



P A R K E R B . F R A N C I S
F E L L O W S H I P
P R O G R A M

Class of 2012

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 790 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 leading 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 2012.

Class of 2012

Megan N. Ballinger, Ph.D.



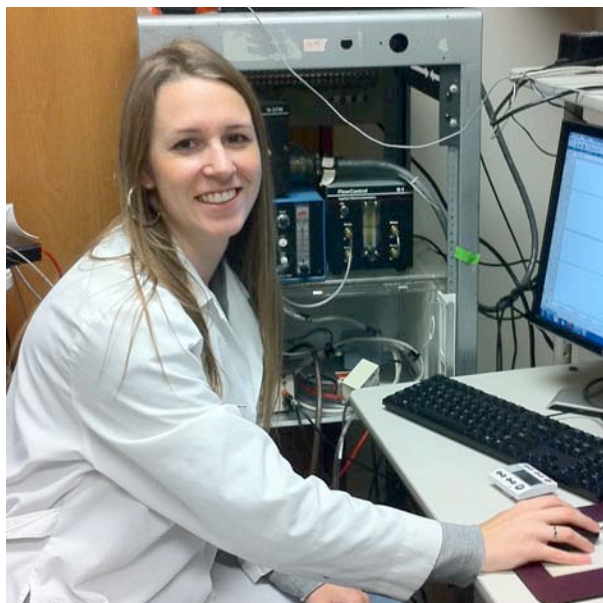
Mentor: Theodore J Standiford, M.D.

Institution: University of Michigan

The role of IRAK-M in regulating hyperoxic injury

Oxygen is the most prescribed drug on the market today. However, despite the therapeutic benefits that supplemental oxygen provides, mechanically ventilated patients suffer long-term side effects, such as increased incidence of respiratory failure and enhanced susceptibility to lung infections. Thus, additional research is needed to understand the mechanism by which supplemental oxygen therapy causes oxidant damage. Our works shows a novel mechanism by which the protein, IRAK-M, limits the early generation of antioxidants leading to decreased lung injury after oxygen exposure. We show that IRAK-M, which plays an important role in shutting down inflammation, can also inhibit the induction of antioxidants. However, additional research is needed to further elucidate how IRAK-M inhibits lung injury as a result of supplemental oxygen therapy.

Andrea E. Corcoran, Ph.D.



Mentor: Eugene E. Nattie, M.D.

Institution: Dartmouth College

Effects of brainstem serotonin manipulations on hypoxic responses in neonates

Sudden Infant Death Syndrome (SIDS) is the leading cause of death in infants. Examination of brainstems from SIDS cases show abnormalities in one of the brain's messaging systems: the serotonin system, which is involved in breathing, temperature and heart rate control as well as responding to low oxygen (implicated in SIDS deaths). We will use two rodent models to further understand the role of serotonin in responding to low oxygen: a genetic mouse where we can "switch off" serotonin cells with a simple injection, and rat pups born to mothers fed a poor diet (resulting in lower serotonin levels). We will expose these young rodents to different levels of oxygen and assess their breathing and heart rate responses.

Class of 2012

Mai K. ElMallah, M.D.



Mentor: David D. Fuller, Ph.D.
Institution: University of Florida

Upper airway gene therapy in a mouse model of Pompe disease

C Pompe Disease is a genetic disease that affects the muscles and central nervous system (CNS). Children with this disease have a weak diaphragm and upper airway dysfunction and often need a tracheostomy tube and become dependent on a ventilator for breathing. The upper airway problems include a large, weak tongue which results in obstructive sleep apnea, difficulty controlling secretions, difficulty feeding, problems with speech, and aspiration. These problems occur because the tongue and the CNS area controlling the tongue is affected. No treatment currently exists for the upper airway pathology of Pompe Disease. This research will help us better understand the mechanisms of CNS pathology involved in this disease and the role of gene therapy in treating the CNS and muscular component of the upper airway problems.

Daniel C. Files, M.D.



