



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

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## **Class of 2014**

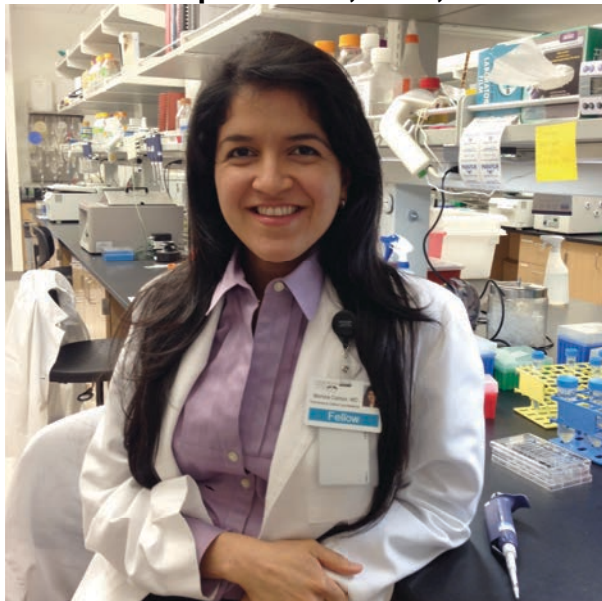
The Parker B. Francis Fellowship Program provides career development support to M.D. and Ph.D. scientists embarking on careers in clinical, laboratory or translational science related to Pulmonary, Critical Care and Sleep Medicine. Funding is awarded for three years to fellows working with experienced 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. Many of the individuals who have received Parker B. Francis Fellowships have become prominent investigators with highly productive careers based at universities in North America and throughout the world. They have published their work in the 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.

We are pleased to provide support for the following new investigators who make up the Parker B. Francis Fellowship Class of 2014.

## Class of 2014

### Monica Campo-Patino, M.D., M.P.H.



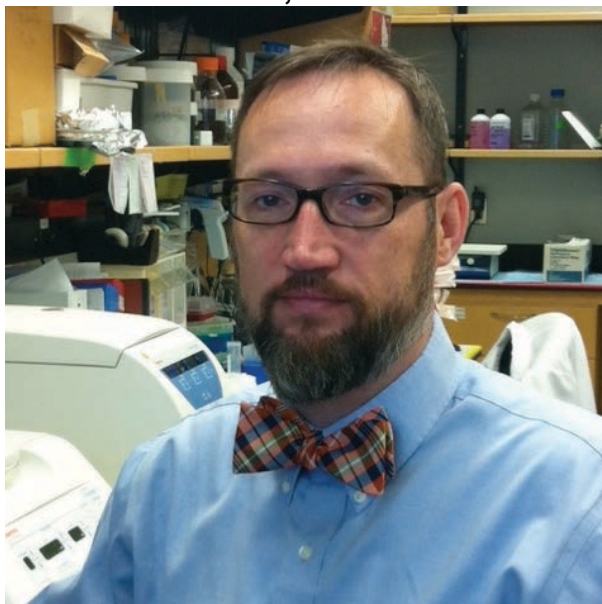
**Mentor:** Thomas R. Hawn, M.D., Ph.D.

**Institution:** University of Washington

#### CD43 and TB immunopathogenesis

A surface receptor on immune cells is a promising target for optimizing tuberculosis vaccines. The development of vaccines is hindered by the complexity of the immune response to tuberculosis and it requires more research. I have evidence that a surface receptor, CD43 is associated with tuberculosis disease and worse outcomes. However the mechanisms by which CD43 operates in the immune response to human tuberculosis are unknown. This proposal focuses on discovering the mechanisms by which CD43 regulates uptake, processing and response of the immune cells to the microorganism that causes tuberculosis. By using advanced immunogenetics techniques and human samples the development of this project will contribute to a better understanding of immunity to tuberculosis. This knowledge will contribute to the developing of better vaccines that will help overcome the human epidemic of tuberculosis.

### Charles A. Downs, Ph.D.



**Mentor:** Douglas C. Eaton, Ph.D.

**Institution:** Emory University

#### RAGE-mediated regulation of ENaC and pulmonary function

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are life-threatening lung disorders that are characterized by excess lung water or edema that decreases oxygen diffusion from the lungs into the bloodstream. Lung edema removal occurs through active salt transport via epithelial sodium channels (ENaC) and ENaC is activated by reactive oxygen species (ROS), small unstable signaling molecules. Activation of the receptor for advanced glycation endproducts (RAGE) results in ROS production which could then activate ENaC. Studies have shown an increase in the soluble form of RAGE in lung edema fluid of patients with ARDS. Soluble RAGE inactivates RAGE. Understanding how RAGE regulates ENaC activity has the potential to lead to treatment modalities to improve lung fluid clearance, and ultimately outcomes, in people with ARDS.

