

MENTORS DIRECTORY

2010 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

Marshall University

Introduction

The WV-INBRE is pleased to offer summer research internships and fellowships to students and faculty, respectively, from colleges and universities participating in the WV-INBRE program. In 2010 the internship/fellowship period will be from June 1 through July 30, with the Summer Research Symposium to be held on July 29th at West Virginia University. Listed in this directory are faculty members at West Virginia University Health Sciences Center and Marshall University who have agreed to participate as mentors in the summer internship/fellowship program. Each mentor has submitted a description of the project(s) that is (are) available to interns and fellows 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 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 **2010 Summer Program. Applications may be submitted by mail or e-mail; however, direct electronic submission is available.**

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 summer research program coordinators.

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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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WVU Mentor Listing According to Area of Research

Cancer Research: Gibson; Ivanov; Jiang; Liu; Olson; Pugacheva; Rojanasakul; Vona-Davis

Cardiovascular Research: Brock, Dick, Frisbee; Hollander; Huber; Liu; Morissette; Mustafa Nurkiewicz; Olfert; Wysolmerski; Yu

Cell & Molecular Biology/Genetics: Gunther; Hillgartner; Lukomski; Perrotta; Salati; Schaller; Wenger; Wonderlin; Yu

Chemistry/Physics: Gannett

Chromosomal Biology: Wenger

Clinical Pathology: Perrotta

Drug Action and Metabolism: Callery; Gannett

Immunology: Sheil

Infectious Disease: Lukomski; Olson

Muscle Research: Alway; Morissette, Olfert

Neuroscience Research: Dey; Hileman; Huber; O'Donnell; Ramamurthy

Obesity Research: Hileman

Pulmonary Research: Dey; Nurkiewicz; Scuri; Wu

Reproductive Biology Research: Goodman; Hileman; Naz

Toxicology Research: Sheil

Mentors at Marshall University

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Marshall University Mentor Listing According to Area of Research

Cancer Research: Claudio; Delidow; Hardman; Niles; Park, Salisbury

Cardiovascular Research: Blough;

Diabetes: Blough; Egleton; Santanam; Valentovic

Drug Action and Metabolism: Valentovic

Genetic Research: Collier; Kim

Immunology: Sollars

Infectious Disease: Yu

Molecular Biology: Collier, Georgel; Yu, Salisbury

Nano-scale Research: Blough

Neuroscience Research: Egleton; Grover

Obesity Research: Kim; Santanam

Pain Research: Santanam

Toxicology Research: Rankin; Valentovic

MENTORS FOR THE 2010 WV-INBRE SUMMER INTERNSHIP AND FELLOWSHIP PROGRAM

I. At The West Virginia University Health Sciences Center

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Title: Microcirculation and Inflammation Research

Currently, my lab is focused on clarifying the pathogenic mechanisms associated with the microvascular and endothelial dysfunction that accompanies systemic inflammatory conditions. Participants in the WV-INBRE program will work alongside graduate students and faculty to provide insight to ongoing microcirculation research projects. This work involves the use of a variety of research instrumentation and techniques depending on skill level and interest such as western blotting; cell culture; elutriation; enzyme assays; microscopy; and animal surgery.

Projects include evaluating vascular control and flow regulation in the kidney and liver microcirculation to determining the effect of various interventional strategies on microvascular function. Specific projects that we are currently working on are:

- 1) Kidney vascular protection in diabetes
- 2) Remote organ damage and protection.

Dr. Patrick Callery

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Title: Drug Abuse Toxicology

Participants in the INBRE program will help study why some cancer drugs may damage the liver as an unwanted side effect. Projects in the laboratory range from studying how these drugs bind to proteins to studying how the body changes drugs into inactive metabolites. These studies are of importance to the understanding of the fate of drugs in the body as it relates to the optimal use of drugs to treat cancer.

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

Project 1 for interns: Determine if a busulfan drug metabolite reacts with proteins. *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.

Project 2 for interns: Similar to project 1, but with a different drug.

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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, 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.

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Title: Ion Channel Research

Participants will work with the sponsor on a project to determine the type(s) of voltage-dependent K⁺ channels expressed in coronary vascular smooth muscle. These ion channels open and close in response to various stimuli to control coronary vascular tone and blood flow to the heart. The project is aimed at determining the molecular identity of the voltage-dependent K⁺ channel(s) in the mouse heart. The applicant will perform molecular (PCR), biochemical (Western blot), and histological studies to determine which of the eight known channel types are present. Gaining this information will allow us to choose the appropriate genetic knockout mouse/mice to use in future physiological studies.

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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 involving animal experimentation or the study of cellular preparations 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 our laboratory is focused on the former of these two definitions, where we study cardiovascular function and dysfunction in rodent models of cardiovascular disease risk factors (e.g., obesity, dyslipidemia, hypertension) and how these conditions lead to a progressive impairment in vascular function. Additionally, we are also actively engaged in studies in the clinical setting wherein individual patients recruited to our study 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 vascular dysfunction in human subjects with specific patterns of disease risk factors that are so common in our society today. Through external collaboration, 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. basic laboratory animal research
2. community and population research

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.

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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) to determine the effect of the modification on DNA conformational (eg B to Z DNA upon modification) and the biological consequences (mutation, cancer, etc). More recently, we have also become interest in the potential these modified DNAs have in nanotechnology-related applications.

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.

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, 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 with either my students, me, or both. Finally, it should be noted that we have a history of having high school and undergraduate students work in our research lab in addition to graduate students and visiting scientists. We believe we can provide satisfying research experiences regardless of the level of training.

Laura F. Gibson, Ph.D.

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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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The following project is available in my laboratory:

Project: Possible interaction of kisspeptin and dopamine during the non-breeding (anestrous) season

We have identified a specific group of neurons that use dopamine (DA) as a neurotransmitter that play a critical role in suppressing reproduction during anestrus (these neurons are known as the A15 cell group). These DA neurons mediate the ability of the ovarian hormone estradiol to inhibit gonadotropin-releasing hormone (GnRH), and thus luteinizing hormone (LH), which controls ovarian function at this time of year. However A15 neurons do not project directly onto GnRH neurons so they must be inhibiting GnRH via another neural system. One candidate is a set of neurons that use kisspeptin as a neurotransmitter. Kisspeptin was recently identified as a stimulator of GnRH and its expression is inhibited by estradiol in anestrus, raising the possibility that A15 DA neurons act by inhibiting GnRH. This summer, we will test this hypothesis by determining 1) if inhibition of kisspeptin expression using siRNA will disrupt inhibition of GnRH by DA and 2) whether A15 DA neurons synapse on the kisspeptin neurons using a tract tracer and dual immunocytochemistry. The student will have the opportunity to work on either one or both of these experiments and learn the following techniques with the animal involved being sheep: 1) neurosurgical techniques for local administration agents to the brain, 2) surgical removal of the ovaries, 3) blood collection and processing, and 4) radioimmunoassay procedures for measuring hormone levels in the blood, 5) immunocytochemical procedures for identifying specific proteins in tissue slices, and 6) use of a confocal microscope.