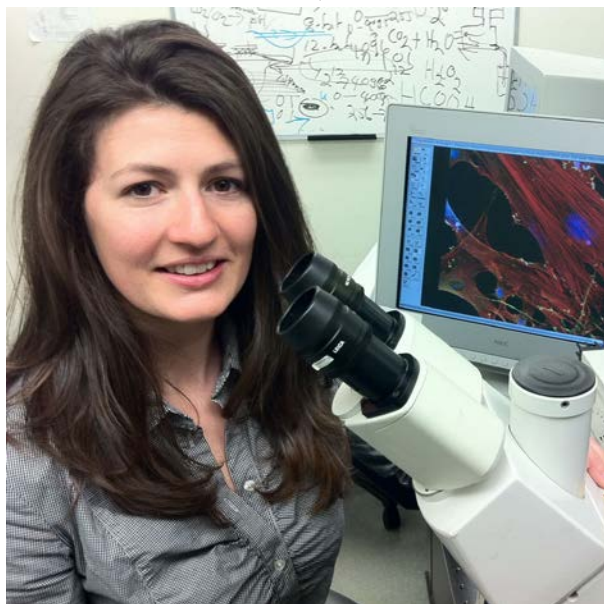
Mentor: Osvaldo Delbono, M.D.
Institution: Wake Forest University

The role of MuRF1 in acute lung injury-induced skeletal muscle wasting

Acute lung injury (ALI) is an illness affecting 200,000 Americans per year. Research has shown that severe weakness of the arm, leg and breathing muscles contributes to ALI associated disability and death. The proposed studies are focused on understanding how ALI causes muscle weakness. We use a mouse model of ALI by instillation of bacterial components into their lungs. We follow the function of the lungs and muscles over time and use laboratory techniques to determine how the muscles of these mice become weak. We will also be taking samples of muscles from patients with ALI in order to add relevance to our findings. By understanding the processes of ALI induced muscle weakness, we hope to learn how to prevent or treat this condition.

Class of 2012

Tillie-Louise Hackett, Ph.D.



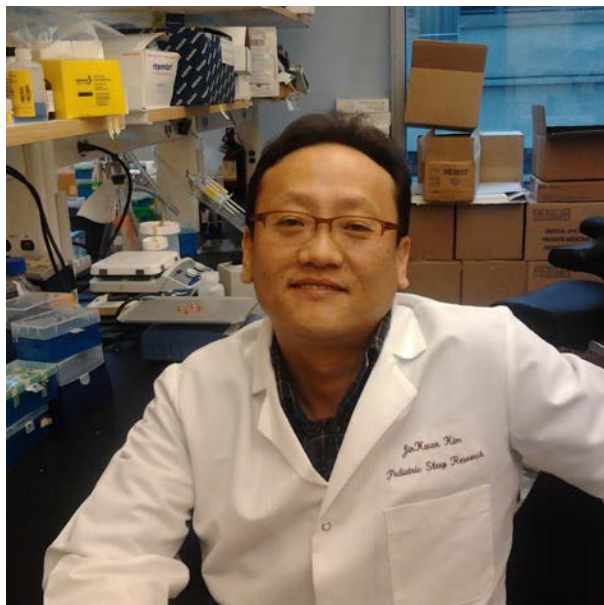
Mentor: James C. Hogg, Ph.D.

Institution: University of British Columbia

Angiotensin II-mediated TGF β 1 signaling in the pathogenesis of COPD

Chronic obstructive pulmonary disease (COPD) is the 3rd leading cause of death in the US, causing one death every four minutes, of which 9 out of 10 are related to smoking. COPD patients have difficulty breathing as their airways – the tubes that carry air in and out of the lung - become partially blocked. Importantly, there are no cures for COPD. The structural cells of the airway called epithelial cells and fibroblasts respond to smoke exposure by promoting inflammation and thickening of the airways, termed fibrosis. Our research is focused on how these cells promote fibrosis by release of Angiotensin-II a molecule also important in heart and kidney fibrosis. With this knowledge medications used for heart and kidney disease could be used to treat COPD.

Jinkwan Kim, Ph.D.



Mentor: David Gozal, M.D.

