Metabolism: Callery; Petros; Gannett
Drug Development: Benedito
Immunology: Naz
Infectious Disease: Olson; Thomas
Muscle Research: Alway; Olfert
Nanotechnology: Gannett; Li; Rojanasakul
Neuroscience Research: Brefczynski-Lewis; Dey; Hileman; Huber; Zhang
Obesity Research: Alway; Hileman; Hillgartner
Pulmonary Research: Dey; Nurkiewicz; Rojanasakul; Wu
Reproductive Biology Research: Hileman; Naz
Toxicology Research: Li; Wu

Mentors at Marshall University

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Dr. Eric Blough	Effects of aging on the heart in male and female rats; Effects of nanoparticles on animal health; Development of new nanosensors for biomedical research	36
Dr. Pier Paolo Claudio	Imaging guided drug delivery in cancer	37
Dr. Simon Collier	Genetic control of cell polarity	38

Dr. Piyali Dasgupta	Anti-cancer activity of a nicotinic antagonist in lung cancer; Capsaicin and small cell lung cancer	39
Dr. Beverly Delidow	Cancer research of melanoma and biology of β -catenin	40
Dr. Richard Egleton	Diabetes and the choroid plexus; Green tea and the blood-brain barrier	41
Dr. Philippe Georgel	Effects of chromatin on nuclear function; Effects of diet on breast and prostate cancers	42
Dr. Lawrence Grover	Mechanisms of action of antidepressant medications; Mechanisms of memory formation	43
Dr. Carl Gruetter	Endogenous intracellular histamine regulates invasiveness of cancer cells	44
Dr. Elaine Hardman	Role of omega 3 fatty acids for suppression of cancer	45
Dr. Jung Han Kim	Genetics of obesity and type II diabetes	46
Dr. Emine C. Koc	The role of mitochondria in Parkinson's disease, cancer, and aging and obesity	47
Dr. Gary Rankin	Kidney toxicology; Metabolism of methadone	48
Dr. Travis Salisbury	Environmental pollutants and breast cancer	49
Dr. Nalini Santanam	Adipose tissue biology in obesity; Pain in endometriosis	50
Dr. Monica Valentovic	The adverse side effects of cancer therapy; Liver damage in acetaminophen overdose; Mechanisms to reduce diabetic renal complications	51
Dr. Hongwei Yu	Biofilm genetics, innate immunity and antibiotic resistance in bacteria	52
Dr. Wei-ping Zeng	T cells and T helper cells	53

Marshall University Mentor Listing According to Area of Research

Cancer Research: Claudio; Dasgupta; Delidow; Georgel; Gruetter; Hardman; Koc; Salisbury; Valentovic

Cardiovascular Research: Blough

Diabetes: Egleton; Kim; Santanam; Valentovic

Drug Action and Metabolism: Valentovic

Genetic Research: Collier; Kim

Immunology: Zeng

Infectious Disease: Yu

Molecular Biology: Collier; Georgel; Salisbury; Yu

Nanotechnology: Blough

Neuroscience/Sensory Research: Egleton; Grover

Obesity Research: Kim; Koc; Santanam

Pain Research: Santanam

Toxicology Research: Rankin; Valentovic

MENTORS FOR THE 2011 WV-INBRE SUMMER INTERNSHIP PROGRAM

I. At The West Virginia University Health Sciences Center

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The following project is available in my laboratory:

Nutritional and genetic interventions to improve muscle function and mass in obesity and diabetes.

Muscle mass decreases in persons that are obese, or have diabetes or those with metabolic syndrome which precedes type 2 diabetes. Likely part of the loss of muscle mass is a result of lipid toxicity, which results in a decrease in function of muscle stem cells (satellite cells) so muscle repair is incomplete. The overall goal of this research is to define cellular and molecular mechanisms of actions of muscle specific genes in muscle growth in diabetes, obesity and metabolic syndrome that may be responsible for loss of muscle and to identify therapeutic interventions to reduce or prevent this loss. We have found an increase in atrophy (muscle loss) and in genes that regulate apoptosis (programmed cell suicide) in skeletal muscles of diabetic and obese animals. Furthermore, loading muscles increases oxidative stress in muscles of obese and diabetic animals and this leads to muscle loss and apoptosis (cell death) in muscle nuclei. Reducing oxidative stress reduces apoptosis and loss of muscle mass with chronic loading. In this project we will use nutritional means (modified diets) and transgenic models (mice) to attempt to improve specific signaling pathways that lead to muscle loss. Mice will undergo hindlimb muscle disuse followed by muscle loading. We will then determine if the nutritional or genetic interventions will help muscle to repair/recover in the period of reloading. The student or faculty member will learn techniques for: 1) working with animals 2) assisting in tissue preparation for small animal surgeries 3) sectioning muscle tissue, 4) staining proteins in tissue sections (immunocytochemistry), 5) measuring the levels of genes expressed, 6) measuring protein expression levels from skeletal muscles (western blotting) and 6) measuring mitochondrial enzyme levels in muscles and isolated mitochondria. They will also have the opportunity to participate in experiments and learn techniques to evaluate muscle function in rodents.

Dr. Taura L. Barr

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The development of a genomic prediction score for stroke outcome

The objective of this project is to develop and test an outcome prediction model for gene expression data. Genes and pathways that predict positive health outcomes following a stroke have been identified in our laboratory and will be further tested in our current project "*Monitoring gene expression post-stroke to predict stroke outcome*". This will help to identify molecular pathways involved in brain recovery and novel targets for stroke therapeutics. A variety of clinical, imaging, and laboratory data that are part of routine standard of care will be available for further analysis (e.g. National Institutes of Health Stroke Scale score (NIHSS), infarct volume, modified Rankin scale (MRS), blood markers of inflammation and coagulation); and outcome will be determined using functional, neurological and psychological measures and combined into a global outcome statistic. Bioinformatics analysis will include gene expression analysis (microarray and PCR), pathway analysis and the development of an injury scoring system based on the degree of gene activation post stroke. Statistical approaches to interpreting gene expression profiles for clinical implementation will also be explored. It is anticipated that this project will result in the development of a genomic-based prediction model for stroke and identify novel avenues to target stroke therapeutics.

Vagner A. Benedito, Ph.D.

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Plants are very important sources of active compounds related to human health. By using tissue culture techniques and genetic manipulations, pharmaceutical compounds can be produced *in vitro* or enhanced *in vivo*, thus increasing production and decreasing costs. Dr. Vagner Benedito's research at WVU include furthering the current understand of secondary metabolite physiology and its regulation by genetic and environmental factors, and how this knowledge can be used to enhance production of pharmaceutical compounds in plants.

Specifically, we are interested in 1) understanding how glandular trichomes develop, by using mutants of the dwarf tomato Micro-Tom, 2) understanding how secondary metabolism is regulated by hormones (e.g., jasmonates and brassinosteroids) and stress (e.g., low K, light regimen, drought), and 3) generating herbs with high-yield pharmaceuticals (e.g., the anti-malarial artemisinin by increasing leaf surface in *Artemisia annua*).

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Stress related to difficult personal encounters is very pervasive yet poorly understood. Such stress over time can lead to physical (e.g. cardiovascular) and mental health (e.g. depression/anxiety) issues. Compassion training is a simple and inexpensive way to help decrease the stressful reactions from difficult personal encounters. The project for the summer will be to examine brain responses (using electroencephalography (EEG)) and heart rate variability and cortisol/alpha amylase responses to aversive stimuli (such as pictures of disliked political figures and narratives). The physiological and neural responses to stressful stimuli will be measured before and after compassion meditation or relaxation meditation training (active control).

This project will provide opportunities to learn:

- how to work with human participants,
- how to do measure event related potential (response to stimuli) using EEG
- how to combine physiological, behavioral, and neural measures.

Dr. Robert W. Brock

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Title: Vascular Function, Oxidative Stress and Inflammation

Currently, my lab is focused on clarifying why the microcirculation doesn't function properly during various pathological conditions, such as transplantation, diabetes and obesity. Participants in the WV-INBRE program will work alongside graduate students and faculty to provide insight to ongoing research projects. The work to be completed will involve the use of a variety of research tools and techniques, such as western blotting; cell culture; enzyme assays; microscopy and animal surgery.

Projects will encompass the evaluation of vascular control and flow regulation in the microcirculation, to determining the effect of various interventional strategies on this function. Specific projects that we are currently working on are:

- 1) Kidney vascular protection in diabetes
- 2) Remote tissue protection in transplantation.

Dr. Patrick Callery

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Title: Drug Discovery

Participants in the INBRE program will help develop a new chemical that could ultimately become a drug for the treatment of cancer. A drug candidate has been synthesized and a target enzyme has been identified. Projects in the laboratory will include studying how well this compound interacts with the enzyme, and whether other enzymes are involved. An application for a provisional patent has been submitted, and additional research data is needed to apply for a full patent.

Participants will work with student and faculty researchers to work with lab instruments and procedures depending on skill level and interest. On-the-job training will be provided.

Projects for interns: Cultured cell systems will be used to study the effects of drugs on enzymes associated with cell growth. *In vitro* studies will be used that do not involve animals. Products from chemical and enzyme-mediated reactions will be monitored by chromatography, and possible by mass spectrometry.