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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.

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Our laboratory has two major interests. One is uncovering brain pathways whereby nutrition influences reproduction. Nutrition is a, if not the, major factor regulating reproduction in mammals. Clearly, the effects of inadequate nutrition are exerted primarily through inhibiting gonadotropin releasing-hormone (GnRH) secretion, a hypothalamic decapeptide necessary for reproduction. However, the mechanism(s) whereby nutrition alters GnRH release are not completely known. The goal of this work is to define the neurobiological pathways controlling food intake and how those pathways are integrated into a system whereby nutrition influences GnRH release and fertility. To accomplish this goal, several neurosurgical, endocrine and molecular biology techniques are employed, including assays, in situ hybridization, immunocytochemistry, neuroanatomical tract tracing and RT-PCR, with sheep being used as the primary model. In particular, current experiments focus on neural mechanisms whereby certain circulating metabolic signals, such as leptin, may mediate nutrition-induced changes in neural systems, like kisspeptin and NKB, that are involved in reproduction.

A second major interest is examining basic neural systems involved in controlling body weight. Obesity is a major health problem in the U.S. and particularly in West Virginia. Since obesity is a contributing factor to such diseases as diabetes and hypertension, a great deal of interest has arisen in defining the neural mechanisms controlling food intake. Current work focuses on determining the role of the neurotransmitter, GABA, in regulating food intake. This involves a transgenic mouse approach and the use of techniques such polymerase-chain reaction for genotyping.

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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.

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Title: Cardiovascular Research

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.

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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 be used in these projects include: animal surgery, stroke assessment, protein and RNA isolation, cellular fractionation, immunohistochemistry, Western blot, microarray, real-time PCR, and bioinformatics.

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Identification of new epigenetic silencers of KRAB-ZNF family overexpressed in breast cancer.

The focus of cancer research, until the last several years, has largely been on the genetic basis of cancer. However, a mounting body of evidence accumulated for the last ~10 years has indicated that non-mutational (epi-genetic) heritable alterations in gene expression patterns may be as equally important for the evolution of all human cancer types. Specific epigenetic changes, i.e. methylation of CpG dinucleotides and histones in the promoters of many tumor-suppressor genes, which lead to their silencing, are now well recognized as one of the critical steps in cancer development. However, the identity of specific DNA-binding transcriptional repressors responsible for the initiation of such silencing is currently unknown. This project will focus on comprehensive analysis of differential expression of KRAB-ZFP transcriptional repressors, the best candidates for the role of epigenetic silencers, in breast cancer and normal breast cells. Students will learn to do cell culture, immunoprecipitation, Western blot and mass spectrometry analysis of proteins during this investigation.

Role of heterochromatin proteins 1 (HP1s) in SUMOylation and cell differentiation.

In gene silencing active repression is initiated by binding of a specific transcriptional repressor protein to the promoter of a target gene and recruitment of cognate co-repressor, which nucleates various repressive protein complexes mediating histone deacetylation and methylation, and ultimately DNA methylation. Specifically, a direct correlation between the histone H3 lysine 9 methylation (H3K9) and DNA methylation has been observed, suggesting that the H3K9 methylation may initiate and help maintain the repressive epigenetic state (Jenuwein, T., FEBS J., 2006). Such mode of action has been proposed to be executed in normal development and differentiation programs. Methylated lysine 9 on histone 3 serves as a binding site for heterochromatin protein 1 (HP1) – an epigenetic regulator which has been shown to directly interact with the DNA methyltransferases and many other repressive complexes. There are three HP1 proteins encoded in the human genome, HP1 α , HP1 β and HP1 γ , which function in different subnuclear compartments. This project will investigate specific requirement of each of the HP1 proteins in differentiation of mesenchymal stem cells into chondrocyte, osteoblast, adipocyte and neuronal lineages in *in vitro* cell culture model. In addition, role of HP1 proteins in SUMOylation, i.e. specific posttranslational modification, of HP1-interacting proteins will be analyzed. Students involved in this project will learn to culture mesenchymal stem cells *in vitro*, to do lentiviral gene transfer and a variety of protein analyses including Western blots and cell staining.

Regulation of transcriptional repression by KRAB zinc finger proteins.

Recent studies undertaking the whole genome analysis of hypermethylated genes identified 11 CAN genes as cancer-specific hypermethylated in breast tumors and 15 CAN genes - in colorectal tumors with highly significant overlap (44%), suggesting that hypermethylation of common target genes is more frequent than mutation and is not restricted to a single tumor type (Chan, T. et al., PLoS Medicine, 2008). Intriguingly, the only gene related to transcriptional regulation among these 11 breast cancer-specific hypermethylated genes was KRAB-ZNF protein ZNF432, which maps to the known

cancer susceptibility locus at 19q13.3. This project will focus on identification and studying gene targets for candidate tumor suppressor protein ZNF432, and ZNF263. Students involved in this project will learn to do cell culture, immunoprecipitation, Western blot analysis of proteins and a variety of gene expression analysis assays.

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PI 3-kinase and Akt are activated upon the activation of protein tyrosine kinase receptors by growth factors. PI 3-kinase and Akt have been shown to promote cell growth and inhibit cellular apoptosis. The PI 3-kinase signaling pathway has been strongly implicated in human cancer. For instance, the gene coding for the catalytic subunit p110 α of PI 3-kinase is amplified in 50% of human ovarian carcinoma cell lines. The genes coding for Akt1 and Akt2 are amplified in ovarian and breast cancers. As an antagonist of PI 3-kinase, tumor suppressor PTEN is often mutated in various cancers including glioblastoma, endometrial carcinoma, prostate carcinoma, and melanoma. A better understanding of the PI 3-kinase signaling pathway is of great theoretic and therapeutic interests.

