



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 2013

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 800 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 2013.

Class of 2013

Vikas Anathy, Ph.D.



Mentor: Yvonne Janssen-Heininger, Ph.D.

Institution: University of Vermont

Influenza virus hijacks host cells' unfolded protein response

Recent reports demonstrate that the influenza virus has developed resistance to the widely used anti-influenza drug, "Tamiflu". Thus there is a need for identifying new drug targets and strategies. These studies propose to use a new strategy to prevent the spread of influenza within the lung by inhibiting host cell proteins (instead of viral proteins) in a specialized structure of the lung cells, called the endoplasmic reticulum, that are used by the invading influenza virus. We believe that this strategy will provide a powerful tool to inhibit influenza virus infection.

Jessy S. Deshane, Ph.D.



Mentor: Victor J. Thannickal, M.D.

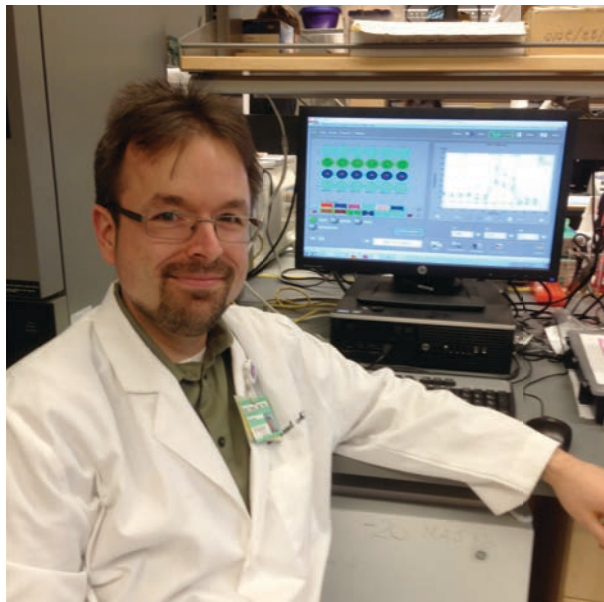
Institution: University of Alabama at Birmingham

Differentiation of regulatory myeloid-derived cells by reactive oxygen species

Asthma is a chronic inflammatory disease of the airways. We demonstrated using mouse models of asthma, that unique populations of white blood cells called myeloid-derived regulatory cells (MDRC) can suppress or worsen asthmatic inflammation by producing different profiles of free radicals and cytokines. Our preliminary studies showed that MDRC subpopulations are also present in the lungs of patients with asthma. Reactive oxygen species (ROS) produced by MDRC increases T cell responses and airway exacerbations. Our studies will investigate whether exposure to antigens triggers oxidative stress which promotes differentiation of proinflammatory MDRC that can then cause asthma exacerbation. These studies will establish MDRC as master regulators of balance between tolerance and inflammation in human asthma and help develop therapeutic strategies for control of asthma exacerbations.

Class of 2013

Joshua P. Fessel, M.D., Ph.D.



Mentor: James D. West, Ph.D.
Institution: Vanderbilt University

Metabolic reprogramming in pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is an incurable, fatal disease that causes loss of blood vessels in the lungs. Currently available drugs do not change the course of the disease. Recent research has shown that in PAH, cells in the lungs burn different fuels in different ways compared to normal cells. This shift in fuel use makes the cells divide more rapidly and die less easily, clogging lung blood vessels. How this shift in fuel use happens is not entirely clear. We will use mouse models of PAH and cells from patients with PAH to examine how the change in fuel use happens and what the consequences are. Understanding this mechanism will point to entirely new options for developing drugs that may halt or reverse PAH.

Adrianne G. Huxtable, Ph.D.