Dr. Paul Chantler

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Title: Cardiovascular responses to exercise

INBRE program participants will work in conjunction with laboratory personnel on projects examining cardiovascular responses to exercise in health and disease. 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 Heart Failure and how they influence the structure and function of the heart. INBRE participants will interact with graduate students and staff members to answer research questions, using a non-invasive comprehensive approach to examining cardiovascular function that includes cardiac/vascular ultrasound, and radial applanation tonometry. Training provided to the participants will include human CV physiology, ultrasound, and applanation techniques, and biochemical analyses.

Dr. Richard Dey

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The research in my lab focuses on neuroanatomical organization of airway innervation, examining interconnections between airway neurons and airway structures (smooth muscle, blood vessels, glands, epithelium), and on determining neuronal responses to inhaled irritants. Different types of nerves including sensory, sympathetic, parasympathetic, and nonadrenergic/noncholinergic supply the trachea and bronchi. Released neurotransmitters mediate bronchial and vascular smooth muscle tone, mucous secretion, inflammation, coughing, and breathing patterns in normal conditions and produce defensive responses after inhalation of irritant substances. Airway nerves may also contribute to lung diseases like asthma, chronic cough, and chronic obstructive pulmonary disease (COPD). Although there is considerable information regarding the actions of neurotransmitters, such as acetylcholine, norepinephrine, vasoactive intestinal peptide, substance P and nitric oxide, the mechanisms through which airway nerves contribute to asthma and other airway diseases is not clear. Combinations of immunocytochemical, molecular biological, neurophysiological and pharmacological approaches are used to investigate pulmonary neural responses to inhaled irritants such as ozone, a photochemical environmental pollutant, and particulate mater, air pollutants released from power plants and diesel trucks.

If you work in my lab, you will be a participant and contributor to regular lab meetings to discuss important papers in the field and share data and ideas about ongoing experiments. The projects will include training and data collection using various technologies including confocal and fluorescence microscopes, cell cultures, and real time PCR.

Examples of specific projects:

1. Evaluating pulmonary function, smooth muscle responsiveness and neuropeptide production in animal models of ozone exposure. Opportunity to learn about effects of ozone (an air pollutant) on the airways. You would learn and collect data using immunocytochemistry, use research microscopes, and measure breathing in lab animals.
2. Evaluating sensory neurons in adult rats exposed to occupational irritants. Do neural tracing between sensory ganglia and the lung or nasal cavity, measure neurotransmitter levels in sensory neurons, collect data using fluorescence microscopy.
3. Study the effect of ozone exposure during early life (2-6 day old rat pup) on the responses to airway irritants in adolescents (28 day old). This project uses similar technical approaches described above, but involves a different question: does exposure to airway irritants in early life cause abnormal responses later. This is intended to investigate the possibility that children are more sensitive to the detrimental effect of airway irritants.

Dr. Gregory M. Dick

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Title: Ion Channel Toxicology of Bisphenol A

Participants will work with the sponsor on a project to understand mechanisms by which bisphenol A (BPA) alters the function and expression of ion channels. BPA is an environmental pollutant that we are exposed to daily – especially from plastic food and beverage containers. BPA actions are complicated in that it can both mimic and inhibit the physiological actions of estrogen. It has been shown that blood levels of BPA correlate to the incidence of cardiovascular disease. Importantly, however, the mechanisms underlying this association remain unknown. Our data show that BPA decreases the expression of some ion channels in smooth muscle. We are trying to determine how this occurs. The applicant will perform molecular (PCR), biochemical (Western blot), and histological (immunostaining) studies to determine mechanisms by which BPA decreases ion channel expression.

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Chaos, Fractal Geometry and Peripheral Vascular Disease

Peripheral vascular disease (PVD) is one of the most significant public health concerns facing Western society and is characterized by a progressive mismatch between tissue metabolic demands and the ability of the microcirculation to effectively deliver and distribute blood flow to that working tissue. However, while there has been an enormous investment in the interrogation of this disease state, its contributing mechanisms and potential ameliorative treatments in animal models and in afflicted clinical populations, effective interventions have remained elusive. Our laboratory has a long history of performing high resolution spatial and temporal studies aimed at understanding how altered microvascular behavior can impact these perfusion demand relationships. While we have developed an extensive understanding of how individual elements in the microcirculation are altered with evolution of PVD, we have recently determined that PVD can be best conceptualized by an alteration to the normal chaotic state within the microvascular network characterized by a shift in the fractal pattern of perfusion distribution at successive arteriolar bifurcations. Essentially, changes to individual elements within the microcirculation integrate to produce an alteration to system behavior.

Much of the emphasis in our laboratory is focused on acquiring a deeper understanding of these shifted perfusion distributions, how altered microvessel behavior contributes to these changes, the quantitative analyses of these data and the potential for ameliorative therapies to restore normal patterns of blood flow distribution.

Our laboratory is pleased to provide opportunities for students to explore their interests in this area of research. Students will work to increase their knowledge and experience with regards to:

1. Animal models of PVD
2. Experimental preparations for the study of microvascular function
3. The application of chaos theory and fractal geometry to biological systems
4. Introduction to data analyses with regard to PVD in these settings

If any or all of these areas are interesting to you and you wish to discuss them further, please do not hesitate to contact us through the WV-INBRE program. We look forward to hearing from you.

Dr. Stephanie J. Frisbee

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Translational Research in Cardiovascular Disease

In a nutshell, “translational research” refers to those investigative efforts that are designed to bridge the gap between traditional laboratory procedures to clinical research involving human subjects. Additionally, a second element of translation spans the gap between the study of the individual human subject to the community or environment in which the individual exists and must interact.

Much of the emphasis in my research program is focused on the latter of these two definitions, where we study the development of cardiovascular risk factors in human subject cohorts and how these are related to the real world issues with which these individuals must exist. This work can involve results from either patients from the clinical setting or individual within targeted communities wherein the recruited individuals to our studies provide extensive data with regard to their lifestyle and medical history as well as tissue samples for subsequent analyses. These data are then used for our investigations into the genesis, mechanistic bases and outcomes of cardiovascular disease risk in human subjects with specific linkages to predisposing factors that can be so common in our society today. Through ongoing collaborations, these data collected from the enrolled subjects are then incorporated into larger databases and models for the study of how the individual interacts with his/her community or environment and how that interaction can predispose an individual to the development of cardiovascular disease.

Our laboratory has opportunities for individual students to explore their interests in any of following two areas, as they relate to the development of cardiovascular disease:

1. Chronic stress and clinical depression
2. Environmental pollutant exposure

If any or all of these areas are interesting to you and you wish to discuss them further, please do not hesitate to contact us through the WV-INBRE program. We look forward to hearing from you.

Dr. Peter Gannett

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Our research group is working in several areas including modified DNA and proteins. A major area of interest is Z DNA, a unique left-handed form of DNA. Certain carcinogens can cause mutations in DNA and the resulting DNA is prone to Z DNA formation. Our research work, with regard to DNA, includes the synthesis modified DNA base adducts used for automated DNA synthesis, the preparation modified DNA oligonucleotides for structural studies (e.g. NMR, Circular Dichroism), determination of the effect the modification has on DNA conformational preferences (e.g. B to Z DNA upon modification), and the biological consequences of the modification (e.g., mutational or carcinogenesis). More recently, we have also become interest in the potential these modified DNAs have in nanotechnology-related applications. A student, selecting this area, can expect to conduct organic synthesis, make, purify and characterize DNA, and/or monitor DNA-protein interactions. Finally, we are making Z DNA binding proteins using molecular biology techniques, measuring binding between them and our modified DNAs, and modeling the DNA-Protein complexes using computational methods.

A second major research thrust is with proteins and drug design, specifically, Cytochrome P450 2C9 (CYP2C9). CYP2C9 is a major human enzyme responsible for the metabolism of approximately 20% of all drugs. It often displays atypical kinetics in which the metabolism of one drug is accelerated by the simultaneous presence of a second drug. We are working to develop a model to predict this type of interaction. To this end, we prepare test drugs, measure the CYP2C9-mediated metabolism kinetics, and use the experimental data to develop computer models. Our current focus is the development of a model liver and relies on nanotechnology. Here, a student will use nanotechnology techniques to make 'model livers' and then measure enzyme kinetics of typical CYP2C9 substrates based on metabolite formation using HPLC and mass spectrometry.

There are numerous areas for undergraduate students to participate in this research including organic synthesis, DNA synthesis, purification, and characterization (UV, CD, NMR, and EPR spectroscopy, molecular modeling, molecular biology, and a range of techniques associated with nanotechnology such as imaging techniques (e.g. atomic force microscopy (AFM) and surface plasmon resonance (SPR)) and surface attachment chemistry. The area a student may work would depend upon their own specific background and interest. Given the time frame of the program, students or faculty who worked with our group would focus their efforts on one of the areas described and work my students, me, or both. Finally, my lab has considerable experience hosting high school and undergraduate students and we believe we can provide a satisfying research experience regardless of the level of training a student may have.

Dr. Laura F. Gibson

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Chemotherapy induced cell signaling

While significant progress has been made in the treatment of various types of leukemia, there remains disease that is resistant to standard chemotherapy. Leukemic cells not successfully eradicated by treatment often remain viable in the bone marrow, and later begin to grow and contribute to relapse of disease after cessation of treatment. Relapsed leukemia is often more challenging to treat than that presented initially, and has a much less promising prognosis. This project will include using a model system of bone marrow and leukemic cell co-culture to investigate the protective effects of the marrow on leukemic cells, and investigate strategies to attempt to make the cancer cells more vulnerable to treatment. Students will learn to do tissue culture, Western blot analysis of proteins, flow cytometry, and confocal microscopy during this investigation.