Our primary interest is to further investigate the role of PI 3-kinase in cell growth and tumorigenesis as well as to explore potentially new functions of the pathway. Our study demonstrated for the first time PI 3-kinase signaling pathway in angiogenesis. Angiogenesis is required for tumorigenesis and its inhibition represents one of the most promising approaches in cancer therapeutic treatment as well as in certain vascular diseases. We therefore plan to further study the roles of PI 3-kinase and PTEN in angiogenesis. It is known that PI 3-kinase is activated *in vitro* by a variety of growth factors. Several of these growth factors are known to induce angiogenesis. Accordingly, we will determine whether all or only some of the growth factors-mediated angiogenesis requires PI 3-kinase activation *in vivo*. We have also performed representational difference analysis to identify novel Akt targets involved in angiogenesis. We have obtained several new targets that have growth regulatory functions. We will characterize their expression profiles in human cancer, study their regulation patterns by various growth factors and oncogenes, and determine their role in angiogenesis and tumorigenesis. In addition, we have recently found that PI 3-kinase activates expression of hypoxia-inducible factor 1 (HIF-1). HIF-1 plays an important role in normal physiological process as well as in pathological conditions. HIF-1 activity is commonly elevated in human cancer. One project that is available will study how the PI 3-kinase signaling pathway regulates HIF-1 expression, determine whether HIF-1 is regulated by various oncogenes and tumor suppressor genes, and investigate the role of HIF-1 in angiogenesis and carcinogenesis. To study the molecular mechanisms of angiogenesis and tumorigenesis induced by PI 3-kinase signaling, and to develop novel therapeutic agents for many human diseases including cancer.

Depending on the project selected, an intern/fellow will use primary cells and cell lines from animals or humans, to study how PI3K regulates HIF-1 and angiogenesis. He/She will learn cell culture, protein preparation, RNA isolation, Western blot, Northern blot, cell migration and invasion.

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

1. Tumorigenesis 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-regulated during epithelial-mesenchymal transition. Furthermore, we have developed animal tumor models and are investigating 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 spatial 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; animal tumor models; immunohistochemistry; and cell co-culture system.

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Project Title: "Distribution and sequence polymorphism in collagen-like genes of the pathogenic fungus *Aspergillus fumigatus*"

Pathogenic fungi represent serious health problem, especially among immunocompromised patients, such as cancer and HIV patients. Infections due to *A. fumigatus* can be life-threatening and are not easy for anti-microbial treatment. Furthermore, the diagnosis of fungal infections, like those with *A. fumigatus*, is hampered by the lack of specific biomarkers. Our bioinformatic analyses have identified two related collagen-like proteins that are presumably expressed by *A. fumigatus*. However, the sequence data were only available for two *A. fumigatus* strains.

The scope of this project is to isolate genomic DNA from a large collection of *A. fumigatus* strains and to develop a PCR-based method for detection of genes, designated *aclF1* and *aclF2*, encoding the collagen-like proteins. The frequency distribution of *aclF1* and *aclF2* genes among *A. fumigatus* strains will be determined. In addition, the project will also investigate sequence-length polymorphism within the *aclF1* and *aclF2* alleles present in various strains and assess whether this polymorphism can be used in strain fingerprinting.

This project will be done in collaboration with NIOSH.

Additional projects related to the role of the collagen-like proteins in the pathogenesis of group A Streptococcus are available for consideration.

Relevant literature: Leski *et al.* 2009. Identification and classification of *bcl* genes and proteins of *Bacillus cereus* group organisms and their application in *Bacillus anthracis* detection and fingerprinting. *App. Environ. Microbiol.* **75**(22): 7163-7172.

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Signal Transduction Pathways in Cardiac Hypertrophy

This WV-INBRE summer research program opportunity would provide an appropriate experience for a student/fellow/intern/or faculty member.

Postnatal heart growth is primarily characterized by an increase in the cell size, or hypertrophy, of cardiomyocytes. Cardiac hypertrophy is thought to be a functionally adaptive response to increased stress or demand on the heart that accompanies pathologic conditions such as hypertension or remodeling after a myocardial infarct. Although hypertrophy is initially beneficial, continued growth and remodeling in the heart ultimately leads to heart failure. This contrasts with exercise-induced, or physiological hypertrophy, which does not lead to heart failure.

A student or faculty member would be involved in the elucidation of novel molecular signal transduction pathways that lead to physiologic versus pathologic cardiac hypertrophy. Depending on the area of interest and expertise of the student or faculty member, the project could include induction of hypertrophy, through exercise training (physiologic) or pressure-overload (pathologic), followed by Western blotting and quantitative real-time PCR to examine changes in proteins, phosphorylation of proteins and transcription. To determine if these changes are causally related to the induction of hypertrophy we will utilize an *in vitro* heart cell-culture model (cardiomyocytes and fibroblasts) along with manipulation of gene expression (via transfection, infection, or siRNA).

The student or faculty member may also be involved in understanding the signal transduction pathways downstream of a well-known inhibitor of skeletal muscle growth, myostatin. We have recently found a role for myostatin in the regulation of heart growth as well. This project would include the techniques mentioned above, as well as the utilization of transgenic models that have enhanced or inhibited myostatin activity specifically in the heart.

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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.

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We have two projects for summer for WV-INBRE students.

Project 1: Development of a peptide/DNA vaccine based upon sperm antigens for contraception

Our laboratory is actively involved in the development of a vaccine targeting sperm for contraception for humans. One of the crucial steps in the vaccine development is identifying antigens that are specifically expressed only on sperm and no other somatic tissue, and has a role in fertilization and fertility. We have identified two such antigens namely FA-1 antigen and YLP₁₂ peptide on human sperm that are involved in binding to the human eggs. The genes encoding these molecules have also been cloned from human testes. The vaccines using these antigens cause up to 70% contraceptive effect in female mice, the model used for testing the efficacy of the vaccine. To increase the efficacy of the vaccine, we are continuing our search to identify/clone/sequence additional antigens that are sperm-specific and have a role in fertilization. These projects will be continued during summer 2009. The student will have the opportunity to work/associate with these projects and learn the following techniques: 1) isolation of RNA/DNA, 2) polymerase chain reaction, 3) cloning and sequencing, 4) in-vitro expression of protein, 5) semen analysis, 6) immunization of animals, and 7) sperm functional test using immunocytochemistry and fluorescent microscopy.

Project 2: Human antibody engineering for development of specific diagnostics and non-steroidal immunocontraceptives

Phage display technology has been widely used to obtain a variety of engineered antibodies, including single chain variable fragment (scFv) antibodies against several antigens. ScFv is an antibody fragment that plays a major role in the antigen-binding activity, and it composed of variable heavy (VH) and variable light (VL) chains connected by a peptide linker.

