Biomedical Research and Mentoring Program (RaMP)
Mentor Project Descriptions 2017-2018 Cycle
Updated 10/17/2017

Mentor: Perwez Alam, Postdoctoral Fellow
Dept: Department of Pathology and Laboratory Medicine
Facility: UCCOM

Project: **CRISPR/Cas9 mediated genome editing to induce adult cardiomyocyte proliferation**

Myocardial infarction (MI) is the major contributor of all the cardiac associated causalities. It causes the death of tissues and scar formation in infarcted area, which leads to the cardiac remodeling, reduced heart function and, thus, cardiac failure. In contrast to cardiomyocytes (CM) of zebra fish and neonatal mice, which have ability to regenerate and repair cardiac injury; adult animals like, humans lack this ability and thus, cardiac repair after injury. Recent studies demonstrate the scope to induce the adult cardiomyocyte (ACM) cell cycle re-entry and identify the factors associated with ACM senescence phenotype that includes cell cycle inhibitors. Therefore, we are using CRISPR/Cas9 mediated knockout of cell cycle inhibitors to induce ACM proliferation, which may lead to reduced infarct size and improved heart function. It will help to extrapolate their therapeutic roles following myocardial infarction in adult animals. The undergraduate student will learn genome editing, immunocytochemistry, fluorescent microscopy, PCR, and agarose gel electrophoresis.

Mentor: Xiaoxian An, PhD Student
Dept: Pharmaceutical Sciences
Facility: College of Pharmacy

Project: **Biodegradable Magnesium (Mg) Improve wound healing through anti-inflammation**

In this project, we propose that local delivery of Mg\(^{2+}\), either through corrosion of Mg metal particles or infusion of Mg salt solution, could attenuates inflammatory reactions led by biomaterial implantations. We also hypothesizes Mg\(^{2+}\) could induce M2-phenotype macrophage polarization, which has been proved to be anti-inflammatory. The potential clinical application is to incorporate Mg into current surgical mesh materials to promote wound healing. Students will participate in the animal experiments and learn to perform immunostaining, RT-PCR using dissected animal tissues. Also, we have parts of the work from another project expected to be finished. In this project, we used electrospun polycaprolactone nerve conduits with Mg metal particles to aid nerve regeneration in the sciatic nerve injury. Students will work on image and statistical analysis using multiple software in helping with the publication.

Mentor: Bill Brinkman, MD, MEd, MSc
Dept: General & Community Pediatrics
Facility: CCHMC

Project: **Goal Setting and Shared Decision Making in Pediatric Settings**
Our research focuses on interventions across a wide-range of clinical contexts that make it easier for pediatric patients, their parents, and healthcare team members to work together to develop treatment plans that are well aligned with family goals, preferences, and values. Current project opportunities include: 1) development of a machine learning algorithm to categorize the degree to which patients and parents are involved in medical decisions during clinical encounters which have been video recorded, and 2) qualitative analysis of goals elicited from parents of children with medical complexity. For the first project, the student would help transcribe the audio from clinical encounters and learn how machine learning algorithms are developed to classify this information. For the second project, the student will learn qualitative data analysis techniques to develop and apply a coding scheme to categorize the goals that were elicited from parents of children with medical complexity.

**Mentor:** Yuqi Cai, Research Associate  
Dept: CBDI  
Facility: CCHMC

**Project: Develop a novel tube formation system to study venous malformation**

Venous malformation (VM) is slow-flow vascular lesions composed of growing, enlarged and abnormally shaped veins. VM is a chronic condition first seen at birth or during childhood. Germline or somatic TEK (TIE2) mutations are considered one of the genetic cause of VM. The underlying biological mechanisms in VMs are still not very clear. We are building a 3D tube formation models to understanding the process of VM formation as well as testing novel targeted therapies. A genetic modified gene mutation mouse is also under progression. Using these models, we will understand the mechanism underlying VMs. Using these knowledge, we can find the new drugs to treat VM kids. The new drugs can be directly used in phase II clinical trial. Come and join our lab. You will have a chance to see how we can change the outcome together!

**Mentor:** Vandana Chaturvedi, Ph.D, Research Associate  
Dept: Immunobiology  
Facility: CCHMC

**Project: From Bed to Bench side and Bench side to Bed**

In healthy humans, the immune system is well balanced and in a state called “homeostasis”. During infections or other immunological insults, this balance is disturbed. In normal conditions, immune cells fight the disease and bring the immune system back to a well-balanced state. However, in certain genetically determined immune disorders the balance is disturbed and homeostasis is not restored. Our lab focuses on one such immune regulatory disorder, called Hemophagocytic Lymphohistiocytosis (HLH). HLH is a rare and life threatening disorder characterized by excessive immune inflammation due to a broken ‘off switch’ affecting critical areas of the immune system. Cincinnati Children’s is a world leader in caring for these complicated patients and our lab has pioneered a mouse model to study this disease. The study of HLH in mice has provided unique insights into immune regulation, defined disease pathophysiology, and suggested several strategies for the targeted therapy of human HLH. Multiple groups have studied the therapeutic potential of blocking interferon gamma (IFN-γ), JAK/STAT signaling, and other conventional or novel approaches in mice. Whilst all these approaches conventionally block the cytokine signaling and the ensuing cytokine storm, it is still not clear how well therapy reflects clinical realities in patients, or how these therapies may compare with, or complement each other. It is essential to delineate a careful kinetics of HLH development for interpreting the results of therapeutic
studies in murine models. Studying the outcome of specific therapies in the mouse model will have a significant impact on clinical contexts. This approach is revealing innovative and potentially optimal combinations for targeted therapy of human HLH.