Chemotherapy effects on bone marrow stromal cells

The bone marrow provides a unique setting for development of blood cell formation, with the regulatory components of the marrow that direct production referred to collectively as the "microenvironment". While the microenvironment is not the intended target of chemotherapy, it is exposed to various drugs during treatment, and can suffer damage from them. We are investigating changes in the microenvironment that result from chemotherapeutic insult, and how these changes may negatively impact patient recovery. This work is focused on alteration of SDF-1, VCAM-1 and disruption of the extracellular matrix subsequent to dose escalated chemotherapy. Students involved in this project will learn to do chemotaxis assays, to culture bone marrow stromal cells *in vitro*, and to do a variety of protein analyses including Western blots and ELISA.

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Superoxide dismutase, mitochondria, and Lou Gehrig's Disease.

Work in my laboratory has focused on discovering the molecular mechanism behind development of Amyotrophic lateral sclerosis (ALS) (also known as Lou Gehrig's disease). About 3% of all cases of ALS result from the inheritance of a mutant form of the gene encoding the enzyme copper-zinc superoxide dismutase (SOD). Several lines of experimental evidence support a role for mitochondrial dysfunction in ALS pathogenesis. We have found that expression of the mutant SOD protein (but not the wild type or no SOD protein) in yeast (*Saccharomyces cerevisiae*) results in decreased mitochondrial electron transport activity that is accompanied by decreases in the content of essential heme cofactors (Gunther et al., 2004, Arch. Biochem. Biophys. 431:207-214). Several currently active projects in my laboratory will follow up on those results.

We are currently attempting to determine the mechanism of the decreased mitochondrial electron transport activity in the strains of *S. cerevisiae* that express the mutant human SOD proteins. Those experiments will involve the isolation of mitochondria from the yeast and assaying the isolated mitochondria for correct assembly of the electron transport complexes using 2-dimensional polyacrylamide gel electrophoresis, Western blotting, and physical biochemical techniques. Because we have observed decreased concentrations of the essential heme cofactors in mitochondria of yeast expressing the mutant human SOD proteins, we predict that assembly of the most affected electron transport complexes has been compromised. These experiments will also be continued in recently developed strains of another aerobic yeast that expresses the mutant human SOD1 proteins. We are also in the process of assaying the enzymatic activities of other mitochondrial proteins to determine whether the electron transport chain is the primary target of the mutant human SOD1 proteins.

Dr. Stan Hileman

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Our laboratory is interested in uncovering brain pathways underlying puberty onset and photoperiodic control of reproduction. Clearly, the timing of puberty onset or the effects of photoperiod on fertility are exerted primarily through changes in gonadotropin releasing-hormone (GnRH) secretion, a hypothalamic decapeptide necessary for reproduction. However, the neural systems involved in these alterations in GnRH release are not completely understood. The goal of our work is to define these neurobiological pathways. To accomplish this goal, several neurosurgical, endocrine and molecular biology techniques are employed, including assays, in situ hybridization, immunocytochemistry, and neuroanatomical tract tracing, with sheep being used as the primary model. In particular, current experiments focus on neural mechanisms whereby certain circulating signals, such as leptin or estradiol, may mediate changes in neural systems, like kisspeptin and neurokinin B, that are involved in reproduction.

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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 hepatokine 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

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

INBRE program participants will work in conjunction with laboratory personnel on projects examining cardiac diseases. Projects in the laboratory focus specifically on understanding the role played by proteins thought to be protective against cardiac ischemia, diabetes, and aging. The goal of these studies is to provide insight into the mechanism of action of these proteins, with the goal of designing therapeutics to treat cardiac disease state.

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, cell culture models, and protein analyses. Training will be provided to the participants, which includes molecular cloning, whole heart physiology, RNA, DNA, and protein manipulation, and biochemical analyses.

Dr. Jason Huber

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Role of ageing on stroke severity

Age is the single greatest risk factor for stroke; yet, most stroke models use young animals. Using animal stroke models that ignore age-related changes to the brain may, in part, explain the failure of successful neuroprotectants in animal studies to translate into clinically effective therapies in humans. Our research uses an interdisciplinary approach on a clinically relevant stroke model to investigate cell-cell communication and interactions between cellular components of the neurovascular unit following an ischemic/reperfusion brain injury. Our current research projects are focused on gaining a better understanding of how age-related changes in IL-6 like cytokines in the brain influence stroke damage and recovery following a middle cerebral artery occlusion. The techniques to used in these projects include: animal surgery, stroke assessment, protein and RNA isolation, cellular fractionation, immunohistochemistry, Western blot, microarray, real-time PCR, and bioinformatics.

Dr. Alexey Ivanov

Research Assistant Professor

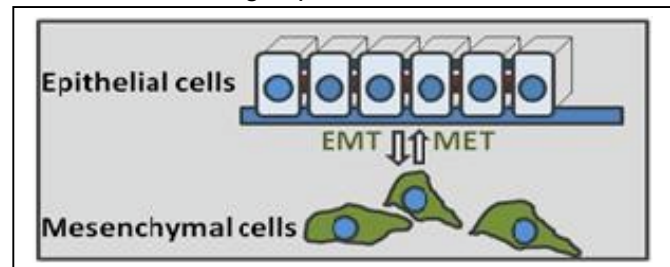
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“Cancer is a disease of gene expression”. Through studies of breast cancer we are trying to understand general principles of gene regulation in normal versus cancer cells with particular emphasis on gene transcription and microRNAs. Vast majority of 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 apoptosis. Our working hypothesis (put forward by many researchers in the field) is that this later metastasis stage of cancer is associated with epithelial-to-mesenchymal transition (EMT). Normally activated 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. We found that Snail and ZEB act in part through a family of transcriptional repressors called KRAB zinc finger proteins and their co-repressor protein KAP1.

Thus, the goals of our current research, using various genome-wide profiling approaches and animal studies, are several-fold. First, is to characterize specific transcriptional events occurring during Snail/ZEB-induced EMT of normal mammary epithelial cells, and during the reverse process, MET in cancer cells experimentally manipulated to switch Snail or/and ZEB genes off. Second, is to determine the role of KAP1 and KRAB-ZNFs in breast cancer progression and EMT. And the third is to identify candidate protein targets required for maintaining of the EMT program in cancer cells and to develop cell-based assays for future screening of potential therapeutic compounds capable to reverse EMT.



Dr. Bingyun Li

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Title: Nanomedicine

Nanomedicine is the medical application of nanotechnology. Participants in the INBRE program will help develop *nanotechnology*-based approaches to prevent implant-associated infections or to treat cancer. Two projects are available in the *nanomedicine* area: **(i) Project #1: Antimicrobial peptide nanoparticles targeting intracellular pathogens.** Antimicrobial peptide nanoparticles have been synthesized and conjugated with ligands. Participant will determine the targeting capacity of the nanoparticles and the internalization of nanoparticles inside human cells (e.g. osteoblasts). The participant will be trained to prepare experimental protocols, conduct cell culture and flow cytometry studies, characterize nanoparticles, etc. **(ii) Project #2: Cellular toxicity of drug-carrying nanoparticles.** Participant will synthesize and characterize nanoparticles and determine the cellular toxicity of the nanoparticles by incubating nanoparticles with a variety of cells. The participant will gain familiarity with nanoparticle synthesis, surface modification, cell culture, cell viability testing, etc. In both projects, participants will work with graduate students, post-doctoral fellows and faculty researchers in the lab. Potential participants are strongly encouraged to visit our research website at <http://www.hsc.wvu.edu/som/ortho/nanomedica-group/>.

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Research interests: My lab focuses on the role of caveolin in tumorigenesis, metastasis and angiogenesis.

1. Epithelial-mesenchymal transition (EMT) and metastasis: Many features of tumor progression, including increased mitogenic signaling, insensitivity to antigrowth signals, unlimited replication potential, resistant to apoptosis, sustained angiogenesis and elevated invasiveness and motility are influenced by caveolin-1. In the early stages of cancer, caveolin-1 is down-regulated in order to avoid its inhibitory effects on cell growth, whereas its expression is elevated as the cancer advances in order to promote tumor progression. However, the mechanism that regulates caveolin-1 expression during tumor progression remains unclear. My lab has recently identified a novel signaling pathway that governs caveolin-1 up-regulation during epithelial-mesenchymal transition.

Furthermore, we have developed animal tumor models to investigate how caveolin affects the interaction between tumor cells and endothelial cells, a key step for tumor cells invading (intravasation) and exiting (extravasation) blood vessels.

2. Cell signaling, cytoskeleton and cell motility: We have identified a sequence motif that controls caveolin polarity in migrating cells and demonstrated that loss of caveolin polarity impedes cell polarization and directional movement. By using the caveolin depolarization model, we are investigating the role of caveolin in spatiotemporal organization of cell signaling, cytoskeleton arrangement and cell migration.

3. Angiogenesis: Angiogenesis, i.e., new blood vessel development, is essential for tumor growth and metastasis. The mechanisms underlying the pathogenesis of neovascularization are not yet fully understood, but involve endothelial cell migration, proliferation and differentiation. Our lab has demonstrated recently that caveolin plays an important role in the regulation of endothelial cell proliferation and directional movement. We hypothesize that caveolin may represent a novel therapeutic target for human cancers.