We have synthesized fully functional human scFv using lymphocytes from infertile men and women in vitro that react with human sperm and block its function. These antibodies are being investigated as immunocontraceptives which will not have any side effects. This project will be ongoing during summer 2009. The student will have the opportunity to work/associate with the graduate/post-doctoral fellow doing this project. The student will learn several molecular biology, immunological, and reproductive biology techniques involved in this project.

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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) 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 residual oil fly ash 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 PM 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. The student or faculty member will have the opportunity to develop surgical and experimental techniques associated with animal studies. These techniques include: rat surgery, intravital microscopy, in vivo measurement of oxidative stress and various micropipette-based techniques.

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Molecular Psychopharmacology

The effects of antidepressants as well as drugs used to treat other psychiatric illnesses emerge over time with repeated treatment. Many theories have been proposed to account for this observation, including changes in neurotransmitter receptor sensitivity, altered intracellular signaling mechanisms, and growth of new nerve cells in certain regions of the brain. Recent work in our lab has identified important roles for cyclic nucleotide phosphodiesterase enzymes (PDEs) and neuronal monoamine transporters as mediators of the long-term behavioral effects of antidepressant and anti-anxiety drugs. Specific ongoing projects include examination of the role of specific subtypes of PDE4 in mediating neurogenesis and antidepressant effects on behavior, the assessment of PDE2 as a pharmacological target for the development of novel anti-anxiety drugs, and examination of the role of norepinephrine and serotonin transporter regulation in mediating the long-term behavioral effects of antidepressant drugs. All of these projects involve the use of behavioral, neurochemical, and molecular approaches to identify molecular mechanisms that mediate psychopharmacological effects.

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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 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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Our laboratory studies how bacteria manipulate host cell function, cause infections, form biofilms and affect tumor cell function. A variety of projects are available that examine these types of processes. Projects will involve: 1) culturing bacterial and eukaryotic cells (sterile techniques); 2) Western blot analysis to monitor the effects of *Pseudomonas* on tumor derived cell lines; and 3) drug treatment studies to identify host cell processes targeted by the toxic effects of *Pseudomonas*.

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Title: Clinical Laboratory Testing

Participants in the INBRE program will work side-by-side with faculty and staff at the Medical and Translational Clinical Laboratories at the WVU Health Sciences Center. These laboratories are responsible for developing and evaluating tests that are used by physicians across the state. The labs are staffed by clinical pathologists with expertise in clinical chemistry, molecular diagnostics, microbiology, blood banking, informatics and other specialized areas. A variety of projects are available that are appropriate for undergraduate students. Examples of the types of projects students can be involved in include: (1) comparing 2 different immunoassay instruments head-to-head that will be used in clinical laboratories to test patient samples; (2) evaluating and testing a molecular diagnostics instrument that will be used to test patients for respiratory viruses like the swine flu; (3) validating a new test that will be used to diagnose *Clostridium difficile* infection, which is an important problem in hospitalized patients; (4) developing a computer algorithm that can help clinicians select appropriate laboratory tests for their patients; (5) evaluating a new technique that will be used to measure the fractions of cholesterol in blood, a major risk factor for heart disease. Other opportunities may be available based on the interest and experience of the student. On-the-job training is provided so that the student can actively participate in all of the steps that are used to evaluate laboratory instruments and techniques.

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Molecular mechanisms of lung cancer metastasis

While significant progress has been made in the treatment of lung cancer, there remain substantial problems in metastasis treatment. Tumor cells not successfully eliminated by treatment often remain dormant, and later begin to grow and contribute to relapse of disease after cessation of treatment. Relapsed tumors are often more challenging to treat than that presented initially, and has a much less promising prognosis. This project will include using a model system of cultured lung cancer cells of different origin and tumor stage to investigate the effects of adhesion molecules of Cas family on tumor cells migration, invasion and proliferation properties, 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, migration and invasion assay, flow cytometry, and confocal microscopy during this investigation. Later stages of the project will include animal imaging and immunohistochemistry.

Regulation of cell cycle progression by Aurora family kinases

The tumor cells provide a unique setting for analysis of cell cycle malfunctions and identification the new regulatory components that direct constitutive cell proliferation. One of the cell cycle stages called mitosis is the most vulnerable stage of cell division. Inhibition of mitosis is the most widely used chemotherapy target. But most of those inhibitors are not specific for tumor cells. Thus the most promising targets for cancer treatment will be those molecules which specifically expressed in tumor cells. Aurora kinases are mitosis activators. They dramatically overexpressed in almost all types of cancer, but not in normal cells. New small molecule inhibitors were developed to target Aurora kinases, but they have not been effective in treatment of solid tumors. In our laboratory we are investigating changes in the mitosis of epithelial cells derived from solid tumors that result from Aurora inhibitors application, and how these changes may impact tumor growth. This work is focused on alteration of mitotic signaling cascade and disruption of the actin/tubulin cytoskeleton subsequent to dose increase. Students involved in this project will learn to do cell cycle assays, to culture human normal and tumor cells *in vitro*, and to do a variety of protein analyses including Western blots and Immunoprecipitation.

Cell cycle regulation of primary cilium

Primary cilium is a microtubule based protrusion on the apical surface of the almost every cell of human body. The biology of primary cilia was mostly studied on green algae. Little is known about ciliary dynamics in human cell. Most ciliated cells of human body use it as extracellular antenna to sense the microenvironment. Cilium is a dynamic organelle. Primary cilium gets build up and then disassembles depending upon environmental cues like growth factors, Ca²⁺ concentration, and pressure. Cilium gets disassembled during mitosis and the molecular mechanisms of this event are unknown. Tumor cells do not have primary cilium. We hypothesized that cilium is a negative regulator of cell cycle progression and could be potentially used for future drug target therapy. Using a model of the RPE1 cells (retina pigmentosa epithelial cells) that are well characterized ciliated human cells we are investigating the signals that are important for cilia disassembly in the context of mitosis. This project involves tissue

culture of a variety of cell types, protein analysis by Western blot and a lot of confocal microscopy. In addition, the student will learn to do live cell imaging.

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Title: Gene therapy

The main focus of our research group is to understand the molecular and biochemical basis behind blinding diseases that affect humans. Participants in the INBRE program will work along with our team of graduate students, postdoctoral fellows and faculty to contribute to this National Eye Institute (NEI) funded research. Projects range from studying the role of genes, in which defects result in defective vision to treatment of these debilitating diseases using viral or nano particle mediated gene therapy.