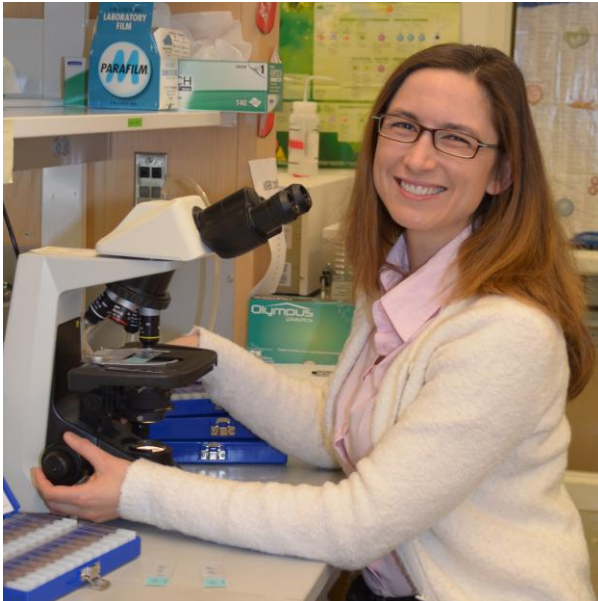
Institution: University of Chicago

T regulatory cells and insulin resistance in a murine model of sleep apnea

Obstructive sleep apnea (OSA) is a highly prevalent disorder that is associated with obesity and currently affects as many as 18 million individuals in the United States alone. OSA promotes the risk of insulin resistance and may induce or exacerbate weight gain. The recent discovery indicating that special lymphocytes called T regulatory cells (Treg) play a mechanistic role in obesity and insulin resistance prompted the hypothesis that the multiple and recurring arousals from sleep that characterize OSA may alter Treg populations via increased oxidative stress, and thus facilitate the metabolic and obesogenic consequences of OSA. Confirmation of such mechanistic pathways will open the way for novel therapies aiming to reduce the prominent metabolic morbidity of OSA.

Class of 2012

Tereza Martinu, M.D.

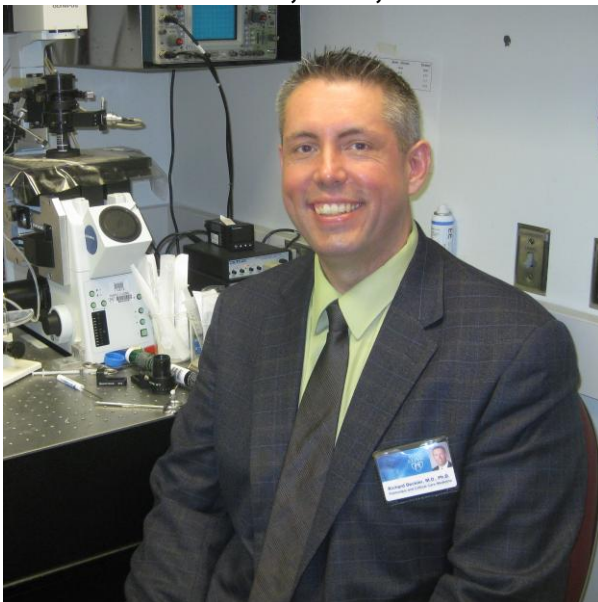


Mentor: Scott M. Palmer, M.D.
Institution: Duke University

Role of dendritic cells in pulmonary graft-versus-host disease

Pulmonary graft-versus-host disease (GVHD) occurs in up to 50% of bone-marrow-transplant (BMT) patients and can lead to progressive and fatal lung inflammation and scarring. Research shows that inhaled infections and toxins may trigger pulmonary GVHD. We have developed a mouse model of pulmonary GVHD potentiated by an inhaled bacterial toxin and have further identified increased recruitment of inflammatory dendritic cells (DCs) into the lungs of these mice. We hypothesize that inflammatory DCs cause pulmonary GVHD by causing accumulation of T cells in the lung. We will study the effect of DCblockade on different T cell processes in our model. This study will show exactly how and to what extent DCblockade can decrease pulmonary GVHD and whether this strategy may prevent pulmonary disease in BMT patients.

Richard A. Oeckler, M.D., Ph.D.



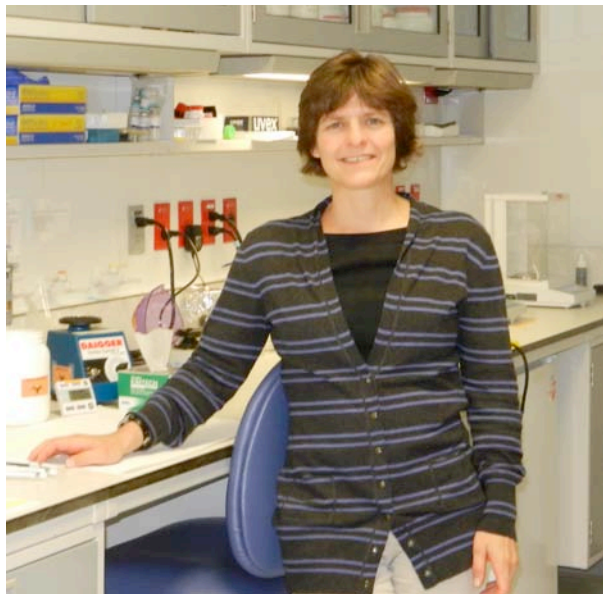
Mentor: Rolf D. Hubmayr, M.D.
Institution: Mayo Clinic, Rochester

