PARKER B. FRANCIS
FELLOWSHIP
PROGRAM

Class of 2011

The Parker B. Francis Fellowship Program provides career development support to M.D. and Ph.D. scientists embarking on careers in clinical, laboratory or translational science related to Pulmonary, Critical Care and Sleep Medicine. Funding is awarded for three years to fellows working with experienced mentors in diverse areas of research related to lung disease.

Since 1976 the Francis Family Foundation through the PBF Fellowship Program has supported more than 780 new investigators. These fellows have made remarkable discoveries working in laboratories and clinics in North America and throughout the world. They have published their work in the best-known scientific and medical journals, and their research has improved patient care and identified preventive strategies to decrease the incidence of pulmonary disease, disability and death.

Many of the individuals who have received Parker B. Francis Fellowships have become prominent investigators and international leaders in pulmonary research.

We are pleased to provide support for the following new investigators who make up the Parker B. Francis Fellowship Class of 2011.

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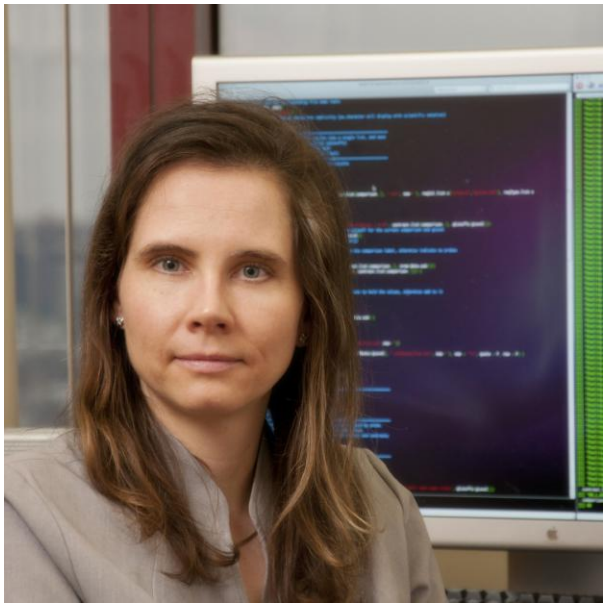
Annerose Berndt, D.V.M., Ph.D.



Mentor: Steven D. Shapiro, M.D.
Institution: University of Pittsburgh

Genetic determinants of the common origins of lung cancer and COPD in inbred mice

Chronic Obstructive Pulmonary Disease (COPD; i.e., emphysema or chronic bronchitis) and lung cancer are major leading causes of death in the U.S. and worldwide. In Western societies, both diseases are mainly caused by cigarette smoking. While some smokers develop COPD others develop lung cancer. Interestingly, smokers who get COPD are at high risk for lung cancer. This suggests that genetic factors play a role in the development of both diseases and may be responsible for the increased lung cancer risk in COPD. In this study we will identify genetic factors responsible for the higher risk for lung cancer in COPD, which will ultimately help to assess risk factors and to develop individualized preventives and therapeutics.

Taylor S. Cohen, Ph.D.

Mentor: Alice Prince, M.D.
Institution: Columbia University

Type I IFN signaling in airway epithelial immune response

The type 1 interferon signaling pathway has been shown to be involved in the host response to numerous bacterial pathogens and our preliminary data suggest that another major human pathogen *Pseudomonas aeruginosa* also induces this pathway. We propose to determine how this bacteria activates signaling, elucidating the mechanism though which the bacterial product LPS is internalized and trafficked to its receptor, as well as how cellular acidity regulates signaling. We will use a pneumonia model of *P. aeruginosa* infection to determine the immune cell populations responsible for bacterial clearance. Understanding of how the epithelium regulates the immune response to *P. aeruginosa* will be directly applicable to treatment of patients with ventilator induced pneumonia and cystic fibrosis whom are commonly infected with this pathogen.