Participants join an active team of experienced researchers to work with a variety of animal models that mimic the diseases and techniques depending on skill level and interest. Techniques include creation of transgenic and knock out mouse models, electrophysiology to measure retinal function, molecular techniques such as PCR, cloning, gene expression in prokaryotes and tissue culture cells, protein purification by FPLC, western blotting and enzyme assays.

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Cancer Cell Apoptosis and Chemotherapy

Abnormal regulation of apoptosis or programmed cell death is the foundation of neoplastic evolution and cancer development. Most cancer cells have impaired apoptosis regulatory mechanisms and are resistant to chemotherapeutic agents. Therefore, strategies that increase their sensitivity to apoptotic cell death by chemotherapeutic agents would be of great value for cancer treatment. Our laboratory investigates the mechanisms of apoptosis induction by chemotherapeutic and environmental agents with a goal of identifying key molecular targets for drug therapy and disease prevention. The student will learn techniques for 1) growing and transfecting cells in culture, 2) detecting cell apoptosis by microscopic and biochemical methods, and 3) analyzing protein expression by immunoblotting or flow cytometry.

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My laboratory studies how gene expression is regulated. My laboratory has discovered a novel way in which this can be regulated: increasing and decreasing the rate of pre-mRNA splicing. 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 this regulation. For instance, which of insulin's signaling pathways enhances G6PD gene expression? 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:

- subcloning portions of the G6PD gene to provide better DNA constructs for identifying the RNA element
- measuring amounts of intermediates in the insulin signal transduction pathway
- analysis of amounts of G6PD RNA produced in response to various treatments and from various DNA constructs.

These projects would introduce the student to the standard techniques of Cellular and Molecular Biology including restriction enzyme digestion, PCR, transformation, and DNA purification. More advanced techniques would include cell culture, RNA isolation, Western analysis, Northern analysis and probe synthesis.

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 G6PD expression.
- maintenance of cell lines in tissue culture and tests of G6PD expression in response to various treatments. These tests would include not only expression of the endogenous gene but also transfected DNA constructs.
- 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.

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Project Titles:

- 1. Combined effects of nanoparticles and Respiratory Syncytial Virus on lung development and neurogenic inflammation**
- 2. Investigating the mechanisms linking obesity and maternal diet to asthma and cardiovascular dysfunctions**

Our ongoing research in the field of childhood asthma include projects ranging from the study of the effects of viruses on the plasticity of nerves in the airways to the expression of several mediators of neurogenic inflammation in a rodent model of childhood asthma as well as in human samples. Understanding the basic mechanisms underlying airway diseases in infancy and early childhood is of great importance in the effort to identify therapeutic targets for novel treatments which may prevent or lessen the severity of these pathological conditions in young individuals.

Participants will work with pediatric residents, graduate students and faculty members and will be involved in a number of research techniques that may include RT-PCR, immunohistochemistry, cell culture and animal surgical procedures. Training will also include participation in lab meeting, journal clubs and data management.

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The major research focus of our laboratory group for faculty and students involved in summer research with the WV-INBRE program is as follows:

A major concern with diagnosing and treating environmental exposure effects due to pesticides is the lack of a definable disease relationship following exposure. We are particularly interested in better understanding the harmful effects of pesticides to the body's immune system and establishing such a disease relationship. Specifically, our research concerns the pesticide, propanil, and its reported adverse effects on cell-mediated immunity. Since exposure to many immunotoxic pesticides (including propanil) results in a variety of ill-defined pathologic effects, it is difficult to correlate pesticide exposure with a particular disease consequence.

Recent studies from our laboratory demonstrate that propanil exposure has a delayed but clearly inhibitory effect on the function of cytotoxic T cells, which are the key effector cells of cell-mediated immunity. An important observation is that the early effects of propanil exposure on cell-mediated immune function are minimal, but the long-term effects after a single initial exposure result in a complete loss of functional reactivity for these cytotoxic T cells. These effects bear a striking resemblance to those seen in a variety of specific disease states – including HIV infection and AIDS, cancer, and various chronic virus diseases – which share a common disease mechanism, involving what is known as the PD-1/PD-L1 pathway. This project will examine whether this same disease mechanism is responsible for the observed effects following propanil exposure. ***This study could be especially important in terms of its implications for the diagnosis of disease and treatment following exposure to environmental contaminants in general.***

Techniques that will be used in these projects include cell culture, flow cytometry, computer modeling, T-cell proliferation assays, mixed lymphocyte response assays, ⁵¹Cr-release assays, and protein purification methods. This research project will be conducted in the context of a larger, interactive laboratory group including 3 faculty collaborators.

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BIOFILMS (Anti-Koch/Anti-Pasteur)

Microorganisms exist as free living phenotypes (planktonic) and attached phenotypes (biofilms), never mutually exclusive. However, given the opportunity, 99.9% of microbes prefer the biofilm phenotype, given its legacy of survival, emphasizing microbial diversity, heterogeneity and co-aggregation. Biofilms emphasize cooperation (the “We” concept (Metchnikoff) vs. the “I” concept (Pasteur)).

Recently, a growing list of human diseases, both oral and medical, have been linked to biofilms and hastened further understanding of their mechanisms of communication (Quorum Sensing), 3-D structures and methods of avoidance of the immune system; means of treatment is still lacking.

Students will learn extensive molecular and non-molecular (culture) techniques, advanced imaging and CT-radiography to unmask this unique community via four divergent, but connected areas of translational research (listed below), working simultaneously with investigators and students from Cardiff University, Wales, UK and the National University of Singapore, Singapore. Given the translational nature of our research, students may spend time with physicians in the ICU

1. Hospital Associated Pneumonia / Ventilator Associated Pneumonia (VAP)

The most costly Nosocomial infection in the ICU is VAP, adding upwards of 15 days and \$150,000 per patient while utilizing 50% of the ICU resources. Our investigations focus on the endotrach as a “biofilm engine”, emphasizing poor oral hygiene. In addition to evaluating impact of a silver coated endotrach using a unique VEL Model (Ventilator-Endotrach-Lung), (<http://www.hsc.wvu.edu/biofilms/velModel/index.asp>) we are currently very interested in defining the relative rate of genetic exchange (antibiotic resistance) under the growth conditions of an endotracheal biofilm during Mechanical Ventilation for a patient with COPD or ARDS.