Role of student

The student after getting trained will help us in handling and processing tissues from infected mice and clinical samples. They will also analyze how the new potential therapy will work, and how the treated tissue will be different from untreated tissues.

**Mentor:** Ana Cheong, PhD, Research Associate  
Dept: Environmental Health  
Facility: UCCOM

**Project:** Environmental exposure and prostate cancer

This project utilizes cell-based and animal models to study the effect of adult exposure to environmental agents, such as synthetic estrogens and metals, on prostate stem cell functions and the risk of developing prostate cancer. The role of the student is to assist with the planning and designing of the research work, perform experiments using molecular biology and epigenetic tools, and analyze the data. It will involve literature search and lab bench work. Throughout the program, the student will be trained with cell culture and basic molecular biology techniques such as RNA extraction, real time PCR, western blotting analysis, cloning, bisulfite sequencing for studying changes in DNA methylation, and presentation skills for scientific research work.

**Mentor:** Alexandra Eicher, Graduate Student  
Dept: Developmental Biology  
Facility: CCHMC

**Project:** Engineering a human model system to study the development of the gastric enteric nervous system

The enteric nervous system (ENS) is an intricate network of peripheral neurons and glial cells that colonizes the gastrointestinal (GI) tract and regulates GI motility, epithelial permeability, secretion, and blood flow. Developmentally, the ENS arises from neural crest cells (NCCs) that migrate into the foregut and continue along the GI tract, colonizing the gut between 4 and 7 weeks of human gestation. While complications arising from improper ENS development are common in the intestine, little is known about the specific impact the ENS has on the developing gastric system. Due to inherent differences between mouse and human development, an in vitro human-specific system would provide a novel way to study gastric/ENS interactions in human tissue. We hypothesize the ENS plays a key role in gastric development. We are developing a directed differentiation, in vitro approach using human embryonic stem cells (hESCs) to examine the specific roles the ENS is playing in gastric development. We aim to incorporate hESC-derived NCCs into developing human gastric organoids (HGOs) to recapitulate normal gastric ENS development. We then use innervated HGOs to explore the specification and patterning differences between human gastric tissue with and without a functional ENS.

The student will become familiar with cryosectioning, immunohistochemistry, confocal microscopy, RNA isolation, and/or polymerase chain reactions (PCR).
**Mentor:** Christopher Holmes, PhD Student  
Dept: Biological Sciences  
Facility: UC Main Campus

**Project:** *Impact of mosquito hydration status on their physiology and immunology*

Mosquitoes are a major contributor in the transmission of arthropod-borne diseases, such as Zika virus. Despite extensive focus on the relationship between mosquitoes, environment, and disease transmission, the role of dehydration on mosquito biology and disease transmission is vastly understudied. Recent research in the Benoit lab found that mosquitoes exposed to short bouts of dehydration resulted in increased activity, host landing, and blood feeding. These results suggest dehydration stress prompts mosquitoes to seek a bloodmeal as a rehydration mechanism and this shift will likely alter disease transmission. This research will begin to address the lapse in knowledge that currently exists in the effects of dehydration on mosquito biology and the subsequent effect on mosquito vectorial capacity. Students will have the opportunity to be exposed to a variety of techniques since this research will incorporate observational biology (blood feeding behavior, water retention, particle retention), molecular biology (RNA isolation, polymerase chain reactions, gene knockdown, etc.), biochemistry (nutritional reserve assays, western blotting), and bioinformatics (transcriptomics, primer design).

**Mentor:** Vinothini Janakiram, PhD/RA  
Dept: EH&CANBIO-STEM CELL BIOLOGY  
Facility: CCHMC

**Project:** *Hematopoietic stem cells in obesity*

Studies have shown that obesity is a significant risk factor for blood cancers. Obese persons have a greater risk of developing the disease and their treatments are often more difficult. However despite their clinical importance, little is known about the mechanisms linking obesity and leukemia. Working with mouse models that mimic human leukemia and display obesity features, we are analyzing how obesity affects normal blood production and leukemia development. Notably we focus our analysis on the hematopoietic stem cells (HSC), a small pool of cells in the bone marrow that are responsible for the controlled production of all blood cells during the entire life of the individual. Importantly HSCs, when they acquire mutations, become dysregulated and produce high number of blood cells in an uncontrolled manner. As such these rogue HSCs are often at the root of blood cancers. In this project, we are investigating the mechanisms by which obesity impact on the normal HSC and could promote the development of hematopoieticpathologies. Techniques utilized in the lab includes: animal handling, cell culture, genotyping, DNA and RNA isolation, FACS, qPCR, Western blot, RNA seq, ATCA seq, Chip Seq and Immunofluorescence. Student will be trained to perform experiment, analyze data and interpret the results.