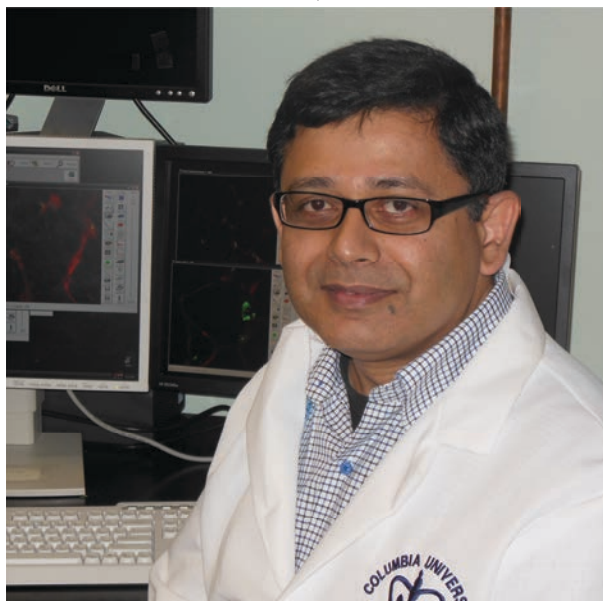
Mentor: Gordon S. Mitchell, Ph.D.
Institution: University of Wisconsin-Madison

Inflammation impairs spinal respiratory plasticity

Respiratory plasticity is a fundamental property of the neural system controlling breathing and is triggered by multiple factors (i.e., intermittent hypoxia, pregnancy, obesity, altitude, neural injury, aging). Plasticity preserves adequate drive to breathe during changing physiological conditions. Inflammation is associated with virtually all clinical disorders that challenge ventilatory control (incl. lung and neurodegenerative diseases and spinal injury), yet virtually nothing is known concerning its impact on respiratory plasticity. Here, we test the hypothesis that respiratory motor plasticity is impaired by inflammation, but can be restored with anti-inflammatory drugs. We will then identify key inflammatory cellular events that impair plasticity. A greater understanding of inflammation and its impact on respiratory plasticity will be of considerable importance as we begin to harness plasticity as a therapeutic approach to restore breathing capacity in disease/injury.

Class of 2013

Mohammad N. Islam, Ph.D.



Mentor: Jahar Bhattacharya, M.D., Ph.D.

Institution: Columbia University

Alveolar protective mechanism of mesenchymal stem cells in acute lung injury

Acute Lung Injury (ALI) affects upwards of 200,000 patients in the US yearly and carries high mortality (~40%) rate. No specific therapy exists for ALI, probably because our understanding of the pathology is incomplete. Mitochondria are the source of energy. In ALI, mitochondria become dysfunctional leading to loss of energy. Therefore, restoration of mitochondrial function can be protective. Our published work indicates that bone marrow-derived mesenchymal stem cells (BMSCs) transfer mitochondria to native cells lining of peripheral air sacs. As lung-cells acquire fresh mitochondria, their energy production improves. These studies aim to define how mitochondria get dysfunctional in ALI and how mitochondrial function is restored by the BMSCs. This will increase our understanding of the disease and give valuable insight into a possible therapy.

R. Matthew Kottmann, M.D.



Mentor: Patricia J. Sime, M.D.

Institution: University of Rochester

Lactate dehydrogenase, lactic acid and pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a progressive scarring disease of the lung that affects over 200,000 people in the U.S. The mean survival period from the time of diagnosis is 2.9 years, and unfortunately, there are currently no effective therapies. We recently identified that lactate dehydrogenase (LDH), an enzyme responsible for the generation of lactic acid during periods of low oxygen concentration, may play an important role in the development of scar tissue. This project will explore the 'pro-scarring' role of LDH and the 'anti-scarring' potential of LDH inhibitors. Ultimately, LDH inhibitors may become important therapeutics for IPF. The anti-fibrotic effects of LDH inhibitors may also be applicable to scarring diseases in the heart, liver, kidney, and skin, thus further enhancing the impact our studies.

Class of 2013

Stephane Lajoie, Ph.D.