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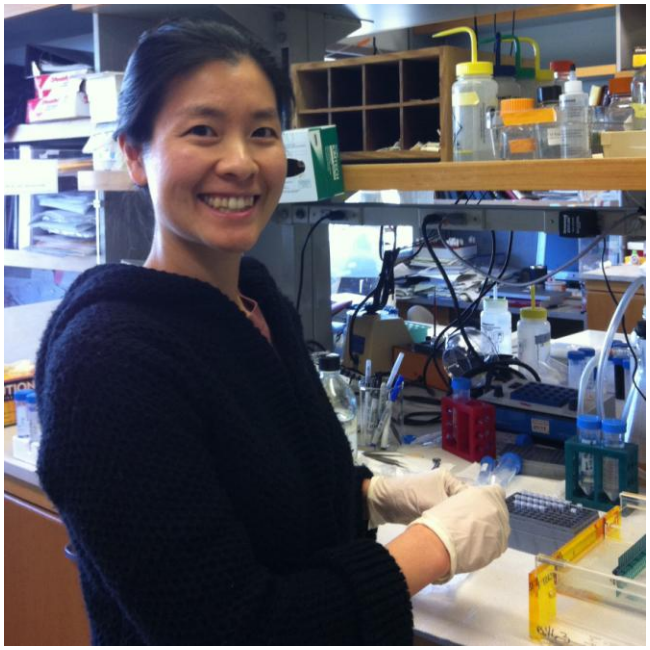
Molly F. Franke, Sc.D.

Mentor: Megan B. Murray, M.D.
Institution: Harvard University

Modifiable risk factors for tuberculosis disease in children

Tuberculosis disease (TB) is an important source of morbidity and mortality among children living in resource-poor settings. Easily implemented preventive strategies are urgently needed, particularly in areas with high levels of anti-TB drug resistance, where isoniazid preventive therapy is likely to be less effective. Preventing TB in children is especially important because they traditionally have been under-represented in TB research, and therefore may not always benefit from advances in TB treatment and prophylaxis. We aim to identify modifiable risk factors for TB in children. We hypothesize that parasitic helminth infection, second-hand smoke exposure in the home, and certain patterns of dietary intake are associated with an increased risk of TB. If so, interventions targeting these factors may prevent TB-related morbidity and mortality.

Christin S. Kuo, M.D.



Mentor: Mark A. Krasnow, M.D., Ph.D.
Institution: Stanford University

Identifying pulmonary neuroendocrine cell progenitors in development and injury

Pulmonary neuroendocrine cell abnormalities are detected in many pediatric and adult respiratory diseases, including sudden infant death syndrome (SIDS), neuroendocrine cell hyperplasia of infancy (NEHI), and small cell cancer, a highly aggressive and metastatic form of lung cancer. Neuroendocrine cells form innervated clusters of cells within the airways and produce secreted signals that may regulate physiologic respiratory responses. Despite their involvement in diverse lung diseases, little is known about their normal development and maturation. Using both genetic and imaging methods, we are identifying neuroendocrine cell progenitors to understand how they may contribute to disease. Understanding this process will ultimately lead to new therapies for targeting excessive cells associated with respiratory disease.

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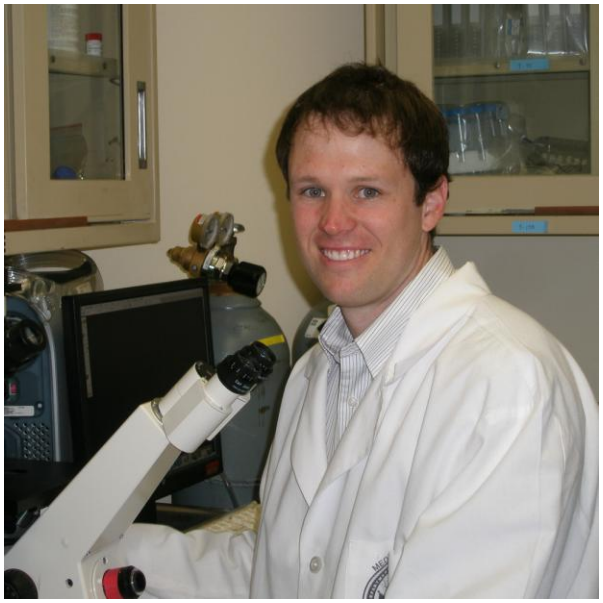
Michael J. LaFamina, M.D.