**Mentor:** Emily Jennings, PhD Candidate  
Dept: Biological Sciences  
Facility: Arts & Sciences

**Project:** *Dehydration and mother-offspring conflict in a live bearing cockroach*

Background: Reproducing by giving live birth has evolved independently on many occasions for both vertebrates (like humans) and invertebrates (like insects). One such insect is the beetle mimic cockroach,
in which mothers provide nutrients and fluids to embryos using a unique organ that acts as a uterus and placenta. It has been widely shown that experiences in the womb have direct consequences on prenatal health and may generate effects that extend from birth into adulthood as diseases. The extensive and complex interactions between cockroach mothers and developing offspring provide an opportunity for their womb, as an environment, to make lasting impacts on progeny. My research aims to model the impact of stresses, like dehydration, during pregnancy on offspring during prenatal and juvenile development and as adults; ultimately investigating whether these effects are inherited by future generations.

Student Project: The student may be involved in many aspects of this project such as characterizing changes in prenatal and post-natal growth, ability to fight oxidative stress, or assessing other interactions between mothers and developing embryos. The student will learn about experimental design, techniques in molecular biology and physiology as well as data analysis while learning to thrive in a team oriented lab environment.

Mentor: Stephanie Kidder, PhD, Postdoctoral Fellow
Dept: Molecular Cardiovascular Biology
Facility: CCHMC

Project: Developing a better mend for broken hearts

Heart disease is a devastating illness with poor prognosis; it is the leading cause of death worldwide. Research in our lab is centered on the causes of and possible treatments for heart failure (HF), the end-stage manifestation of most heart disease. Fibrosis is a central characteristic of HF. In response to injury, scar tissue (fibrosis) initially forms to help protect the heart from further damage. However, over time this scar becomes detrimental to proper cardiac function. Communication between different cell types in the heart, as well as how these cells interact with their tissue environment, mediates pathologic fibrosis. Using various mouse models and human tissue, we investigate molecular mechanisms and novel therapeutics with which we can target the beneficial cell-cell interactions while decreasing pathologic fibrosis. Although we are primarily focused on HF, we also have begun to examine fibrotic remodeling in other organs (e.g., liver, kidney) to investigate possible similarities and differences across tissues that could be leveraged for future therapeutic development.

Motivated students will have the opportunity to participate in innovative, translational research and will be exposed to an array of laboratory techniques, ranging from mouse genetics, cell biology, western blotting, PCR, cell culture and imaging microscopy, to experiments with human tissue samples.
**Mentor:** Christopher King, PhD  
Dept: Anesthesia  
Facility: CCHMC  

**Project:** *Psychosocial determinants of pain*

The current project is looking at factors contributing to the experience of clinical pain in adolescents with musculoskeletal pain (e.g., low back pain). We will be using several techniques to examine the role of psychological functioning, sleep, and social factors with surveys, actigraphy, and quantitative sensory testing. We will also be tracking these outcomes and changes in clinical pain following rehabilitation.

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**Mentor:** Chaochang Li, PhD Candidate  
Dept: Developmental Biology  
Facility: CCHMC  

**Project:** *The role of Six1 in craniofacial development*

Craniofacial microsomia (CFM) occurs in 1:3000 to 1:5000 live births. CFM results in alterations in the upper airway, facial movement, speech, feeding, and hearing. We are interested in the Six1 gene, which is expressed in various tissues during development and perform crucial functions in differentiation, morphogenesis and organogenesis. In humans, duplication of the chromosomal region containing the SIX1 gene has been associated with CFM. Six1 null mice exhibit similar craniofacial defects in CFM patients, including maxillary and mandibular hypoplasia, malformation of the zygomatic process and malformation of outer and middle ear. So far, it remains unknown how loss of Six1 causes shortened mandible. In this study, we will uncover the role of Six1 in the development of mandible.

The involvement of students will depend on their goals and interests. For example, if the student is very interested in the craniofacial defects of Six1 null embryos, which is similar to the defects in CFM patients, the one will participate in experiments related to morphology and phenotypes, such as HE staining, skeletal preparation, etc. Our research includes a wide range of techniques including mouse genetics, biochemistry (western blot, immunofluorescence), molecular biology (molecular cloning, PCR, RNA isolation, RT-qPCR), cytogenetic technique (*in situ* hybridization), imaging and so on. The student will also gain some knowledge on developmental biology, and start learning how to conduct scientific research.

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**Mentor:** Jaclyn McAlees, PhD  
Dept: Immunobiology  
Facility: CCHMC  

**Project:** *Allergic Asthma Development*

The Lewkowich lab uses in vitro cell culture, mouse models, and clinical based methods to research the development of allergic asthma. A student researcher would have the opportunity to learn and utilize
cell culture and molecular biology techniques to examine the different cell types and intracellular signaling pathways that play a role in the development and progression of allergic asthma.