During training in my lab, students and faculty members will learn the following techniques: gene subcloning, transfection and expression; Western blot analysis; immunofluorescence microscopy; live cell imaging analysis; animal tumor models; immunohistochemistry; and cell co-culture system.

Dr. S. Jamal Mustafa

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The following project is available in my laboratory:

Involvement of A_{2B} Adenosine Receptor in Nitric Oxide Production in Coronary Endothelial Cells from A_{2B} Knockout mice.

Adenosine, a purine nucleoside acts through its cell surface receptors namely A₁, A_{2A}, A_{2B}, and A₃ via its coupling to G-proteins. Adenosine causes dilation of the coronary artery mostly through A_{2A} adenosine receptor. However, the involvement of other adenosine receptors in the modulation of coronary artery relaxation is not known. Recently, we have indirectly shown the involvement of A_{2B} adenosine receptor in endothelium-dependent relaxation of porcine coronary artery possibly through nitric oxide (NO). Also, both porcine and human coronary endothelial cells showed an expected PCR product size for A_{2A} and A_{2B} adenosine receptors. This was further confirmed by western blots for and A_{2A} and A_{2B} adenosine receptors. Our recent data using the A_{2A} adenosine receptor knockout mouse support indirectly the involvement of A_{2B} receptor in coronary flow regulation.

This study will directly address the role of endothelial derived mediators including NO from the mouse coronary endothelial cells from the A_{2B} knockout and wild type animals. Recently, we have successfully established a protocol for isolating mouse coronary endothelial cells and maintaining them in culture. Using these cells in culture, we will activate the various adenosine receptors using selective agonists to characterize the A_{2B} receptor. NO will be measured as nitrite using the Griess reaction. The expression of various adenosine receptors will also be measured using Real-Time PCR. This will be confirmed by western blot using specific antibodies for adenosine receptors. It is expected that the data generated from this study will directly support the role of endothelial A_{2B} adenosine receptor and its role in coronary flow regulation by adenosine.

Dr. Rajesh K. Naz

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My research interests are in the area of sperm-specific gene expression, mucosal immunity, contraceptive vaccines, fertilization and infertility.

Novel Vaccinology and Nanotechnology Projects For WV INBRE Students

The population explosion (6.91 billions) and unintended pregnancies (80 million/year; 45 million abortion/year) continue to pose major public health issues worldwide. Additional health issues faced by sexually active women include sexually transmittable diseases (1 million new cases/day), vaginal infection/inflammation, and cervical cancer.

Better methods that can prevent conception, STDs, and cervical cancer are needed.

Also, the method has to be long-term, reversible, non-steroidal, affordable, and without any side effects, with potential to be used by both men and women for shared responsibility. Here are five projects which INBRE students can do:

1. Nanotechnology for Developing Genetically Engineered Contraceptives.

Curcumin/analogue will be incorporated into biodegradable nanoparticles and conjugated to antibodies and tested on human and mouse sperm motility and function *in vitro*.

2. Development of Single-shot, Intranasal, Long-acting Contraceptive Vaccines.

Our laboratory has cloned several novel sperm-specific and pregnancy-specific genes. These proteins will be used for development of vaccines using nanotechnology and vectors such as recombinant attenuated Salmonella vaccines (RASVs) for activation of mucosal immunity and contraceptive vaccine development. These will be tested in the mouse model.

3. Examination of Signal Transduction Pathways by Which Curcumin and Various Antibodies Inhibit Sperm Motility and Function. We will specifically focus on protein kinase, tyrosine phosphorylation and other signal transduction molecules.

4. Better Diagnostics and Vaccines for Prostate Cancer. Several novel prostate-specific genes have been cloned in the laboratory. These genes are up regulated in prostate carcinogenesis and are androgen-dependent. The sera from patients with prostate cancer will be tested for reactivity with these proteins using ELISA and Western blot procedure.

5. Better Diagnostics for Infertility. Several sperm-specific proteins will be tested for reactivity with sera from patients (men and women) having infertility using ELISA and Western blot procedure

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Project Title: 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.

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Title: Skeletal muscle responses to exercise

INBRE program participants will work in conjunction with laboratory personnel on projects examining skeletal muscle responses to exercise in health and disease. Projects in the laboratory focus specifically on understanding the proteins responsible to for regulating the formation of muscle blood vessels in response to exercise, or the loss of muscle blood vessel in disease (such as heart failure, lung disease, and/or diabetes). The goal of these studies is to provide insight into the mechanism of action of these proteins, with the goal of designing therapeutics to treat skeletal muscle pathology.

INBRE participants will interact with graduate students and staff members to answer research questions, using a multidisciplinary approach that includes genetic modification of the skeletal muscle, whole animal exercise testing/training, and protein analyses. Training provided to the participants will include whole animal physiology, basic surgical and microscopy techniques, RNA, DNA, and protein manipulation, and biochemical analyses

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How bacteria interact with host cells to initiate an infection

An opportunistic pathogen is an organism that infects individuals who have a compromised immune system or injured skin barriers. Our laboratory examines how infections are initiated at the cellular level, specifically examining the nature of the cellular compromise that allows the opportunistic pathogen, *Pseudomonas aeruginosa*, to establish an infection. The project to be explored by an INBRE participant this summer will explore the mechanism underlying the increased sensitivity of tumor cells to *Pseudomonas* infections. The studies will involve culturing human and bacterial cells, and monitoring bacterial infections using confocal imaging. The long-term goal of the project is to identify novel strategies for inhibiting *Pseudomonas* infections that are highly resistant to normal antibiotic therapies.

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The following project is available in my laboratory:

Evaluation of the Influence of Tobacco on Anti-Cancer Drug Disposition

Tobacco ingestion is associated with multiple types of cancer, yet patients often continue such during cancer treatment. A number of physiologic processes are altered by ingestion of tobacco, leading to potential changes in the processing (pharmacokinetics) of drugs used to combat cancer. Patient-to-patient variability in drug pharmacokinetics explains why some experience adverse effects while others do not. Our lab is investigating some of the mechanisms and implications of tobacco related physiologic changes on anti-cancer drug pharmacokinetics. The student or faculty member will learn techniques such as: 1) protein binding, 2) liquid chromatography/mass spectrometry or atomic absorption spectrophotometry, and 3) pharmacokinetic modeling. In addition, they will be exposed to various other projects which involve evaluation of anti-cancer drug clinical pharmacology.

Dr. Yon Rojanasakul

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Nanotechnology and Cancer Research

Nanotechnology—the study of controlling matter on a molecular scale and creating devices that are functional at this level—is a field of research that is rapidly growing. The effects of this field of research on the health of those working around nanomaterials and using products containing these materials are not well understood. Our laboratory is interested in the health effects of carbon nanotubes—one of the most widely used nanomaterials. Because of their small size, they can enter the lung and penetrate the tissue, potentially causing fibrosis and cancer. The student will learn research techniques for 1) studying nanomaterial- lung cell interactions, 2) growing and experimentally manipulating cells in culture, 3) identifying biomarkers for lung fibrosis and cancer using various cell and molecular biology techniques.

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My laboratory studies how gene expression is regulated and in particular a novel mechanism: changes in the rate of pre-mRNA splicing in response to hormones and nutrients. To study this interesting step, we use a model gene: glucose-6-phosphate dehydrogenase (G6PD). This enzyme functions in the synthesis of fatty acids in liver and in providing substrates to support growth and protection from oxidative stress in all cell types. Thus, expression of this gene is key to cell growth and development. Our current interests are to determine the cellular signals involved in causing the splicing of this gene to change. For instance, which of insulin's signaling pathways enhances G6PD splicing? Do fatty acids inhibit G6PD expression directly or by interfering with the insulin signal transduction pathway? Experiments are currently underway to understand the cellular signals responsible for this regulation. Undergraduate students or faculty working in the laboratory this summer would be involved in these ongoing experiments. This represents an opportunity to study fundamental aspects of how cells function.

Examples of student projects might be:

- using adenovirus to express splicing regulatory protein in liver cells and measure changes in the splicing of candidate genes
- determining if signaling kinases can phosphorylate splicing regulatory proteins

These projects would introduce the student to the standard techniques of Cellular and Molecular Biology including PCR, transformation, and RNA isolation. More advanced techniques would include cell culture, Western analysis, and adenovirus production and infection of cells with the virus.

Faculty members could choose projects that allow them to learn a new technique that would help them in future work. Such projects might include:

- conducting animal studies to understand the role of insulin in regulating liver function.
- if we are at the point, the faculty member may be able to participate in experiments using micro-arrays to measure splicing specific changes in response to splicing factor overexpression or knock down in cells.
- the possibility also exists for faculty members to use protocols already in the laboratory to perform experiments related to their own particular research interests. My laboratory routinely does most standard techniques of Molecular Biology, eukaryotic cell culture including stable and transient transfection, and the specialized techniques of RNA biology.

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FAK is an important enzyme that plays a key role in regulating axonal guidance and angiogenesis during embryogenesis and has been implicated in the development of human cancer. Major efforts in the lab are dedicated to determining molecular mechanisms regulating FAK activity and function.

Molecular basis of ligand binding to FAK

We have identified phospholipids as ligands for FAK that lead to its activation. One important goal is to determine how different phospholipids bind to FAK and a mutational approach will be used. Students will learn site-directed mutagenesis, protein expression in bacteria and mammalian cells, Western blotting and fluorometric techniques to measure protein/ligand interactions.