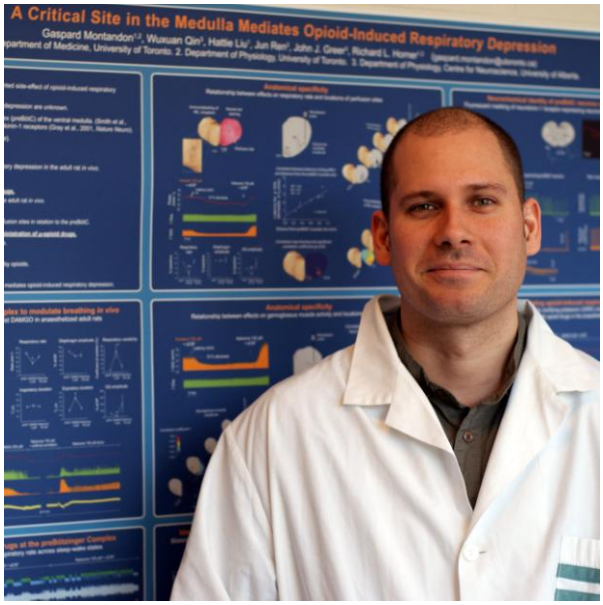


Mentor: James A. Frank, M.D.
Institution: UCSF

Claudin-18 regulation of alveolar epithelial barrier function

Acute lung injury is a common cause of respiratory failure and mortality in critically ill patients. Flooding of the lung with fluid is a hallmark of this disease. Tight junctions are protein complexes that limit the movement of fluid between cells into the lung. Claudin-18, a tight junction protein with high expression in the lung and altered function in the setting of lung inflammation, may be critical to flooding of the lung in this disease. This study will determine the importance of claudin-18 in mouse and human lung injury models and will examine the mechanism of altered claudin-18 function. As there remain no specific pharmacologic therapies for this devastating disorder, an improved understanding of tight junction regulation in the lung is urgently needed.

Gaspard Montandon, Ph.D.



Mentor: Richard L. Horner, Ph.D.
Institution: University of Toronto

Mechanisms mediating opioid-induced respiratory depression

Opioid analgesics such as morphine or fentanyl are widely used clinically to reduce pain, but present the unwanted side-effects of respiratory depression that can be lethal with overdose. My research proposes to elucidate, for the first time, the still-unknown mechanisms mediating respiratory depression with opioid drugs. Using unique new approaches to investigate neurotransmission *in vivo*, this research will identify the sites of action in the brain where opioid drugs act to cause suppression of breathing during sleep. I will also elucidate the cellular mechanisms mediating respiratory depression with opioids which is critical to develop new pharmacological approaches to prevent or reverse the secondary effect of life-threatening respiratory depression without reducing the beneficial analgesic properties of opioids.

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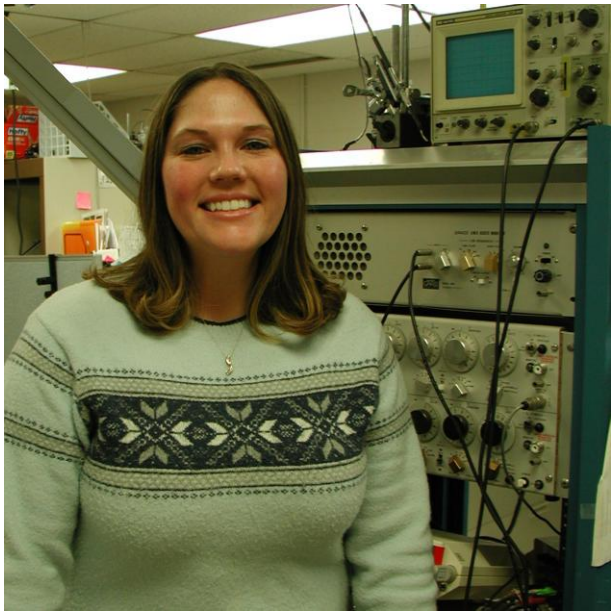
Nicole L. Nichols, Ph.D.



Mentor: Gordon S. Mitchell, Ph.D.
Institution: University of Wisconsin-Madison

Novel strategies to improve respiratory function in a rat model of ALS

ALS is a devastating disease, leading to paralysis and death from ventilatory failure. Our goal is to preserve or restore respiratory function in a rat ALS model ($SOD1_{G93A}$ rats). We will attempt to preserve respiratory motor neuron survival using stem cell based therapies; we hypothesize that stem cells, by becoming healthy astrocytes, repair the environment and improve respiratory motor neuron survival. We will enhance respiratory function by inducing plasticity with acute intermittent hypoxia, increasing contributions from surviving motor neurons and preserving ventilatory capacity. Treatment combinations may be more effective yet. This project may lead to novel therapies that extend and improve life for ALS patients by preserving ventilatory function. These approaches may also work in other motor neuron pools or neurodegenerative diseases.

Angela J. Rogers, M.D., M.P.H.