## Class of 2014

### Maha R. Farhat, M.D.



**Mentor:** Megan Murray, M.D., Ph.D.

**Institution:** Massachusetts General Hospital

### **Genetic determinants of drug resistance in mycobacterium tuberculosis**

Drug resistant tuberculosis (TB) is an important global pulmonary public health threat. A rapid diagnostic test for the presence and extent of TB drug resistance would allow clinicians to identify and initiate appropriate therapy early in the course of treatment, thereby improving treatment outcomes and interrupting the further spread of drug resistant TB. Resistance is caused by genetic mutations. Detection of these resistance mutations has been used successfully to detect resistance to 2 drugs. This study will investigate the genetic sequences of 28 known and 39 candidate resistance genes for a large panel of TB drugs. We will determine which mutations predict the extent of resistance and use this information to guide the development of improved diagnostic tests for resistance.

### Joe L. Hsu, M.D., M.P.H.



**Mentor:** Mark R. Nicolls, M.D.

**Institution:** Stanford University

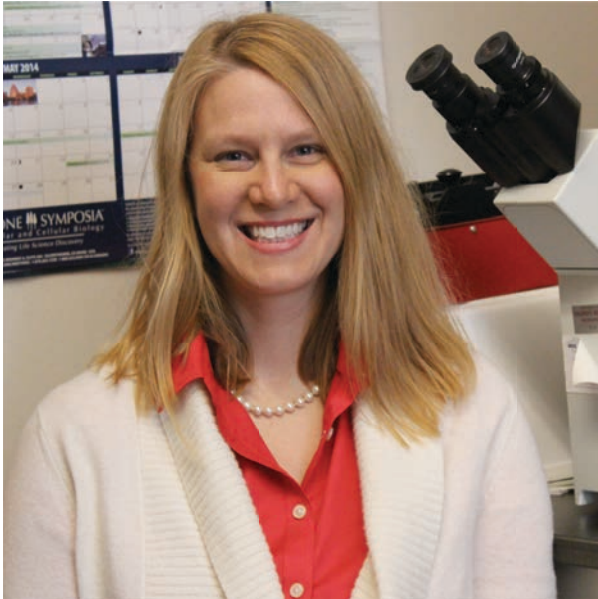
### **The role of HIF-1 in limiting Aspergillus invasion in airway transplants**

Lung transplantation can be a life saving therapy for persons with end-stage pulmonary diseases. Yet, posttransplant survival is often limited by pulmonary infections and chronic transplant rejection. Included among these infections is *Aspergillus fumigatus*, a ubiquitous fungus that causes life threatening pneumonias and accelerates lung transplant rejection. In a previous mouse model of *Aspergillus* infection after airway transplantation, we linked poor blood flow in the transplanted organ with a more aggressive behavior of the fungus. In the current study, we will improve the host's capacity to maintain a healthy blood supply and determine the effect on *Aspergillus* infection. We believe that by improving the health of blood vessels in the transplant that we can reduce the burden of these common infections in lung transplant recipients.



## Class of 2014

### Kristin M. Hudock, M.D.



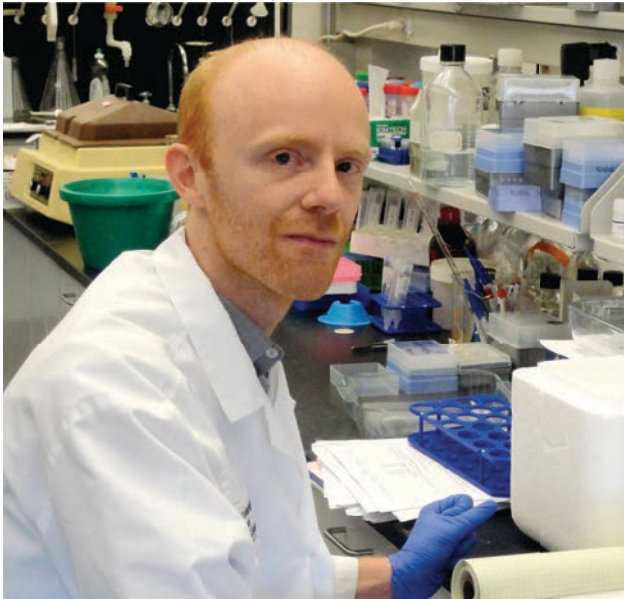
**Mentor:** G. Scott Worthen, M.D.