**Mentor:** Rhyanne McDade, PhD, CHES  
Dept: Behavioral Medicine and Clinical Psychology  
Facility: CCHMC

**Project:** *Sickle Cell Disease Self-Management and Community Engaged Research*

The Crosby Research Lab conducts a wide range of translational and health services research. Chief research foci include community engaged research and Sickle Cell Disease research (SCD) with specific interests in adherence and self-management, early childhood health, social and emotional functioning, and using technology in psychological interventions within the SCD population. As of to date, SCD is the most common genetic disorder in the U.S. affecting approximately 100,000 individuals, the majority of whom are African American (approx. 1 in 400 African American births). SCD encompasses early onset of medical complications including but limited to: renal and cardiac dysfunction, stroke, pulmonary hypertension and chronic pain due to organ damage. Within this population, self-management and medication adherence are extremely low and are further exacerbated by social-cultural and economic blockades. Through extensive research and program development, the Crosby Lab is dedicated to improving Quality of Life in this population. Current research projects include: 1.)Engaging Parents of Children with Sickle Cell Disease and their Providers in Shared Decision Making for Hydroxyurea, 2.) SCManage: Improving Self-Management in Adolescents with Sickle Cell Disease, 3.) SCD Pain Mechanism: Examining Clinical Factors Associated With Transition for Acute to Chronic Pain and 4.)Community Health Workers and Mobile Health for Emerging Adults Transitioning Sickle Cell Disease Care (COMETS Trial).

The student will learn several skills, including survey development, program evaluation, qualitative and quantitative data analysis. Students may also have the opportunity to hone writing skills via protocol and manuscript development.

**Mentor:** Hadas Nahman-Averbuch, PhD, Postdoctoral Fellow  
Dept: Anesthesia  
Facility: CCHMC

**Project:** *Why do people feel pain differently?*

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Individuals that receive the same painful stimuli may have different experience of the stimulus. Psychological, physiological and anatomical factors can contribute to the individual differences in pain sensitivity. Identifying these factors can allow prediction of chronic pain development and treatment outcomes.

The proposed study research will determine the effect of various factors on pain sensitivity in healthy human subjects and chronic pain patients such as migraine patients. The honors student will conduct tests that evaluate the subject’s pain processing mechanisms. These tests include delivering heat, cold and pressure stimuli in paradigms that are designed to evaluate both sensitivity and ability to inhibit pain. In
addition, the student will use questionnaires to assess psychological factors such as anxiety and depression, and their interaction with pain mechanisms.

**Mentor:** Takahisa Nakamura, Assistant Professor  
Dept: Pediatrics/Endocrinology  
Facility: CCHMC

**Project:** *Role of RNA networks in the regulation of metabolism in obesity*

This project is to investigate the role of RNA networks in metabolic tissues, such as liver, and circulation and how these networks are deteriorated and induce metabolic abnormalities in obesity.

**Mentor:** Megan Narad, PhD, Postdoctoral Fellow  
Dept: Physical Medicine & Rehabilitation  
Facility: CCHMC

**Project:** *Head Injury Research Center*

The Head Injury Research Center is focused on understanding the short and long term effects of traumatic and other acquired brain injuries (e.g., brain tumors) in childhood including: behavioral functioning, attentional and executive functioning, academic performance, social functioning, and family functioning. Additional focus includes the development of interventions for children and families impacted by pediatric TBI, brain tumors, and epilepsy. These interventions include a telehealth problem solving intervention, an online parenting skills intervention, a medication trial to address attentional impairments after injury, an app based intervention to promote social participation, and the use of animal-assisted therapy to promote engagement during inpatient physical and occupational therapy. The overarching goal is to learn how interventions can improve child/family functioning following acquired brain injuries and which interventions work best for which patients.

We have a very active lab with projects in a variety of stages. A number of projects have completed data collection and findings are being summarized for publication. The animal-assisted therapy project, an intervention development project for children injured prior to the preschool years, and a parent-focused intervention development project were all recently funded and data collection will be starting soon. Additionally, we are always planning future projects and funding opportunities. Therefore, the student will have the opportunity to gain experience in a variety of projects at all stages of development including protocol/SOP development, data collection and protocol execution, data entry and management, and summarizing findings and assisting with the develop of publications and/or funding applications. Specific student activities will depend a bit on the needs of the lab at the time as well as his/her goals and interests and the type of skills they would like to learn.
**Mentor:** Md Nasimuzzaman, PhD  
Dept: EHCB  
Facility: CCHMC

**Project:** *Sickle cell anemia Pathogenesis*  
(No description at this time)

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**Mentor:** Yoshi Odaka, Research Associate  
Dept: Pediatric Ophthalmology  
Facility: CCHMC

**Project:** *Investigating Notch and mTOR pathways in hyaloid vascular regression*  
Our lab investigates development of blood vessels, how they form and regress. The study of blood vessels, vascular biology, has significant implications to human health as many disease conditions, such as retinopathies and malignant solid tumors, exhibit abnormal growth of blood vasculatures. Currently we are investigating how Notch and VEGF/mTOR signaling pathways participate in development of intraocular blood vessels in perinatal mice using extensive mouse genetics and biochemical analyses.