Mentor: Scott T. Weiss, M.D.
Institution: Brigham and Women's Hospital

Copy number variation and airways obstruction in asthma

Asthma affects more than 20 million Americans. It is an obstructive lung disease whose severity is measured in terms of lung function. Both asthma and lung function are influenced by genetics, but only a small number of genes that cause asthma have been discovered. Copy Number Variants (CNV), largescale segments of deleted or duplicated DNA, are now recognized to be much more important in human genetics than previously imagined. CNVs across the genome can now be accurately tested; such genomewide testing has never before been done in people with asthma. We will test asthmatic children and find CNVs that affect lung function. This has high potential to improve our understanding of asthma and airways obstruction, and to identify new targets for asthma therapies.

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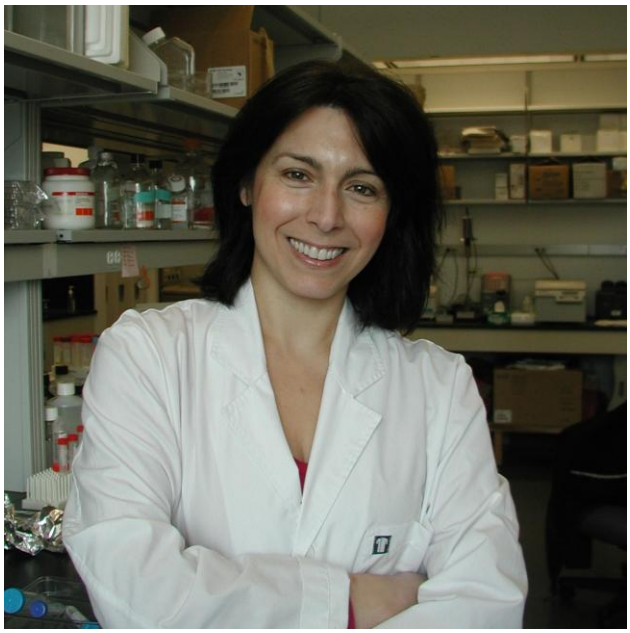
Renat Shaykhiev, M.D., Ph.D.

Mentor: Ronald G. Crystal, M.D.
Institution: Weill Cornell Medical College

Smoking-induced EGF-dependent reprogramming of airway basal cell function

Early changes associated with the development of smoking-induced diseases, e.g., COPD and lung cancer, the two commonest causes of death in U.S., are often characterized by abnormal airway epithelial differentiation. Airway basal cells (BC) are stem/progenitor cells necessary for generation of differentiated airway epithelium. Based on our preliminary observations that epidermal growth factor receptor, known to regulate airway epithelial differentiation, is enriched in BC and its ligand EGF is induced by smoking, we hypothesized that smoking-induced EGF alters the ability of BC to form normally differentiated airway epithelium. To test this, airway BC will be purified using a cell-culture method established in our laboratory and responses to EGF will be analyzed using genome-wide microarrays and an *in vitro* air-liquid interface model of airway epithelial differentiation.

Sophie Toya, M.D.



Mentor: Asrar B. Malik, Ph.D.
Institution: University of Illinois at Chicago

VEGF signaling and endothelial adhesion of stem cell-derived progenitors

Acute lung injury is a form of severe lung disease which occurs in patients with severe infections and might lead to respiratory failure or even death. We have found that differentiated cells derived from stem cells may be protective against acute lung injury in an animal model. These cells are only protective when they can stick firmly (adhere) to the endothelial cells of the animal vessels. Our studies will further explore ways to improve the ability of these differentiated cells to better adhere to the endothelial cells and thus greatly improve their capacity to heal the injured lung. The results of these studies may provide an important therapeutic tool for a severe form of lung disease for which there is no etiologic treatment so far.

Class of 2011

Curtis H. Weiss, M.D.

Mentor: Jacob I. Sznajder, M.D.
Institution: Northwestern University

Novel quality improvement clinical decision support in the Intensive Care Unit

Physicians in the intensive care unit (ICU) must integrate a tremendous amount of data in order to make effective medical decisions for their patients. Clinical decision support (CDS) tools that assist in this process are not yet streamlined or optimized for issues related to quality improvement or for the complexity of the ICU. This study aims to apply the results of preliminary research to create a new clinical decision support tool focusing on the use of empirical antibiotics (antibiotics administered to patients for strongly suspected, but not confirmed, infections). This study is highly relevant to public health as it will establish an efficient, generalizable, and exciting new approach to quality improvement decision-making for critically ill patients.