Role of phospholipids in regulating FAK in response to endothelial shear stress

Shear stress is an important factor in the development of atherosclerosis and FAK is activated in response to this mechanical stimulation. Pharmacological, siRNA, dominant negative and overexpression approaches will be used to evaluate the role of several regulators of phospholipids in controlling FAK activation in response to shear stress. Students will learn tissue culture, protein expression in mammalian cells, transfection and Western blotting.

Dr. Peter Stoilov

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Targeting alternative splicing in cancer therapy.

Alternative pre-mRNA splicing is the major mechanism responsible for the creation of hundreds of thousands proteins from the approximately 23,000 genes in the human genome. Misregulation of pre-mRNA splicing is frequently involved in human pathology and is likely to be a significant part of the molecular mechanisms of carcinogenesis. On a global scale, tumors of different origin share common splicing patterns that are distinct from those of the tissues of origin. Similarly, a global shift in splicing accompanies the epithelial to mesenchymal transition (EMT), a process characterized by loss of cell adhesion contacts and increased mobility, both of which are critical components of metastasis. Such tumor and cell lineage specific reprogramming of pre-mRNA splicing, and the resulting cancer specific protein isoforms provide a unique opportunity to selectively target the malignant cells in therapy.

The research in the lab is focused on investigating the roles cancer specific protein isoforms play in the development of malignancy and discovering drugs that target cancer specific alternative splicing. There are two projects that are available for students joining the lab:

Project 1. Roles of alternative protein isoforms in carcinogenesis. We have identified several exons that show EMT and cancer specific splicing patterns and there is an effort under way to expand this exons set. This projects aims to determine how protein variants created through the alternative splicing of these exons contribute to tumor formation. Students will learn tissue culture, cloning, mammalian expression using transient transfection and retroviral vectors, RNAi, RT-PCR and western blotting.

Project 2. Screening for drugs that target cancer specific alternative splicing. We have created a unique two color fluorescent reporter designed to detect changes in alternative splicing. This project will incorporate the splicing reporter into an assay that will allow us to rapidly screen large collections of chemical compounds (100,000 or more structures) for drugs that correct the cancer specific alternative splicing of the PKM2 transcript. Students involved in this project will learn tissue culture, mammalian expression, fluorescent techniques for measuring protein expression, flow sorting, RT-PCR, experiment automation and data analysis.

Dr. John G. Thomas

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Probiotics or “Restorative Microbiology”

Global resistance is a recognized international problem. MRSA, VRE and MDR are all major antibiotic resistance related problems; and are a direct consequence of environmental pressures including medical/dental/veterinary and industrial overuse! Probiotics, first described by Metchnikoff in the 1880's, are an established alternative to new treatments. “Paradigm shift” or “Culture Change” are focusing on new study options for probiotics.

Our laboratory is evaluating multiple probiotic strains, both dental and medical, in models or Pre-Clinical Trials for: 1) Tumor Therapy and Diagnosis, 2) Chronic Wounds (TriPhasic PLUS Wound Model), and 3) VAP (Ventilator Associated Pneumonia) via Colonization of the ETT (Endotracheal Tube) in our Adult-VEL (Ventilator-Endotrach-Lung) Simulation Model. All focus on the emerging concept that “Normal Microbial Flora” is similar to an “organ” and needs constant maintenance to maximize its function.

Linda Vona-Davis, Ph.D.

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PROJECT: NEUROPEPTIDE Y, ADIPOSE TISSUE AND BREAST CANCER

Obesity and excess adipose tissue is considered a risk factor for cancer progression. Human fat cells from adipose tissue secrete leptin together with other factors which causes many cancers to grow, while the protein neuropeptide Y (NPY) from the nervous system inhibits it. Both are highly relevant to understanding the connection between obesity and breast cancer progression. We questioned whether NPY would reduce the growth of breast cancer cells and whether NPY would inhibit the fat-stimulated growth and migration of breast cancer tumor cells. Our work has shown so far that NPY inhibits human breast cancer cell growth. Furthermore, when cells were treated with NPY, some cells stopped their cell cycle while others progressed into cell death. In contrast, cell migration was stimulated when they were exposed to fat-conditioned media and this was dependent on the presence of fat cells in close proximity to the breast cancer cells. In conclusion, it appears that fat cells promote breast tumor survival, while NPY limits its growth. To further our studies, we intend to use a variety of experimental techniques to understand how NPY and adipose influence cell migration and breast tumor cell metastasis. Among these are advanced imaging using state-of-the-art molecular fluorescent staining and electric cell–substrate impedance sensing to monitor attachment and spreading of breast cancer cells quantitatively and in real time.

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A project is available for a summer intern in the cytogenetics research laboratory, which will examine rates of survival of different cell lines within the same individual. With mosaicism, the abnormal cell line decreases over time in culture. The loss of the abnormal cell line will be determined using three different techniques.

1) Telomeres cap the ends of all chromosomes and shorten each time a cell divides.

When telomeres become very short, the cell stops dividing and dies. Telomeres can be targeted using a fluorescent-labeled probe and visualized through a fluorescent microscope. The fluorescent signal can then be measured using a computer image capturing system. Telomere length will be measured to determine if telomeres are shorter in the abnormal cell line compared to the normal cell line.

2) A cell line that divides slower will decrease in number. Cells will be cultured for several days with a tagged nucleotide that can help determine the number of divisions a cell in metaphase has completed. Number of cell divisions will be compared between normal and abnormal cells to see if cell division occurs at a slower rate in the abnormal cell line.

3) Cultured cells will be targeted with an antibody to identify cells that are going through programmed cell death. Measurements will be compared to determine if the rate of cell death is higher in the abnormal cell line.

Protocols that may be used for this project include sterile culture technique, culturing and harvesting cells for chromosomes, preparing slides, hybridization of probes to chromosome preparations. Equipment that will be used include centrifuge, automatic pipettes, water bath, slide warmer, inverted, light and fluorescent microscopes, digital imaging system, and computer program for visualization and measurement of fluorescent signals. Collection of data and statistical analysis will also be necessary.

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The following project is available in my laboratory:

Measuring the permeability of the endoplasmic reticulum to small molecules.

The endoplasmic reticulum (ER) is an intracellular organelle that plays an essential role in signal transduction, the synthesis of secretory and integral membrane proteins, and cellular homeostasis. We have discovered that small molecules can move between the cytosol and the lumen of the rough ER via the same pathway used by newly-synthesized proteins—the pore of a ribosome-bound translocon complex. Our next step is to determine if changes in the molecular traffic through a ribosome-bound translocon can be altered during disease, potentially leading to cellular stress and cell death. We have some exciting preliminary data indicating that the movement of molecules through these ribosome-bound translocons is stimulated by aggregates of proteins formed during the development of neurodegenerative diseases such as Parkinson's Disease, and we hypothesize that the increased "leakiness" of the endoplasmic reticulum might contribute to neuronal death.

The summer project will use a combination of physiological and biochemical techniques to identify how aggregates of proteins that are known to cause Parkinson's and Huntington's disease might affect the movement of molecules through ribosome-bound translocons.

This project will provide specific opportunities to learn:

- how to grow cells in culture,
- how to perform a fluorescence assay
- how to separate proteins by gel electrophoresis and identify them by western blot
- how to purify proteins using column chromatography

Dr. Zhongxin Wu

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Neurobiology and Anatomy

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Asthma is one of the most common chronic respiratory diseases. It is a complex genetic disease resulting from interactions between multiple genes and environmental factors. My laboratory focuses on environmental factors which increase the incidence of asthma. Recent studies in my laboratory found that exposure to secondhand smoke *during utero* (maternal exposure) and early postnatal life produce the changes of lung function that lead to asthma later in life. Our current research figure out the possible changes in respiratory nerve systems after secondhand smoke exposure during early life that potentially leads to increased susceptibility and occurrence of asthma later in childhood or as adults.

Ongoing projects conducted in our laboratory are 1). To identify neurotransmitter genes that alter lung function after exposure to secondhand smoke *in utero* or during infancy. 2). To determine the effects of airway innervation in the secondhand smoke-induced asthma.

Dr. Han-Gang Yu

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Cardiac death is the endpoint of many diseases including diabetes, particularly in patients that are overweight and obese. Cardiac arrhythmias (defined as abnormal electrical activity in the heart) are direct causes of sudden cardiac death. Currently, we are focused on understanding of two conditions related to arrhythmias.

Project-1: Mechanisms of Cardiac Bradycardia

Bradycardia is slow heart rate (<60 beats per minute). There is no pharmacological treatment. Without treatment, it can turn to atrial fibrillation, the most common arrhythmia in clinic; it can also develop to ventricular arrhythmias, the less common but lethal leading to cardiac death. The only effective treatment is the implantation of electronic pacemaker, which requires surgery.

Why there is no alternative pharmacological treatment for bradycardia? Largely due to unknown mechanisms that cause the disease. Recently, mutations in a protein called pacemaker channel have been found and directly linked to patients with bradycardia. We are studying and developing the molecular tools to correct the mutated channel with hope to translate our findings to treat bradycardia.

Project-2: Long-QT in Obesity induced Insulin Resistance

Prolongation of QT interval on electrocardiogram (ECG) is an independent predictor of high cardiovascular risk in type 2 diabetic patients that are overweight or obese. Close to 75% of insulin resistant patients die of heart disease. How does an obese induced insulin resistant heart develop long-QT remains an open question.