A student who joins the lab will be exposed to various research tools and techniques for biological inquiry and gain scientific knowledge not only in development of blood vessels but also in neuroanatomy and metabolism due to projects that other members in the lab participate.

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**Mentor:** Marla Perna, PhD  
Dept: Neurology  
Facility: CCHMC

**Project:** *Mitochondrial bioenergetics in BD*  
Bipolar disorder is a devastating mental disorder that affects roughly 3% of the population. People with Bipolar disorder experience periodic, alternating episodes of depression and mania. There are several medications that help with the symptoms of Bipolar disorder, but there is still no cure. While the cause of Bipolar disorder is unknown, more recent evidence suggests that mitochondrial function is disrupted in these people. Mitochondrial dysfunction results in insufficient ATP to support normal cellular processes in the body, and most importantly, in the brain. The focus of my research is to examine mitochondrial function in neurons and how disruption of mitochondrial respiration may lead to Bipolar disorder.

While working with me, you will have the opportunity to learn basic lab techniques including experimental design, quantitative PCR, genotyping, cell culture, and respirometry. You will also have the opportunity to learn fluorescence microscopy and how to measure mitochondrial output.
**Mentor:** Emily Pitzer, Graduate Student  
Dept: Neurology  
Facility: CCHMC

**Project:** *Developmental effects of pesticides on brain and behavior in Sprague Dawley rats*

Our lab focuses on developmental exposure to drugs or environmental compounds (i.e. pesticides) and how they affect the brain and behavior later in life. My research focuses on the effects of developmental exposure to deltamethrin (DLM), a pyrethriod pesticide which is highly prevalent in the environment. We have previously observed that exposing rats early in life to DLM results in learning and memory deficits in adulthood. In addition, we have found that developmental DLM also alters long term potentiation (LTP), which is an increase in the synaptic strength following high frequency stimulation. LTP is considered to be one of the major cellular mechanisms that underlie learning and memory. Although we have observed these behavioral and LTP changes in our developmental model the mechanism underlying these alterations is still unknown. The main focus of my project will be to elucidate the mechanism of action for DLM in a developmental model.

The student will learn many skills in the lab including drug administration and animal handling. Also, the student will learn to conduct molecular assays to test protein expression in specific brain regions particularly affected by the drug exposure. The student may also learn to conduct some behavioral assays testing learning and memory in the rodents.

**Mentor:** Samantha Regan, PhD Graduate Student  
Dept: Neuroscience  
Facility: CCHMC

**Project:** *Latrophilin 3: A Knockout Model of ADHD*

Attention deficit hyperactivity disorder is a complex heterogeneous neurodevelopmental disorder that affects 10% of children and adults in the United States. Recently, genome wide association studies have been used to investigate genes that are implicated in ADHD. Using fine mapping linkage studies in a genetically isolated population in Colombia, researchers found that the Latrophilin 3 gene is found within both children in adults that have ADHD. In our lab, we have used Crispr Cas 9 technology to delete the Latrophilin-3 gene within Sprague-Dawley rats. Previous projects with the animals have been to look at the behavioral phenotype of the animals. Currently, however, the study is looking into the behavioral effects of medications, such as ritallin, has on these animals. We are also looking into the mechanism behind the genetic knockout itself, using immunohistochemistry, RT-PCR, and various other wet lab techniques.
**Mentor:** Debora Sinner, PhD  
Dept: Neonatology and Pulmonary Biology  
Facility: CCHMC

**Project:** Molecular basis of respiratory tract formation

The goal of my lab is to understand the molecular mechanisms underlying the formation of the mammalian respiratory tract during embryogenesis and their relationship to birth defects affecting trachea and lungs. We focus on the interactions between two major components of the developing lung: the pulmonary epithelium - that gives rise to the conducting airways and the respiratory surface of the lung - and the mesenchyme - that gives rise to cartilage, muscle, connective tissue - . Cross talk between epithelium and mesenchyme is required for differentiation of pulmonary cell lineages. We are currently investigating mechanisms by which muscle and chondrocyte cells are established in developing trachea. Our experimental approaches include genetic studies using transgenic mice and in vitro cell and organ culture.

The student will investigate the role of candidate genes in cartilage and muscle differentiation of developing trachea. The student will perform molecular biology techniques including DNA and RNA isolation, PCR, cell and tissue culture, immunofluorescence, microscopy. If desire, the student will learn how to handle mice.

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**Mentor:** Sneha Sitaraman, Graduate Student  
Dept: Division of Pulmonary Biology  
Facility: CCHMC

**Project:** Alveolar type II epithelial cells in lung health and injury

We have three projects in the lab focusing to the role of alveolar type II epithelial cells in maintenance of lung homeostasis and health.

**Project 1:** We have identified a subset of type II cells in a mouse model of surfactant protein C mutation that were unexpectedly resistant to both single and repetitive doses of bleomycin. The primary focus of this project will be to identify molecular signatures for these specific subsets of type II cells under both homeostasis and conditions of lung injury.