Hypercapnic modulation of plasma membrane repair in the ventilator-injured lung

Although a lifesaving intervention in the critically ill patient, mechanical ventilation may result in ventilator-induced lung injury (VILI), a potentially preventable hospital-acquired condition responsible for 74,000 deaths each year in the U.S. alone. Central to VILI is the wounding of lung cells during a delivered breath. Lung protective ventilator strategies often lead to increased carbon dioxide (hypercapnia), and hypercapnia alters the repair rate of wounded cells through a pH-sensitive, but otherwise unknown mechanism. This study attempts to discover this mechanism by targeting key pH-sensitive mediators of the cellular repair machinery. By understanding how CO₂/pH controls the repair process, the proposed studies will lay the groundwork for future translational approaches with the goal of prevention or effective treatment of VILI in the clinical setting.

Class of 2012

Sarah L. Sayner, Ph.D.



Mentor: Troy Stevens, Ph.D.

Institution: University of South Alabama

Bicarbonate transporters are required for AC10-induced endothelial barrier disruption

Endothelial cells line the inside of blood vessels and form the pulmonary endothelial barrier. The integrity of this barrier is critical to maintain efficient gas exchange. Signaling compartments exist within cells such that where a signal originates affects endothelial barrier integrity. Cyclic AMP signals generated at the periphery of the cells strengthen the pulmonary endothelial barrier while cAMP signals made in the cytosol disrupt the barrier. This project examines the role of bicarbonate transporters in permitting bicarbonate influx into the cytosol. Once within the cytosol, bicarbonate activates a cytosolic enzyme capable of generating cytosolic cAMP. Endothelial cells are continuously exposed to bicarbonate, which can be elevated in certain pathologies but currently we are unclear how this bicarbonate affects endothelial barrier integrity.

Damian L. Turner, Ph.D.



Mentor: Donna L Farber, Ph.D.

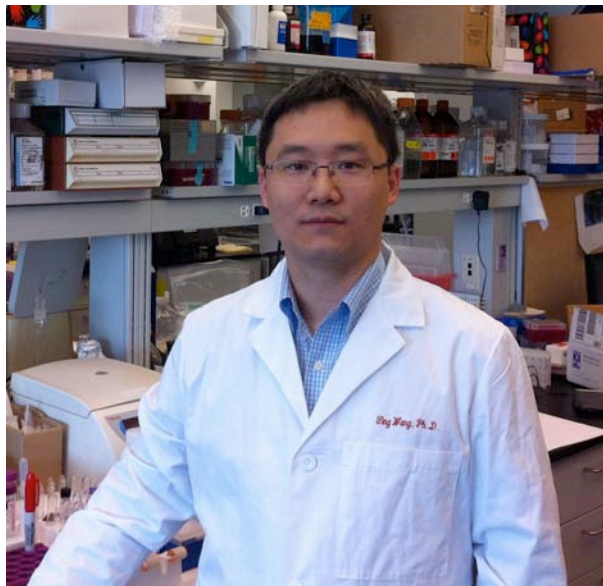
Institution: Columbia University

Resident and recruited memory CD4 T cells in respiratory immunity and pathology

The respiratory immune system, which protects the body from inhaled pathogens, often causes deleterious effects on lung tissue. In many human diseases, the resulting immune-mediated damage disrupts normal lung function and accounts for much of the morbidity and mortality seen with viral and bacterial pneumonias. We found that T cells that permanently reside within the lung protect against infection without causing damage to lung tissue, while T cells recruited from lymphoid reservoirs fail to control infection and cause greater tissue damage. This study aims to better understanding the dichotomy between the two populations, with the intent to improve current treatment options for inflammatory lung disease. This study will provide tools to enhance immunity to respiratory pathogens and also ways to prevent immune cell-mediated lung damage.

Class of 2012

Ting Wang, Ph.D.



Mentor: Joe G.N. Garcia, M.D.

Institution: University of Illinois at Chicago

Mechanisms of particulate matter-induced cardiac arrhythmias

Exposure to ambient particulate matter air pollution (PM) worsens a variety of cardiovascular diseases, including heart failure and can lead to the development of fatal arrhythmias. We will investigate mechanisms of PM-mediated cardiac arrhythmias in mouse models. We propose that PM toxicity involves lung vascular leakage, autonomic dysfunction, and heart ion channel dysregulation. The presence of heart failure is a key predisposing factor for these adverse effects of PM and contributes to the cardiac arrhythmias induced by PM.