We have made initial findings of one ion channel that is dysfunctional in an obese induced insulin resistant animal model, leading to long-QT. We hope our discoveries may find applications in treatment of cardiac arrhythmias associated with diabetes patients.

Students participating in the projects will have the opportunities to learn a variety of experimental techniques including the in-vivo recordings of the whole animal, the isolated single myocyte patch-clamping, cell culturing, viral-based DNA recombination, viral infection, DNA analysis (restriction enzyme digest, electrophoresis, sequence analysis, PCR mutagenesis, RT-PCR), protein chemistry (Western blotting, biotinylation, co-immunoprecipitation), cell biology (immunohistochemistry, fluorescence imaging), and RNA Interference.

Given individual background, interested students will be assigned to a specific small project such as (1) ion channel trafficking to plasma membrane, or apoptosis in cultured mammalian cells, (2) altered protein tyrosine phosphorylation state, (3) altered channel function caused by mutations directly linked to arrhythmias, (4) altered cardiac function and electrical properties in disease animal models.

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Neuropsychopharmacology

Alzheimer's disease (AD) is a neurodegenerative disorder commonly found in people over age 65. About 20 million people worldwide and nearly 5 million people in the United States suffer from AD. The most obvious characteristic of AD is progressive loss of memory, which is caused by misfolded proteins called beta amyloid (Abeta).

Phosphodiesterases (PDEs), the enzyme superfamily containing 11 families (PDE1-11), help in the breakdown of the important intracellular second messengers cyclic AMP (cAMP) and cyclic GMP (cGMP). Among these enzymes, PDE2, PDE4, PDE5, and PDE9 play an important role in the mediation of memory and may contribute to cognition deficits in AD. Substances that inhibit these PDEs enhance memory, help new cells grow, and block inflammation in the brain; they may reverse memory deficits produced by Abeta. All these effects are beneficial for the treatment of AD. We propose experiments to find out whether reducing activity of one of the PDE enzymes in the hippocampus reverses Abeta-induced deficits of memory and reduction of cAMP/cGMP signaling. The experimental approaches range from behavior (such as Morris water maze, passive avoidance, and novel object recognition for memory measurements and microinfusions for brain drug administration), neurochemistry (such as Western blotting, ELISA, enzymatic assay), and molecular biology (such as PCR, RNA interference).

II. Mentors at Marshall University

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Participants in the INBRE program will join an active and dynamic laboratory and will work side-by-side with graduate students, post doctoral fellows and faculty to contribute to ongoing physiological research. The laboratory staff is dedicated to providing the best possible educational experience available. Three projects are available. Each project is appropriate for faculty and/or students. On-the-job training will be provided.

Title: Effects of aging on the heart in male and female rats.

The long term objective of this project is to investigate how sex influences cardiovascular (vascular, cardiac) structure, intracellular signaling and function. These questions are addressed using a variety of different models (animal, cell culture, ex-vivo tissue preparations) along with molecular (RT-PCR, immunoblotting, protein isolation), morphological and physiological (Echo, EKG, muscle physiology) tools.

Title: Effects of nanoparticles on animal health

The long term objective of this project is to determine the effects of different nanoparticles on animal health and toxicity.

Title: Development of new nanosensors for biomedical research.

The long term objective of this project is to develop new types of nanosensors that will be used to diagnose, monitor and treat chronic diseases.

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The focus of our laboratory is to understand the molecular mechanisms governing malignant transformation in order to tailor novel therapeutic strategies. Toward this end, we have carried out in the past 15 years studies to understand the crosstalk between those factors that contribute to cancer progression versus those that protect from it.

Gene therapy offers great potential for combating and curing a wide range of pathologic lesions. One of the major limiting factors in gene therapy has been the development of safe and effective delivery systems.

Imaging guided drug delivery

The emphasis of our most recent research efforts is on imaging guided drug delivery. The recent emergence of "molecular imaging" has set the stage for an evolutionary jump in diagnostic imaging and therapy. The ability to incorporate drugs or genes into detectable site-targeted nanosystems represents a new paradigm in therapeutics that will usher in an era of image-based drug delivery.

We have developed a novel gene therapy system based on the use of commercially available ultrasound contrast agents and adenoviruses that enhance the specificity of gene transfer *in vitro* as well *in vivo*. Ultrasound-mediated microbubble destruction improves the efficacy and reduces the non-specific expression of gene therapy vectors providing a useful tool for manipulating gene expression in the living animal. We are currently working on further developing this useful targeting gene therapy tool to help closing the gap that still exist between laboratory bench and bedside application.

Students involved in this project will experience working with animals and with human cancer cells. Students will learn novel techniques aimed at eradicating growth of cancer cells *in vivo*. Students will also participate in the analysis of the molecular mechanisms underlying tumor growth and progression.

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Genetic control of cell polarity: Cells within epithelial cell layers normally all face in the same direction, like a crowd of people at a concert. This property of epithelial cells is called Planar Cell Polarity (PCP). The precise control of PCP during animal development is vital for the function of many tissues and organs including the eye, ear and kidney, as well as our cardiovascular and nervous systems. Furthermore, a failure in the genetic control of PCP is responsible for some cases of familial spina bifida. Clearly, a better understanding of PCP genetics will benefit the biomedical research community. The Collier lab uses both vertebrate cell culture assays and model organism (*Drosophila*) studies to characterize the roles and activities of PCP genes.

Project 1: Human PCP Effector gene function: The PCP Effector genes are required to organize a cell's cytoskeleton in response to directional signals within the tissue. This activity is vital for normal PCP. The PCP Effector genes were first identified in the fruit fly (*Drosophila*), but have recently been shown to be critical in vertebrate embryogenesis including neural tube closure and skeletal development. The project involves expressing human PCP Effector gene products in cultured vertebrate cells and investigating the molecular activities and interactions of these proteins. **Methods:** Vertebrate cell culture, cell transfection, cell staining (e.g. immuno-cytochemistry), fluorescence microscopy, protein studies (Western blot, immunoprecipitation), DNA work.

Project 2: Genetic control of PCP in *Drosophila*: Our understanding of PCP in vertebrates is primarily based upon genetic studies in the fruit fly, *Drosophila*. This project uses the power of *Drosophila* genetics to investigate the genetic control and outcomes of PCP signaling events and to identify new genes required for PCP. **Methods:** *Drosophila* culture and genetics, tissue preparation and staining, (e.g. immuno-histochemistry), fluorescence, light and electron microscopy.

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The following projects are available in my laboratory:

1. **Anti-cancer activity of nicotinic antagonists in lung cancer:** Smoking bears a strong correlation to the development of a type of lung cancer called lung adenocarcinoma. In our laboratory we study the signaling pathways of how nicotine and NNK (components of cigarettes) promote the growth of lung cancer. Specifically, students working on this project will examine whether compounds which block the effect of nicotine can be useful for lung cancer therapy. Other techniques the students will learn are (i) to measure the effects of nicotine on the growth of human lung cancer cells (ii) the measure the anti-cancer activity of compounds (that inhibit the effects of nicotine) in human lung adenocarcinoma.
2. **Capsaicin and small cell lung cancer:** Capsaicin is the major active ingredient of chilli peppers. Preliminary data in our laboratory shows that capsaicin can inhibit the growth of human small cell lung cancer cells. We are interested in investigating molecular pathways contribute to this process. If you are interested in this project, you will learn (i) to perform specific assays to determine whether capsaicin can cause cell death in human small cell lung cancer cells (ii) to examine the biochemical mechanisms underlying this growth-inhibitory activity of capsaicin

TECHNIQUES:

The techniques that are routinely performed in our laboratory:

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

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1. Inhibitors of Wnt/ β -catenin signaling alter tumor behavior 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. β -catenin is a signaling protein known to play a central role in several cancers, however comprehensive study of the role of β -catenin in melanoma is lacking. Following up earlier studies, we are examining the effect of blocking Wnt/ β -catenin signaling in melanoma. Our data show that β -catenin inhibitors are able to block migratory behavior of melanoma tumor cells, even in advanced lines that are resistant to treatments such as retinoids. This suggests that inhibition of the Wnt pathway may be a productive route for developing new therapies. The summer researcher would be invited to participate in experiments to continue examining the effect of β -catenin inhibitors in melanocytes and melanoma cells by a number of means. The likely techniques would include migration and invasion assays, subcellular fractionation, western blotting, fluorescent immunocytochemistry, RNA isolation, real-time PCR, transfection and reporter gene assays.

2. Regulation of pituitary cell function by the multifunctional protein, β -catenin. β -catenin performs functions as both a cell adhesion molecule and as a transcriptional regulator. We have evidence that pituitary tumor cells require β -catenin to maintain high levels of prolactin production. This is of interest for two reasons. 1. Excess prolactin secretion results in reproductive difficulties and is one of the presenting symptoms of prolactin-secreting tumors. These tumors are currently usually controlled by drugs that have significant side effects. Finding an alternative means of treatment would be an advantage. 2. The pituitary tumor cells use prolactin as a self-stimulating growth factor and will grow continuously. Treatment to control prolactin levels usually controls tumor growth, but a small percentage of tumors escape drug sensitivity. Controlling that growth is critical to treatment of pituitary tumors because of their location next to the optic nerve and brain vasculature. We are currently exploring the mechanism of the link between β -catenin and prolactin gene expression, using a variety of cellular and molecular techniques. A summer researcher joining this project would have the opportunity to participate in experiments involving cell culture, transfection and reporter gene assays, chromatin immunoprecipitation, western blotting and real time PCR.