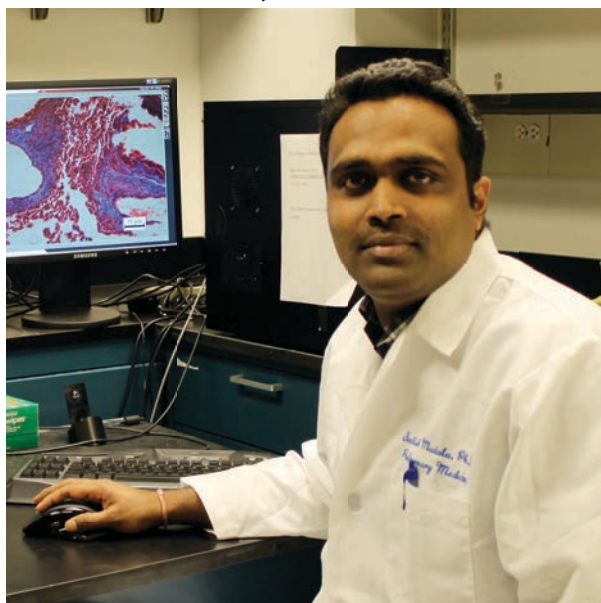


Mentor: Marsha Wills-Karp, Ph.D.
Institution: Johns Hopkins University

Innate immune regulators of IL-23/Th17 inflammation drive corticosteroid-refractory asthma

Corticosteroids are the main treatment options for asthma and are successful for the majority of asthmatics, but those with very severe asthma are uncontrolled by treatment. These patients are more likely to die or require hospitalization. A more tailored treatment modality for these patients might provide a significant improvement in quality of life and productivity. In these patients, as well as in a mouse that develops steroid-refractory asthma, there is an aberrant amount of interleukin-17A that drives severe disease and is unresponsive to corticosteroids. And we think an innate arm of the immune response that is resistant to steroids may drive this effect. A better understanding of how these signals are dysregulated may promote the development of life-saving therapies for severe asthmatics.

Satish K. Madala, Ph.D.



Mentor: William D. Hardie, M.D.
Institution: Cincinnati Children's Hospital

Molecular mechanisms of TGF α -driven pulmonary fibrosis

Pulmonary fibrosis is an incurable lung disease due to collagen-producing cells that form scar tissue and impair lung function. Our studies will identify disease-causing cell types and their functions responsible for pulmonary fibrosis and determine how these cells can invade the dense tissue matrix of the lung. We will identify cells involved in the formation of scar tissue in both the early and late stages of lung disease. We anticipate that our results will lead to new molecular targets for the development of novel therapeutic agents to be used for the treatment of pulmonary fibrosis.

Class of 2013

Carmen R. Mikacenic, M.D.



Influence of TLR polymorphisms on regulatory T cell function in ALI

Acute lung injury (ALI) is an inflammatory syndrome of the lung occurring in response to severe illness. It causes up to 200,000 deaths annually, but there are few interventions positively affecting outcomes. Specific immune cells, called T regulatory cells (Treg), suppress inflammation and are important in resolving ALI in an experimental mouse model, but little is known in humans. In patients with sepsis, we have also found a common genetic difference in a receptor that recognizes bacteria that is associated with outcomes in ALI. We think this genetic difference may alter how Tregs respond in lung injury. Therefore, we hope to understand the role of Tregs in ALI, how genetic differences in people may affect how they function, and harness this knowledge towards new therapies.

Mentor: Mark M. Wurfel, M.D., Ph.D.
Institution: University of Washington

Jin-Ah Park, Ph.D.



Bronchial epithelial cells as a source of angiogenic factors

Despite the devastating consequences of airway remodeling — a process that causes irreversible structural changes in the airway in patients with asthma, the mechanisms underlying this process remain to be elucidated. Angiogenesis is a key component of airway remodeling that occurs early during the process and is associated with decreased lung function, airway narrowing, and sustained chronic inflammation. Prevention of airway angiogenesis could potentially forestall later remodeling events that lead to the onset of chronic inflammation. We propose to use novel ideas and novel methods to determine the physical, physiological and molecular mechanisms at work in airway angiogenesis. If successful, the results of this study could be used to design new therapeutic approaches for the prevention and treatment of asthma.

Mentor: Jeffrey J. Fredberg, Ph.D.
Institution: Harvard School of Public Health

Class of 2013

Kathryn A. Radigan, M.D.