2. Triphasic Chronic Wound Model

Growing evidence links biofilms to chronic wounds and the lack of tissue regeneration and wound closure. Using methods refined with the VEL Model (above) and Cardiff University, Department of Tissue Engineering and Regenerative Science, we have developed a triphasic wound model, using both procaryotic (bacteria) and eucaryotic (human) cells, which are layered to mimic a wound environment, to study the interface between the two, and the potential use of “replacement therapy” (probiotics) to initiate closure. Students will learn histologic techniques, cell culture, biomarkers and biofilm 3-D imaging with CLSM (Confocal Laser Scanning Microscopy).

3. Biofilms Mimicking Tumors: A New Approach to Cancer Management

We have recognized that biofilms and tumors share at least eight key characteristics, most importantly, staging of community growth into four specific universal sequences (I-IV). By evaluating anti-tumor drugs against standard biofilms grown in a reverse gel (Ploxamer), we can select therapeutics that defines the best stage for recalcitrant

biofilms, while simultaneously treating a tumor. This concept has received recent notoriety with the successful elimination of catheter biofilms by 5-FU, a known anti-cancer agent.

4. COHRA – Center for Oral Health Research in Appalachia

West Virginia University and the University of Pittsburgh

In 2000, the US Surgeon General Reported on the Oral Health in America; it was the first ever federal report that highlighted profound disparities in oral care, particularly in Appalachia. COHRA was created to integrate the resources of WVU and Univ. of Pitt Schools of Dentistry, focusing on genetic contributions. Our laboratory complements the investigations of 500 low-income families with multiple oral cultures, creating an Oral Microbial Signature (OMS) and Liability Index based on prevalence of *Staphylococcus aureus*, *Candida albicans*, and Group A Beta *Streptococcus* to unmask high risk patients for oral disease. Students will learn studies in epidemiology, public health and the use of statistics to highlight important demographics and interface with faculty at the University of Pittsburgh. There will also be application of the data acquired by the NIH in the Microbiome Studies, and metagenomics.

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PROJECT: NEUROPEPTIDE Y, LEPTIN AND BREAST CANCER

The neuropeptide Y (NPY) Y2 receptor is expressed in normal breast tissue whereas primary human breast carcinomas express the Y1 receptor (Y1R) subtype. NPY is known to inhibit estrogen-induced cell proliferation through Y1R; however, it is not known if activation of leptin, an adipokine produced by adipose tissue, plays a role in the induction of Y1R. To investigate this possibility, we will use estrogen receptor-negative (ER-) human breast carcinoma cell lines, MDA-MB231 and MDA-MB486, and (ER+) MCF-7, with SK-N-MCF human neuroblastoma cells (positive control) and examine the effect of leptin on Y1R gene expression. Total RNA extracts from cells will test the expression of Y1R gene expression in breast cancer cell lines using RT-PCR. We will test the effect of NPY treatment on cell proliferation in combination with obesity levels of leptin and with Y1R-specific blockade using BIBP-226. We hope to show that NPY plays an important role in the up-regulation of neuropeptide Y1R gene expression which in turn inhibits leptin-induced proliferation in breast cancer.

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Two projects are available for summer interns. Both projects involve telomere measurement. Telomeres cap the ends of all chromosomes and shorten each time a cell divides. At some point, the telomeres become very short, at which point the cell stops dividing and dies. Telomeres can be targeted with a fluorescent-labeled probe. Telomere length can then be measured by size of the fluorescent signal at the ends of chromosomes using a computer image capturing system.

One project in the cytogenetics research laboratory is to measure telomere length in metaphase and interphase cells to determine if consistent results can be obtained between these two measurements for a given cell line. Cell lines that will be used will have normal or abnormal number of chromosomes.

The second project will study chromosomally normal and abnormal cells that are in the same individual, known as mosaicism. As an individual with mosaicism ages, the abnormal cell line disappears from the blood. The purpose of the project is to determine if the telomere length differs between the two cell lines, providing an explanation for loss of the abnormal cell line (shorter telomeres).

Protocols that may be used for these projects include sterile culture technique, 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 compartment that plays an essential role in signal transduction, the synthesis of secretory and integral membrane proteins, and cellular homeostasis. Recent studies from our laboratory have indicated that small molecules can move between the cytosol and lumen of the rough ER via the same pathway used by newly-synthesized proteins—the pore of a ribosome-bound translocon complex. Our long-term goal is to understand how 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 preliminary data indicating that these ribosome-bound translocons are 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 focus on identifying the mechanisms whereby protein aggregates can stimulate the opening of ribosome-bound translocons and how that stimulation affects the endoplasmic reticulum. This project will provide opportunities to learn techniques in cell biology, protein biochemistry, fluorescence assays, and cell culture.

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There are abundant epidemiological studies linking embryonic and early postnatal environmental tobacco smoke (ETS) exposure with childhood asthma and wheezing, but the underlying mechanisms that occurs in utero and early postnatal periods to explain this link remains unknown. Human lung development consists of five stages: embryonic phase, pseudoglandular phase, canalicular phase, terminal sac phase and alveolar phase. During these periods, growth of epithelial and connective tissues, blood vessels and nerves is highly coordinated in order to maintain the normal structural and functional relationships of the respiratory system. Neurotrophic factors, including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), are essential in promoting and maintaining differentiation, growth, and survival of the central and peripheral nervous systems, including innervation of the airways. Disruption of normal synthesis and release of these neurotrophic factors and resulting changes in airway innervation after inhalation of toxic material is well documented in adult lungs and leads to disease-related abnormalities in respiratory system. The goal of this projects to study effects of prenatal, neonatal and early postnatal ETS exposure on lung function, neurotrophin expression and the resulting altered control of airway innervation.

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The overall aim of the laboratory is to define the events that initiate and regulate endothelial cell contraction in an effort to elucidate the basis of increased vascular permeability. The primary hypothesis underlying the proposed work dictates that exposure to inflammatory mediators activates the endothelial cell actomyosin based contractile system. Calcium (Ca^{2+}) dependent and/or Ca^{2+} -independent stimulated phosphorylation of the myosin II regulatory light chain results in myosin II filament formation, an obligatory step leading to endothelial cell motility and contraction. In nonmuscle cells, myosin II is a major cytoskeletal protein which has the ability to convert the chemical energy of ATP into the mechanical work of cell contraction through its interaction with actin. Myosin light chain kinase (MLCK) -catalyzed phosphorylation results in mono- and diphosphorylation of myosin II regulatory light chains at site Ser19 or sites Ser19 and Thr18, respectively. In endothelial cells, we have shown that a small GTPase dependent enzyme, p-21 activated kinase (PAK2), catalyzes Ca^{2+} independent activation of nonmuscle myosin II by phosphorylation of the regulatory light chain that is restricted to site Ser19. This PAK2-mediated monophosphorylation results in a less forceful contractile response than when the regulatory light chain is diphosphorylated by MLCK. More recent studies have shown that PAK2 also phosphorylates unactivated MLCK which results in inhibition of MLCK activation by Ca^{2+} .