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The following projects are available in my laboratory:

Project #1: Diabetes and the Choroid plexus.

The choroid plexus is a region of the brain that produces most of the brains fluids. During diabetes there is an increased risk of hydrocephalus (water on the brain). In this project we will investigate the molecular changes in the choroid plexus induced in an animal model of diabetes. This project will involve some animal handling, tissue sampling, Western blot analysis, immunofluorescence microscopy, and real-time PCR, as well as using various pieces of equipment to monitor blood glucose and ion concentrations.

Project #2: Green tea and the blood brain barrier.

The blood brain barrier (BBB) protects the brain from various toxins, and promotes optimal conditions for neuronal function. Green tea and its constituents have been promoted as a potential co-therapy in a number of diseases including cancer. There is evidence that EGCG a major constituent of green tea can alter the metabolism of several drugs by regulating the expression of transporters and metabolizing enzymes. The BBB expresses a number of these transporters and enzymes, a change in BBB expression could lead to significant changes in brain delivery of drugs. This project will investigate the effects of EGCG on BBB expression of proteins involved in metabolism and excretion of drugs. This project will involve tissue culture, Western blot analysis, immunofluorescence microscopy, real-time PCR, transport studies and some HPLC.

Instrumentation:

These 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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Research in my laboratory is centered on the effects of chromatin on nuclear functions, with an emphasis on transcription regulation linked to epigenetic modifications. Epigenomic research pertains to studies investigating changes in the regulation of gene expression that reflect altered states of DNA organization rather than direct changes in DNA sequence. Human DNA is packaged into repeated units of nucleoproteins (DNA plus histones) referred to as chromatin. It has long been established that both chromatin remodeling and the equilibrium between chromatin folding and unfolding act as regulating mechanisms of gene activation or repression. We recently designed a method that allows us to make physical measurements of defined chromatin fragments directly cleaved from the genome. Our results strongly suggested that the textbook dogma linking chromatin condensation with gene repression and unfolding with transcription activation was not necessarily true for all genes, and may need to be revised.

My most current research projects are focused on studying the effects of diet on breast and prostate cancers. In the case of prostate cancer (PCa), we investigate the effect of Sulforaphane (SFN), a substance derived from broccoli. We are evaluating SFN effect using PCa cell lines as a model system. Initial experiments indicated that SFN can affect epigenetic modifications. We have identified a link between PCa-specific histone post-translational modifications and sulforaphane treatment. For breast cancer (BCa), in collaboration with Dr. Hardman, we are looking at the importance of fatty acid diet (omega-3 vs. omega-6 fatty acids) on BCa incidence of mice female offspring. We are also investigating the mechanism of action of various chromatin-associated proteins, such as MeCP2 and Sir3, on chromatin compaction and transcription regulation in various *in vitro* and *in vivo* systems.

The project that would be assigned to the selected summer student should involve prostate cancer and/or breast cancer research. It will be highly focused on epigenetic modifications (DNA methylation, chromatin structure and function, as well as microRNA) and their effect on expression of tumor suppressor genes or oncogenes.

Interns will have the opportunity to learn certain of the following techniques.

Molecular Biology: cloning and sub-cloning. Protein over-expression.

Biochemistry: Protein purification (conventional chromatography, affinity chromatography)

Southern, Northern and Western blotting.

In vitro chromatin reconstitution

Electrophoresis mobility shift assay (in agarose or acrylamide matrix).

Immuno depletion assay.

Quantitative Real Time PCR

Site-directed mutagenesis.

Chemical protein cross-linking.

HPLC and FPLC.

Biophysics: Hydrodynamic analysis (utilizing the analytical ultra-centrifuge XLA and model-E from Beckman).

Analytical agarose "Multi-gel" system or Quantitative Agarose Gel Electrophoresis (QAGE).

Cell Biology: Basic cell culture (fibroblasts, Drosophila cells and mouse primary cell culture).

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Two projects are available in my laboratory for INBRE participants to join:

1. 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 function and 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.

2. Mechanisms of memory formation. Memory formation occurs through long-lasting changes in the strength of synaptic communication between neurons. In this project we study synaptic strengthening (potentiation) in order to understand how the brain is altered during formation of new memories. We focus on the hippocampus, which is the major brain structure involved in memory formation. Our goal is to understand the cellular and molecular events that occur during memory formation, in particular, the roles of calcium-permeable ion channels and calcium regulated signaling pathways. By determining the brain mechanisms used for normal memory function we will improve our understanding of how memory is adversely affected by neurological disorders and diseases.

Methods and instrumentation: Students participating in either of these projects will have the opportunity to learn animal handling, techniques for *in vitro* analysis of synapse function (preparation of brain tissue slices and electrophysiological measurement of synaptic responses), and techniques for measuring protein expression (Western blotting, enzyme-linked immunosorbent assay or ELISA). 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, film densitometry, and a plate reader. Students will use standard lab equipment (scales, pH meter, osmometer, pipettors, sonicator, centrifuge, etc) for preparing solutions, reagents and samples.

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Our current research is testing the novel hypothesis that endogenous intracellular histamine regulates invasiveness of cancer cells. Consistent with some previous evidence of increased amounts of endogenous histamine in some other cancer cells, we have recently demonstrated that the histamine level in malignant melanoma cells is more than 200-fold higher than in their counterpart non-cancerous melanocytes (Davis, et al., *Inflamm. Res.* 60:55-61, 2011). To evaluate the potential role of histamine in regulating invasiveness of cancer cells, experiments will be conducted to determine the effects of reduced endogenous histamine levels on the ability of the cultured melanoma cells to invade a substrate which models a normal extracellular environment. The endogenous histamine content of the melanoma cells will be reduced by inhibiting expression of the histamine forming enzyme, histidine decarboxylase (HDC), within the melanoma cells. HDC expression will be inhibited through shRNA transfection to inhibit the HDC gene. Inhibition of the HDC expression will be verified by Western blot analysis and/or real-time RT-PCR. Reduced levels of histamine in the transfected cells will be verified by measuring histamine content using enzymeimmunoassay. It is expected that the results from this research will establish the existence of a novel pathway of cell regulation within melanoma cells and lay the foundation for more comprehensive investigation of the role of endogenous histamine production in the development and progression of melanoma and provide new approaches for the treatment of breast cancer.

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Projects available in my laboratory would relate to the following work:

Role of omega 3 fatty acids for suppression of cancer

We have several funded projects in this laboratory. All the projects relate to the suppression of risk for cancer by changing the fat consumed in the diet. Omega 3 fats are usually obtained by consumption of fish or fish oils, canola oil and some vegetables whereas omega 6 fats are especially high in corn and soybean oil and in the meat of animals fed corn or soybeans. One project is to assess the ability of *in utero* exposure to various types of omega 3 fatty acids in the diet of the mother mouse to prevent or delay the development of breast or prostate cancer in the offspring. Breast and prostate tissues contains many fat cells. The fat cells produce signaling molecules that influence the growth of the potentially cancerous epithelial cells. We assess the change in cancer growth after a dietary change. Some individual projects might be to identify changes in protein expression or changes in cell signaling molecules in the glands. We also have a human clinical trial in progress. Laboratory assays related to this trial include changes in sensitivity to chemotherapy and changes in activity of the transcription factor, NF κ B, in samples from patients. Another potential project would be to determine whether providing omega 3 fat to leukemia cells would slow growth and increase chemosensitivity. After orientation to the laboratory, the participant would contribute to outlining a project that is of personal interest and that would benefit the overall effort in the laboratory. Participants who choose to work in my laboratory might learn: mouse handling, dissection, mouse anatomy, immunohistochemistry for identification of protein expression in tissues, cell culture, gas chromatography, enzyme linked immunoassays, protein assays, polymerase chain reaction, genotyping, microscopy, flow cytometry, diet preparation, protein blotting, basic statistical analysis of data and data presentation graphics.

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Genetics of Obesity and Type 2 Diabetes

My research interest is in understanding the etiology and mechanisms underlying type 2 diabetes and obesity, concomitantly related diseases. Type 2 diabetes is the most common form of human diabetes, accounting for over 90% of cases and obesity at such epidemic proportions creates serious public health problems. There is substantial evidence demonstrating that genetic factors are strongly involved in the development of type 2 diabetes and obesity, and I have focused my attention on the link between gene dysfunction and these diseases. As an internship project in our laboratory for the 2012 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 (ELISA), Luminex assay, polymerase chain reaction (PCR), western blot analysis, and real-time PCR. DNA, RNA and protein will need to be isolated from mouse tissues. Instruments involved in this project include microplate readers, Luminex 100, 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) Parkinson's disease, 2) cancer, and 3) aging and obesity.

Project 1: Regulation of protein synthesis by ribosome associated PINK1.

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

Project 2: Role of MRP expression defects in cancer.

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

Project 3. Role of caloric restriction and various flavonoids on regulation of mitochondrial protein synthesis.

Recent studies suggest that reduced expression of proteins related to protein synthesis by caloric restriction promotes longevity in animals. There is limited information available on contribution of mitochondrial translation components in this process. We will perform quantitative MS-based techniques to identify and quantify changes in the components of the mitochondrial translation

machinery in human cell lines grown at varying nutrition conditions and in the presence of several natural flavonoids known to mimic caloric restriction.