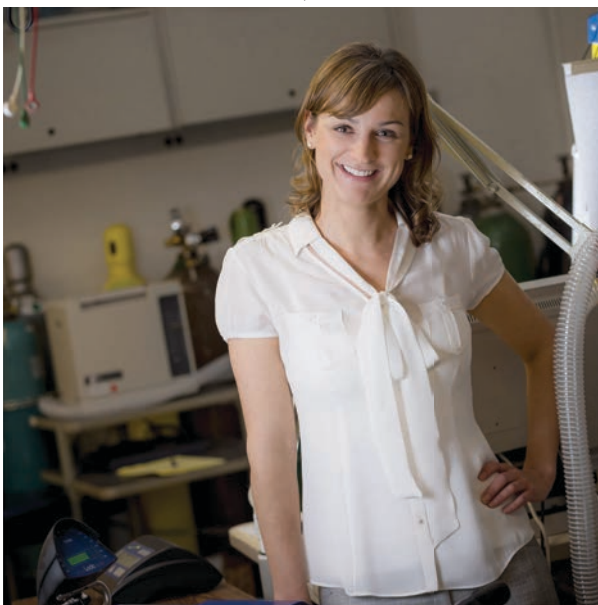
Mentor: Jacob I. Sznajder, M.D.

Institution: Northwestern University

Influenza infection leads to ubiquitin-mediated muscle degradation

Patients with critical illness often suffer from significant muscle wasting that can persist for years after the resolution of their acute illness. In our influenza pneumonia model of critical illness, we will explore the link between resistance to leptin, which develops as a consequence of obesity, and an increased susceptibility to influenza-induced muscle wasting. These studies may identify new drugs to prevent or treat muscle wasting in our critically ill patients.

Tatum S. Simonson, Ph.D.



Mentor: Peter D. Wagner, M.D.

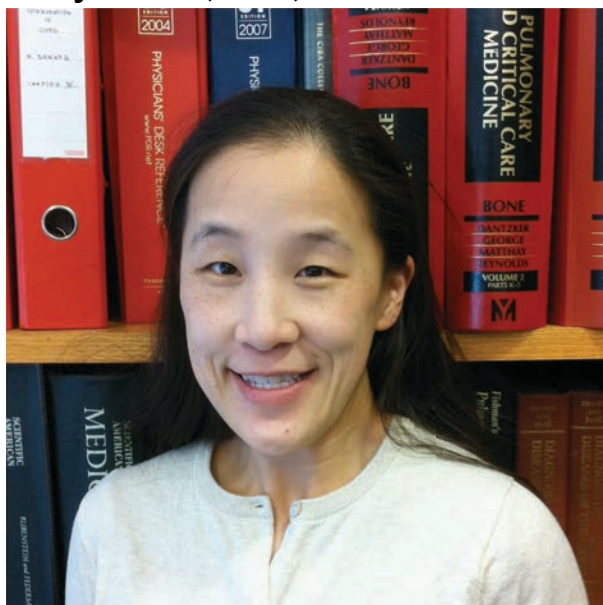
Institution: University of California, San Diego

Integrating physiology and genetics of high-altitude adaptation in Tibetans

In our previous genetic studies, we showed that Tibetans have genetic adaptations to high-altitude associated with lower red blood cell levels, and our physiological studies show that this loss is accompanied by enhanced exercise capacity through increased cardiac output and diffusive oxygen transport in muscle. The goal of these studies is to determine the physiological and genetic factors responsible for Tibetan adaptations by assessing exercise capacity and oxygen transport, precise genetic targets that afford evolutionary advantages, and the relationships among these factors and relatively lower hemoglobin levels in adapted Tibetans. Considering decreased oxygen availability may be a cause or effect of various diseases (e.g., altitude illness, heart and lung disease, stroke, hypertension, and cancer), our results will have broad implications for disease treatment and prevention.

Class of 2013

Emily S. Wan, M.D., M.P.H.



Mentor: Edwin K. Silverman, M.D., Ph.D.

Institution: Brigham & Women's Hospital

Integrative genomic analysis of acute exacerbations in COPD

Chronic obstructive pulmonary disease (COPD) was the third leading cause of death in the United States in 2009. Acute exacerbations are a significant source of death and disability for COPD patients. It is not known why some COPD patients suffer from frequent exacerbations. Epigenetic changes, which are modifications made to the DNA molecule which do not change the sequence of DNA, can reflect environmental exposures and play important roles in regulating genes. DNA methylation, a widespread epigenetic mark, may reflect or contribute to exacerbation susceptibility in COPD subjects; we propose to examine the genome-wide DNA methylation patterns of COPD subjects. Our study has excellent potential to uncover new genes and pathways involved in determining exacerbation frequency and may help to identify new treatment targets.