**Project 2:** Recent reports suggest that type II cells play a critical role in shaping the lung immune microenvironment, primarily through their interaction with innate lymphoid type 2 cells. The focus of this project will be to characterize frequency and activation of immune cells from neonatal lungs using mouse models that harbor mutations in type II cells.

**Project 3:** The ubiquitin-proteasome and autophagy-lysosome systems are two major quality control mechanisms that tightly control turnover of proteins and organelles and are absolutely critical for regulating cellular homeostasis. Dysfunctional quality control systems have been associated with several disorders including chronic lung diseases. We have generated a mouse model with a conditional knock-out of a proteasome regulatory subunit that results in severe loss of type II cells leading to morbidity and lethality. The primary focus of this project will be to identify the mechanisms leading to type II cells loss and the consequent implications for lung disease.
Students will learn immunohistochemistry and immunofluorescence, microscopy and image analysis, Western blot, and ELISA.

**Mentor:** Hannah Stewart, PhD, Postdoctoral Research Fellow  
Dept: Communication Sciences Research Center  
Facility: CCHMC

**Project:** *Learning to listen in noise: A double-blind randomized control trial of OpenSound Navigator*

Noise impairs speech understanding. Children with hearing loss have poorer aided speech reception in noise than children with normal hearing. If speech loudness in noise is inadequate, it impacts negatively on the brain processing of speech, including encoding into language, memory and learning. A recent study investigated the immediate benefit of a noise reduction system (OpenSound Navigator, OSN) in hearing aids on speech-in-noise performance in children with hearing loss. OSN improved speech understanding in uniform, multi-talker noise environments. This result was particularly important for children because spontaneous speech may come from any direction in typical learning environments that tend to be multi-talker, and because children do not always turn in the direction of target speech.

In this study we extend the investigation to the longer-term (6 to 8 months) benefits of OSN and to a much wider assessment of the benefits of OSN, both before and after longer-term experience. The main hypothesis is that longer-term experience of children with OSN will promote learning, both of the optimal benefit to be gained from the noise reduction and listening tactics that would promote that learning. Short-term experience and baseline testing of outcome measures will also be measured during a preliminary phase of the project. Outcome measures include several variants of speech-in-babble noise perception (e.g. audiovisual speech, speeded speech, reverberance, directional cues), assessment of vocabulary growth and novel word learning ability. This study also extends the behavioral project into neuroimaging using MRI to assess cortical structure, function and connectivity associated with changing speech perception and learning in children wearing hearing aids.

The honors student will perform a number of tasks depending on their interest and study needs. Tasks include, but are not limited to contacting and scheduling participants, data collection during study visits (both behavioral and MRI), data entry and analysis.

**Mentor:** Diego Perez-Tilve, PhD  
Dept: Internal Medicine  
Facility: UC Reading Campus

**Project:** *Neural mechanisms involved in the prevention of obesity by time-restricted feeding*

More than one third of U.S. adults are obese. Obesity and related co-morbidities are a leading cause of preventable death and result in nearly 20% of the annual medical spending in this country. Overeating, often due to easy access to highly caloric palatable diets, is the main contributor to obesity. Those diets impair the function of specific circuits in the brain, including the Melanocortin System, necessary for the appropriate control of food intake. Like humans, mice with free access to a high fat diet gradually increase their food intake and become obese.

Interestingly, preventing normal mice from eating during the sleep period (“night eating” in humans) is sufficient to prevent those mice from overeat and from becoming obese. We have found that mice lacking a gene necessary for the function of the Melanocortin System, namely the Melanocortin 4 Receptor
“knockout” mice, continue to overeat and develop obesity, even when not allowed to eat during the sleep period. However, the site of Mc4r action in the brain necessary for the prevention of obesity following this time-restricted feeding is unknown. We hypothesize that this site are the neurons in the Paraventricular Nucleus of the Hypothalamus (PVN), known to be critical for the control of food intake. In this project, we will test this hypothesis by comparing the effect of time-restricted feeding in mice lacking or not the expression of Mc4r specifically in those neurons. To this end, we will perform stereotaxical surgery followed by microinjections to deliver an attenuated adenoviral vector carrying a reporter gene or a gene encoding the enzyme cre-recombinase packed into the PVN of mice. Those mice carry a genetically modified Mc4r gene locus that will be inactivated by the action of cre-recombinase.

The roles of the student researcher will include: the discussion of the experimental design, including the rationale for the inclusion/exclusion of specific experimental groups and the familiarization with the genetic mechanisms involved in the generation of these neuron-specific “knockout” mice; stereotaxic delivery of vectors; metabolic characterization of the mice throughout the duration of the experiment; neuroanatomical validation of the gene deletion using immunohistochemistry; statistical analysis of the results and writing of a brief summary describing and discussing the results. These tasks will be performed under the supervision of the Principal Investigator and other members of the laboratory.