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The following projects are available in my laboratory:

Project #1: Succinimide-induced nephrotoxicity: The succinimide ring is incorporated into hundreds of chemicals used as drugs, agricultural fungicides, and industrial agents. Toxicity to the kidney (nephrotoxicity) has been associated with exposure to succinimide antiepileptic agents and some agricultural fungicides. Recent work has determined that succinimide metabolites are responsible for inducing the kidney damage, females are more sensitive than males to succinimide-induced nephrotoxicity, and the stereochemistry of the metabolites contributes to nephrotoxic potential. This project seeks to determine the exact nature of the toxic metabolites and sub-cellular renal targets of the metabolites, how metabolites gain entry into the kidney and the toxicogenomics of succinimide-induced nephrotoxicity.

Project #2: 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 #3: Methadone is a drug used to reduce the dependence of heroin addicts on heroin. However, some methadone users die unexpectedly when using normal doses of methadone. Preliminary studies have suggested that there may be a defect in the inactivation of methadone in the liver in these individuals who die unexpectedly. The purpose of this study is to determine if genetic polymorphisms are responsible for these deaths.

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

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The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that mediates the effects of environmental pollutants, as well as, endogenous cellular growth. We have discovered that AHR antagonists inhibit adipocyte-breast cancer cell interactions by interfering with IGF1 signaling. Current efforts my laboratory is to test the molecular mechanism(s) by which AHR antagonists inhibit IGF1 signaling in breast cancer cells by studying signal transduction and gene expression. Students in my lab would have the opportunity to study these questions in several lines of human breast cancer cells. Our methods are largely molecular biology based; therefore, students would have the opportunity to use real time PCR machines, electrophoresis equipment, and laminar flow tissue culture hoods. Students will also have a choice as to what technique they would like to learn during their intern. Techniques in lab will include, but are not limited to, real-time PCR, western blot, chromatin immunoprecipitation analysis, interfering RNA approaches to gene knockdown and proliferation assays.

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The following projects are available in my laboratory:

CARDIOVASCULAR DISEASE, OBESITY and DIABETES

Project 1: Novel biomarkers in the blood, fat tissue and arteries: One of the major projects in our laboratory is to identify unique biomarkers that play a role in obesity, diabetes or coronary artery disease. In particular we are interested in identifying and studying the role of microRNAs (small nucleotides that regulate gene and protein expression) in these diseases. We use either animal models of obesity, diabetes or cardiovascular disease or obtain samples from patients with these diseases. If you are interested in this project, you will learn how to isolate and detect miRNA using miRNA isolation and detection techniques. You will also be able to detect differences in miRNA fingerprint in different obese animal and human tissues.

Project 2: Diet, Exercise and Cardiovascular disease: A long time interest of our laboratory is to study the effect of diet and exercise on cardiovascular disease, in particular “atherosclerosis” (blockage of the arteries). We have mouse models that express high levels of antioxidant enzymes (enzymes that decrease oxidative stress) with an obese background. In this project we propose to use these mice to study the effect of dietary fat or exercise on cardiovascular risk.

WOMEN’S HEALTH

Project 3: Oxidative stress, Pain and Endometriosis: Endometriosis is a disease that affects 10-15% younger women. This disease is mostly accompanied by infertility and chronic pain. Endometriosis is also a risk for ovarian cancer. We have long standing interest in studying the etiology of this disease by using both animal models of endometriosis and samples from patients with endometriosis (collaboration with Department of Obstetrics & Gynecology). We are currently studying unique pain specific microRNAs that play a role in this disease.

TECHNIQUES:

The techniques that are routinely performed in our laboratory:

1. Cell culture techniques, isolation of fat cells (adipocytes) and adipose derived stem cells
2. Isolation and quantification of RNA (including miRNA) and DNA from cells or tissues
3. Detection of genes using PCR/Real time PCR
4. Detection of proteins using Western Blotting
5. Detection of reactive oxygen free radicals in cell culture system.
6. Animal studies: Studies on atherosclerosis, obesity and pain

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Our laboratory is dedicated to understanding and developing new modalities to reduce the adverse effects of drugs. Our lab is especially interested in reducing the adverse effects of drugs used to treat cancer. Projects available in my lab:

Projects #1 Identification of ways to reduce the adverse side effects of cancer therapy.

This is an ongoing project federally funded by a grant from NIH. Our laboratory is evaluating new compounds that may reduce the adverse effects experienced by individuals treated with chemotherapeutic agents. In addition, another goal of this project is to come up with methods to improve the effectiveness of the cancer chemotherapeutic agents while lessening the side effects. This project has clear clinical relevance and is translational. An individual involved in this project will investigate cellular changes in toxicity, examine the involvement of oxygen radicals and will examine protein expression and modification by cisplatin.

Projects #2 Identification of ways to reduce the liver damage of acetaminophen overdose.

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

Project #3 Mechanisms to reduce diabetic renal complications:

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

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Dr. Yu's laboratory focuses on biofilm genetics, innate immunity and antibiotic resistance in bacteria. The students will work side-by-side with graduate students and research staff to tackle issues such as what environmental cues that trigger bacteria to form a biofilm, how bacteria invade a host causing the development of pneumonia and how to combat the antibiotic resistance in bacteria.

Project #1: Genetics of Biofilms. Bacteria in nature often grow as aggregating colonies attached to a surface known as a biofilm. Biofilm formation is a leading cause of chronic disease. To grow a biofilm, bacteria need to produce polysaccharides resulting in the formation of slimes. We are studying how bacteria know when to start making slimes. The model microorganism is a ubiquitous biofilm-forming bacterium called *Pseudomonas aeruginosa*. By examining the molecular switch that controls the transition between biofilm and non-biofilm formation, we want to understand how bacteria make biofilms, thus to control biofilms. The faculty or students will be exposed to techniques such as cloning, gene knockout, transposon mutagenesis, and protein overexpression and purification, and Western blot.

Project #2: Resistance to Pneumonia. At any given moment, we breathe in bacteria into our lungs. However, few of us will develop pneumonia. This is because we have a robust defense system to fight off the invading bacteria. The main defenses in the lungs include resident macrophages (big eaters), white blood cells and small proteins with potent antimicrobial activities. We have developed various models in the laboratory to study how these cells eliminate the bacteria, how the host realizes the incoming bacteria by producing a battery of small molecules in order to recruit the white blood cells to the lungs, how to evaluate and boost the activities of novel antimicrobials in pneumonia mouse model. The techniques used for this project include cell culture, plate counts, lung infection mouse models, lung pathology, cytokines measurement and analysis, PCR, real-time PCR, immunohistochemistry, and image analysis using bioluminescent and fluorescent markers.

Project #3: Combating antibiotic resistance. Methicillin-resistant *Staphylococcus aureus* (MRSA) and tobramycin-resistant *P. aeruginosa* (TRPA) are two infectious agents that cause a significant morbidity and mortality in immuno-compromised individuals. There is an urgent need to develop new antibiotics to combat these pathogens. To develop such a therapeutic, we are testing a series of rationally designed peptides with potent activity against bacterial pathogens. We also screen for more of these antimicrobial peptides (AMPs) for candidates with a broad spectrum of anti-MRSA and -TRPA activities. In addition, we want to utilize the natural lytic power of bacteriophage against bacteria to

circumvent the resistance. We hope to identify the novel bactericidal candidates with increased efficacy and reduced toxicity. Students working for this project will learn basic methods and technologies used in the clinical microbiology laboratory.

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Projects in my laboratory are:

Regulatory T cells in allergic and autoimmune diseases: The most common allergic disease is asthma. According to National Institute of Allergy and Infectious Diseases (NIAID), 8.6% of Americans are diagnosed with asthma. On the other hand, 3.13% of Americans suffer from autoimmune diseases, which include diseases such as type 1 diabetes, rheumatoid arthritis, multiple sclerosis, lupus ... etc. Allergic and autoimmune diseases are caused by unwanted immune responses to allergens and autoantigens (antigens derived from one's own tissues), respectively. Therefore, suppressing such harmful immune responses is key to curing these diseases. One type of lymphocytes in the immune system called regulatory T cells or Treg cells can suppress immune responses to allergens and autoantigens, but they can also suppress protective immune responses against infections. Using animal models of asthma, type 1 diabetes and multiple sclerosis, our lab is developing experimental modalities to use Treg cells to specifically suppress these diseases without interfering the protective immunities. In the meantime, we are trying to identify the genes expressed by Treg cells that are responsible for their immune suppressive activities.

Techniques: cell culture, ELISA, flow cytometry, replication-defective (safe) retroviral gene transfer, bioinformatics, animal models

Regulation of gene expression in T helper cell subsets: T helper cells are CD4 T lymphocytes that have acquired distinct functions. Both the protective and pathogenic immune responses are controlled by 3 subsets of T helper cells, the Th1, Th2 and Th17 cells. Each subset produce a distinct set of small proteins that mediate different functions. Our interest is to understand at the molecular level how CD4 T cells differentiate into T helper subsets. Previously we have identified the transcription factor GATA-3 that functions as the master regulator for the differentiation of Th2 cells. Others have identified the transcription factor RORc as the master regulator of Th17 differentiation. We are now investigating how GATA-3 and RORc regulate the expression of the small proteins that mediate the unique functions of Th2 and Th17 cells.

Techniques: DNA recombination/molecular cloning, DNA microarray, real time RT-PCR, DNase I hypersensitivity assay, Western blot, chromatin immunoprecipitation, affinity chromatography