The goal of our studies is to biochemically and morphologically characterize myosin II activation by Ca^{2+} -dependent and Ca^{2+} -independent signaling pathways in endothelial cells. The working hypothesis is that a specific pools of myosin II, determined by the heavy chain isoform specificity (myosin IIA vs IIB vs IIC), are activated by enzyme specific modifications. Functionally, regulated differential phosphorylation of myosin II would allow the endothelial cell to react to a variety of physiological signals with graded contractile responses.

Projects:

- 1) Characterize myosin II heavy chain isoform function. Studies will establish the localization and states of phosphorylation of myosin IIA and IIB in endothelial cell spreading, migration and in agonist stimulated confluent monolayers.
- 2) Investigate the role of Rho-GTPases in endothelial cell contraction. Experiments will be carried out to assess the role of Rho-kinase vs MLCK in basal and agonist stimulated isometric force development.

Students researchers will be exposed to the following techniques in the laboratory: 1) casting 3-D tissue constructs, 2) measuring nonmuscle isometric force production, 3) confocal microscopy, 4) cell motility measurements 5) tissue culture methods for establishing and maintaining endothelial cells, 6) western blots, and 7) transient transfection of endothelial cells.

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. Two projects are available. Each project is appropriate for faculty and/or students. On-the-job training will be provided.

Title: The effects of gender on cardiovascular function with diabetes and aging. The long term objective of this project is to investigate how gender 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. It is anticipated that the data gleaned from these studies will provide important knowledge regarding the etiology and treatment of cardiovascular dysfunction.

Title: Development of a nano-scale protein based cargo transport system. The long term objective of this project is to investigate the potential of using electrical and / or magnetic fields to build a bio-molecular transporter (using the muscle proteins actin and myosin filaments) that could be used to deliver molecular cargo to addressable coordinates on a micro-patterned surface (e.g. a molecular conveyor system).

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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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1. Role of β -catenin in melanoma. The incidence of melanoma has increased to an alarming degree in recent years. While early melanoma is both preventable and treatable, later stages of this disease are very difficult to manage. β -catenin is a signaling protein well-known to play a central role in several cancers, however comprehensive study of the role of β -catenin in melanoma is lacking. We are examining the location and action of β -catenin in mouse and human melanoma cell lines, as well as the effect of the anti-tumor agent, retinoic acid. Our data indicate that retinoic acid reduces the tumor-promoting activity of β -catenin by several mechanisms within melanoma cells. This suggested a coordinated response that might be important for both cancer and development. The summer researcher would be invited to participate in experiments to examine the expression and activity of β -catenin inhibitors in melanocytes and melanoma cells by a number of means. The likely techniques would include subcellular fractionation and 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 problems 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 brain's 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, glucometers, 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.

Our most current research project is focused on studying the effects of Sulforaphane (SFN), a substance derived from Broccoli on Prostate Cancer (PCa). We are investigating 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. 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 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.

RT-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 underlying effects of antidepressant medications on synaptic plasticity and plasticity related molecules. Depressive disorders 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 or serotonin and norepinephrine neurotransmission), the longer term consequences for brain function are still poorly understood. In this project, we are examining synaptic function, plasticity, and 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. Models of signaling mechanisms in long-term synaptic potentiation. 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 the brain mechanisms for memory. 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.

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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 2010 WV-INBRE Summer Research Program, I propose to study inflammatory factors in a genetic mouse model of obesity and type 2 diabetes, TALLYHO. Inflammatory or immunological factors are implicated in both obesity and type 2 diabetes, and characterization of these factors in TALLYHO mice will contribute to elucidating pathogenic mechanisms underlying these diseases. Experimental methods involved in this internship research will include enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR), western blot analysis, and immunohistochemistry. DNA, RNA and protein will need to be isolated from mouse tissues. Instruments involved in this project include microscope, microplate readers, imaging system, and thermal cyclers.

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Projects in my laboratory are:

Vitamin A and Melanoma: The incidence of melanoma is rapidly growing in the US population. In WV, it is the cancer with the highest incidence in the 20-35 year old population. We are studying how the biologically active form of vitamin A, retinoic acid affects the properties of human melanocytes and how this is altered in human melanoma cells, making them resistant to cancer prevention effects of this vitamin. Subprojects include: Characterization of the nuclear receptors for retinoic acid in human melanocytes and melanoma; investigating the metabolism of vitamin A in normal human melanocytes and melanoma.

Techniques: “real-time” RT-PCR, cell culture, HPLC, enzyme assays

Expression and Function of Hypoxia-Inducible Factor-1alpha (HIF-1alpha) in Human Melanoma

Some cells in a tumor encounter a hypoxic (low oxygen) environment. In order to ensure their survival, these cells increase the amount of HIF-1alpha protein which turns-on genes that stimulate new blood vessel formation and genes that shift the fuel metabolism of the cell so energy can be obtained in the absence of oxygen. We have found that more malignant melanoma cells have high amounts of HIF-1alpha under normal oxygen tension. We are studying the mechanism by which these melanomas increase their expression of this factor and the function of a specific gene target, microphthalmia transcription factor (MITF) .

Techniques: cell culture, Western blotting, gene transfections, animal models

Effect of Phytochemicals on melanoma development

We are studying the ability of certain dietary constituents such as quercetin and curcumin to prevent the development and/or progression of melanoma. The molecular pathways that are affected by these phytochemicals is also being investigated

Techniques: cell culture, animal models, gene expression microarrays

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Students in the summer WV-INBRE program will actively participate in on-going cancer research projects and will work side-by-side with faculty and graduate students. The principal investigator (PI) and graduate students will facilitate the best research experience possible. Two projects are available.

Title: Investigating the function of Chmp1A in human colon cancer cells. The long-term goal of this project is to understand the mechanisms of colon cancer development. We found that Chmp1A functions as a tumor suppressor in pancreas. We speculate that Chmp1A may function similarly in colon cancers. To test our hypothesis, we will over-express or knockdown Chmp1A in colon tumor cells. Subsequently we will determine the effect of Chmp1A on colon tumor cell growth and cell cycle signaling activities. The students have a chance to learn cell culture techniques, cell growth analysis, immunostaining, statistical analysis, PCR and Western blot analysis. It is anticipated that these studies will generate results for paper publications and meeting abstracts.