Mentor: Durgesh Tiwari, Postdoctoral Fellow
Dept: Neurology
Facility: CCHMC

Project: Investigating Kv4.2 protein complex in a mouse model of Epilepsy

Epilepsy is characterized by increased nerve cell activity in brain causing excitability which leads to seizures. As per Epilepsy foundation, 65 million people around the world are currently suffering with the condition and 150,000 new cases are diagnosed every year in the United States. At present the available therapies are able to help the condition by controlling brain excitability, but still the disease cannot be cured. Moreover, these treatments do not work in one third of patients which potentially is due to lack of understanding of mechanisms regulating excitability and seizures in the brain. Our lab is focused on investigating a potassium channel protein complex Kv4.2, involved in controlling excitability and its potential in regulating seizures in Epilepsy. The student in the project will investigate the expression of this protein and its subunits in the control mouse brain tissue using immunohistochemistry and western blotting techniques. Also, the protein will be characterized in a knockout mouse model of Kv4.2 to compare the expression and this mouse model will be characterized for their genotypes using polymerase chain reaction.

Mentor: Andrew VonHandorf, Graduate Student
Dept: Environmental Health/EGMT
Facility: UCCOM

Project: Effects of Hexavalent Chromium on Gene Transcription Associated With AP-1 Activation

Hexavalent chromium (Cr(VI)) compounds are well-documented respiratory carcinogens widely used in a variety of industrial processes ranging from electroplating to textile dyes. Though natural forms exist, the majority of chromate exposure is the result of anthropogenic use and occurs predominantly through inhalation, ingestion, and dermal contact with widespread pollution and imperfect waste disposal resulting.
in broad, general populations potentially being exposed to chronic, low doses of these compounds through drinking water and food consumption. However, the adverse human health outcomes following long-term ingestion of Cr(VI) are not as well understood and the mechanisms through which Cr(VI) elicits these endpoints require further elucidation.

Our research is focused on elucidating Cr(VI)’s disruptive effects on regulatory mechanisms required for maintaining normal gene transcription. Using novel sequencing methods to provide insight into the changing accessibility of chromatin, we have found that two major DNA binding proteins, CCCTC-Binding Factor (CTCF) and Activator Protein-1 transcription factor (AP-1), exhibit strong enrichment in regions that are affected compared to controls. In this project, we would like to study the interactions between Cr(VI) and AP-1-associated transcriptional changes in greater detail to determine gene profiles which may be susceptible targets for chromium.

As a project, this provides an excellent opportunity for a student to build strong foundations in several molecular methods related to in vitro studies and gene transcription. The student is an integral team member for this project and will be responsible for validating the expression of target genes identified from the sequencing data. Expected techniques include RNA extraction and quality validation, reverse transcription to cDNA, and measuring gene expression using Real-Time PCR (RT-PCR).

Mentor: Jingjing Wang, Postdoctoral Fellow
Dept: Department of Environmental Health
Facility: UCCOM

Project: Gene-environment interaction (GxE) in dioxin’s developmental toxicity in eyelid closure

Many factors are known to be important in disease causation and these can include an individual’s age, gender, genetic make-up and environmental factors. In other words some individuals are more susceptible while others are less susceptible. The studies in our lab, provide critical insights into the relationships between environmental exposure, biological pathways and disease susceptibility, and facilitate mechanistic-based risk assessment and prevention guidelines to protect vulnerable individuals in a public health context. Most biological phenotypes are the result of a complex interplay between genes and environment, but despite considerable effort to elucidate the biochemical basis of the combined effect, a mechanistic understanding of gene-environment (GxE) interactions is lacking. The primary reason for this lack is the inadequacy of the current research tools available to incorporate environmental factors into genetic studies. This has limited our ability to accurately predict the risks of exposure and effectively translate genetic information into health benefits through environmental protection and modification. To address this challenge and overcome the consequent scientific weakness, we propose to use a mouse model developed in our laboratory, based on embryonic eyelid closure. The eyelid closure defect is genetically and morphologically tractable and accessible, offering an excellent model to study the genetic conditions that modify dioxin susceptibility. Investigating the relationships of GxE is not only important for recognizing the multifactorial etiology underlying disease, but provides an intriguing paradigm to understand the mechanisms of epithelial sheet migration, important for embryonic development, wound healing, tissue regeneration and tumor metastasis.

The newcomer student will work on eyelid development in vitro model. During this period he/she will learn different basis tools and techniques (like western blotting, real time PCR, immuno-cytochemistry etc.), routinely used in the field of cell and molecular biology research.
Mentor: Angela White, PhD Candidate  
Dept: Neurology  
Facility: CCHMC

Project: *p110β Selective Inhibition In A PTEN-deficient Mouse Model For Autism*

Autism affects 1 in 45 children in the US. Patients are from a diverse set of race, gender, and social backgrounds. Patients suffer from communication and social problems, as well as restrictive and repetitive behaviors. It is known that a subset of patients have a mutation in Phosphatase and Tensin homolog (PTEN). These patients generally suffer from macrocephaly and seizures in addition to the general autism clinical signs. The PTEN protein is known to negatively regulate the cell signaling pathway, PI3K. Studies in cancer with PTEN mutations have shown that the inhibition of p110β (a component of PI3K) inhibits cancer growth and suggest this strategy may yield less side effects than other PI3K pathway inhibition therapies. In this project, we will assess if p110β inhibition would effectively treat autism in patients with PTEN mutations.

The first aspect of this project is utilizing a mouse model that has PTEN-deficient neurons, leading to an autism and seizure phenotype. We will give mice a proprietary p110β inhibitor and assess behavior and seizure frequency/duration in these mice as compared to mice treated with GSK6A diluent only.

The second aspect of this project will assess how cell signaling is altered when PTEN-deficient neurons are exposed to p110β inhibition. Additionally, we will assess how the proteins in the PI3K pathway, including p110β, interact with one another in PTEN-deficient conditions.

A compound closely related to our p110β inhibitor is currently under evaluation for cancers which are PTEN-deficient. The repurposing of this compound for autism could be advantageous, as we benefit from insight gleaned from cancer biology.

Mentor: Martin Weichert, PhD, Postdoctoral Fellow  
Dept: Department of Pathology and Laboratory Medicine  
Facility: UCCOM

Project: *What are the molecular processes that turn the mold Aspergillus fumigatus into a human-pathogenic microbe?*

The mold or filamentous fungus *Aspergillus fumigatus* is a microorganism that is globally distributed in the environment. It forms numerous spores, tiny reproductive units that develop into thread-like cells which in turn make even more spores. Every day hundreds to thousands of spores enter the lungs of a human being or animal, where they encounter antimicrobial activity and are usually removed by immune cells. Immunocompromised individuals, however, are susceptible to a life-threatening infectious disease called Aspergillosis, in which the fungal cells rapidly adapt to the host environment and damage tissues and organs.

To better understand infections caused by *A. fumigatus*, Dr. Askew’s research group is interested in the high adaptability of this microbe to stress conditions by using methods of molecular and cell biology, gene expression analyses, microscopy and animal infection models. Recent studies suggest a link between a stress response pathway at the endoplasmic reticulum (ER) in the fungus and signaling processes that involve calcium ions. In the student project, gene knock-out mutants of *A. fumigatus* that lack calcium ion
channels will be characterized for their ability to withstand ER and calcium-related stress. Moreover, live-cell imaging of fluorescently labeled calcium ion channels will be used to further explore calcium signaling in the fungus. These studies aim to expand our knowledge about the molecular features that turn *A. fumigatus* into such a potent, medically relevant human-pathogenic species.

**Role of the student researcher:**

The student researcher will learn essential methods of microbiology and mycology, such as preparing solutions and media, performing microbial experiments using sterile techniques, isolating and growing fungal cells, comparing the growth of different strains under a variety of culture conditions, and using brightfield and fluorescence microscopy. He or she will get insight into primary and secondary literature relevant for the project, understand the principles of gene expression and techniques of gene manipulation, and comprehend the importance of basic research in human medicine. The project will enable the student researcher to formulate and test a scientific hypothesis, design experiments and perform them with precision and reproducibility, critically evaluate data and draw objective conclusions, present the data in a comprehensible manner, and propose a set of future directions for the project. Overall, the student researcher will be qualified to perform research in a laboratory of microbiology and/or molecular biology.

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**Mentor:** Danny Wu, PhD, Assistant Professor  
Dept: Biomedical Informatics  
Facility: UCCOM

**Project:** *Understanding Clinical Workflow Using Time and Motion Studies*

This project aims to understand clinical workflow and its bottlenecks using time and motion (T&M) study. Dr. Wu and his PhD mentors have developed a systematic approach and a tablet-based application to support the conduction of T&M studies. The student researcher will learn the approach and be trained to use the application to observe clinical workflow and activities in a field at UC Health.

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**Mentor:** Xueheng Zhao, PhD  
Dept: Pathology and Laboratory Medicine  
Facility: CCHMC

**Project:** *Metabolic disease study with metabolomics approach*

Metabolites play critical roles in disease development and prognosis. Monitoring their dysregulation can reveal novel insights into genetic and environmental influences. Mass spectrometry is the major analytical instrument for metabolite analysis and is able to analyze wide array of human and animal samples. This approach becomes indispensable in addressing complexity in disease and health. Metabolomics is an ideal platform to investigate patient response to certain interventions such as treatment, diet, to reveal changes in metabolites and to shed light on intervention mechanisms at a cellular level. The data generated from mass spectrometry based metabolomics are usually complex and require bioinformatics tools to deconvolute for statistical and pathway analysis. Our research investigates disease pathogenesis using untargeted and targeted metabolomics platforms.
The honors student will be able to involve in different aspects of the metabolomics research in our lab depending on his/her research interests. Several metabolomics projects currently undergoing include diet intervention studies for various diseases, new method development for clinical application. During the project students will learn metabolomics sample preparation, instrumental analysis, and assist with bioinformatics data analysis. Students may also spend time learning chromatography and mass spectrometry techniques depending on time and interest. Cincinnati Children's will require you to provide your vaccination records and to be up to date with your immunizations.