Title: Investigation of nuclear localization signal (NLS) of Chmp1A in pancreatic tumor development. The long-term goal of this project is to investigate the significance of the NLS domain of Chmp1A in pancreatic tumor suppression. Our preliminary data indicates that Chmp1A inhibits tumor growth through its NLS domain. To test this hypothesis, we generated several deletion mutations of Chmp1A. The students will be involved in the generation/verification of stable cells with various deletion constructs of Chmp1A. Once the stable cells are successfully generated, the students will use these cells to determine the effect of the NLS domain of Chmp1A on tumor cell growth and cell cycle signaling activities. Similar techniques as described above will be used in this study.

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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: Propanil is an herbicide used in agriculture to decrease grasses in rice field. Recent work in our laboratory has demonstrated that propanil is toxic to the kidney. However, the mechanism by which propanil induces nephrotoxicity is unclear. In this project the role of bioactivation of propanil to toxic metabolites is being explored along with possible mechanisms by which propanil or its metabolites induce toxicity to the kidney

Project #4: 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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Dioxins are a family of fat soluble pollutants found in the environment due to their stability, municipal waste incineration, and the manufacture of herbicides and pesticides—resulting in levels of this chemical to range from parts per trillion to parts per billion in humans. While it is clear that this family of endocrine disrupting chemicals (EDCs) have a potent deleterious effect on wildlife species, their impact on human health is still a controversial subject. This lack of clarity is due, at least in part, to too few human studies, and a need for a deeper mechanistic understanding of how exposure to pollutants—like dioxins—may impact human health. We are currently studying how endocrine disrupting chemicals disrupt hormone signaling, and therapeutic drug signaling in the ovary and breast. Students in my lab would have the opportunity to study these questions in human ovarian cancer cells and in 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:

1. **Adipose tissue biology in obesity:** Obesity is a major risk factor for cardiovascular disease and metabolic syndromes. Changes in adipose tissue (the fat storing endocrine organ) composition and function during obesity contribute to the increased risk. There are several projects in my laboratory related to this area. For example,
 - (i) **Adipose specific miRNA isolation and detection:** miRNA are approximately 17-24 nucleotide single-stranded RNA that post-transcriptionally regulate gene expression. Recently adipose specific miRNA has been identified and their role in obesity associated diseases has been proposed. 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.
 - (ii) **Identification and isolation of adipose specific stem cells:** There are reports in the literature that the composition of the adipose tissue changes during obesity. This change might be due to changes in the progenitor stem cells. We are interested in demonstrating these changes in adipose specific stem cells in our ongoing obesity related studies. If you are interested in this project, you will learn (i) to isolate adipose specific stem cells from the adipose tissue obtained from obese animals; (ii) using specific antibodies detect and identify adipose specific stem cells using flow cytometry and immunohistochemistry.
2. **Pain in Endometriosis:** Endometriosis is a disease that affects 10-15% of younger women. The major symptom of this clinical condition is pain. In our laboratory we are conducting cell culture, animal and human studies to understand the pathophysiology of pain in this disease.

TECHNIQUES:

The techniques that are routinely performed in our laboratory:

1. Cell culture techniques, isolation of 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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About five hundred billion blood cells need to be replaced in the human body each day. This feat is accomplished by the exponential amplification of cells from a pluripotent precursor cell known as the hematopoietic stem cell (HSC). The HSC does not generate the required 5×10^{11} cells directly on a daily basis, but instead generates highly prolific progenitor cells that produce the nine major hematopoietic cell types. When developmental decisions go wrong in this system leukemias occur due to the uncontrolled amplification of progenitor cells. Defining the regulation of these progenitor cells is important to our understanding of stem cells, leukemias, and other blood disorders. My laboratory investigates the effects of omega-3 fatty acids (those present in fish oil) on these progenitor cells using the mouse as a model system. The following projects are available in my laboratory related to this area of research:

Project #1: Epigenetic regulation of the wntless-integrin (WNT) pathway by omega-3 fatty acids:

Cells that have identical genomes can respond in markedly different ways to the same stimulus, such as a cytokine, with the outcome being determined largely by the previous developmental history of the cell. This developmental history is recorded as a form of "cellular memory" in an epigenetic format consisting of modifications to the cell's genome, such as DNA methylation. An important biological signaling pathway known as the WNT pathway is regulated by DNA methylation. This signaling pathway has been found to be involved in many cancers including those of the blood, such as leukemias. We are exploring the effect of this regulation on progenitor and stem cell biology by using a mammalian cell culture system and in mice. The student or faculty member will have the opportunity to learn techniques for: a) mammalian cell culture, b) flow cytometry protocols, c) recombinant DNA technologies, and d) mouse dissection techniques.

Project #2: Identification of genes involved in stem/progenitor cell frequencies:

We have concluded a genetic screen for genetic regions involved in stem/progenitor cell biology in the mouse. We are currently determining which genes in these genetic regions are responsible for control of stem/progenitor cell numbers in the mouse. The hypothesis for this research is that different frequencies of progenitor cells in various mice may be exploited to determine what genes are important in the regulation of progenitor cells. The objective of this project will be the identification of new genes involved in this regulation. The student or faculty member will learn techniques for: a) mammalian cell culture and cytokine stimulation of bone marrow, b) mouse dissection techniques, and c) flow cytometry protocols.

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Projects available in my lab:

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

This is an ongoing project funded by NIH. The purpose is to investigate new ways to lower the severe side effects of cancer chemotherapy. The second 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. Students or teachers involved in this project would learn techniques involving protein expression and activity, various biochemical enzyme activities to evaluate alterations in cellular function and markers of oxidative stress. Instruments used in our laboratory include: spectrophotometers, microplate readers, western blot, densitometry and HPLC.

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

This is an ongoing project in my laboratory and has resulted in several publications. 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.

Students or teachers involved in any of the above projects would learn techniques involving protein expression and activity, numerous assays evaluating cellular biochemical enzyme activities and markers of oxidative stress. Instruments used in our laboratory include: spectrophotometers, microplate readers, western blot, densitometry and HPLC.

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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 staffs to tackle issues such as what environmental cues 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. We hope to identify the novel AMPs with increased efficacy and reduced toxicity. Students working for this project will learn basic methods and technologies used in the clinical microbiology laboratory.