**Institution:** University of Pennsylvania

### Uncovering mechanisms of lung injury in CF using iPSC-derived neutrophils

Cystic fibrosis (CF) is a genetic disease characterized by recurrent pneumonias and progressive lung injury, usually resulting in death by young adulthood. We postulate that neutrophils, key immune cells that protect people from bacteria, are dysfunctional in CF and contribute to the development of CF lung disease. In our proposal, we use novel stem cell technologies to determine how CF neutrophils differ from neutrophils of healthy subjects, which could lead to the development of new drugs to treat this incurable disease.

### Glenn Marsboom, Ph.D.



**Mentor:** Asrar B. Malik, Ph.D.

**Institution:** University of Illinois at Chicago

### Fibroblast and vascular cell interactions in pulmonary arterial hypertension

Pulmonary arterial hypertension is a severe disease characterized by narrowing of pulmonary blood vessels. The mechanisms leading to the onset and progression are not well understood and these patients have an unacceptably poor prognosis. This proposal is aimed at better understanding the disease processes at the cellular and molecular level. In the pulmonary blood vessel wall, several blood vessel cell types interact with each other and with a cell type called fibroblasts and I will focus on how these interactions set the stage for the development of the disease. Among the powerful tools to be used will be patient-derived stem cells that can be differentiated into vascular cells and transgenic mice to understand comprehensively the cell interactions, with the objective to ultimately develop novel therapies.

## Class of 2014

### Michael J. McGeachie, Ph.D.



**Mentor:** Scott T. Weiss, M.D.

**Institution:** Brigham and Women's Hospital

#### **Predictive genetics of abnormal lung function**

This investigation of the genetic link between asthma and COPD has the potential to identify genetic variants indicative of a progression from early-life asthma to later-life COPD. Furthermore, since I propose to develop a predictive genetic test for this progression, this research may lead to a personalized genomic test for risk of COPD. The proposed research will lead to an increased understanding of the genetic and thus biological underpinnings of abnormal lung function growth and decline, through identification of 1) these genetic factors and 2) patients at greatest risk, who may be studied further. The present research, both the genetic investigation and the predictive test, are important steps toward reducing the public burden of asthma and COPD.

### Matthew E. Pamerter, Ph.D.



**Mentor:** William K. Milsom, Ph.D.

**Institution:** University of British Columbia

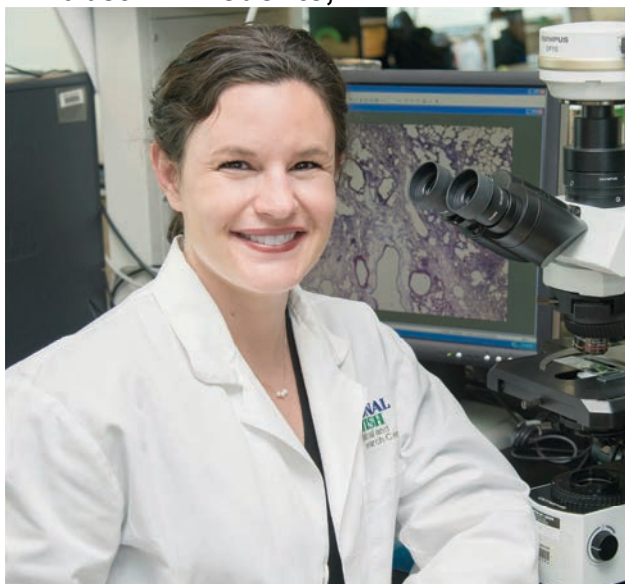
#### **Hypoxia inducible factor in ventilatory responses to chronic sustained hypoxia**

Arterial sensors detect blood oxygen levels and adjust breathing to maintain optimal oxygen availability. Many pulmonary diseases as well as exercise at altitude reduce oxygen in the body and activate reflex increases in breathing to restore normal oxygen balance. Naked mole rats are adapted to life in low oxygen environments and studying the mechanisms that increase oxygen delivery in these organisms will inform therapeutic treatment of hypoxia-related diseases. I will examine signaling pathways that underlie increased breathing reflexes in chronically hypoxic naked mole rats to learn how to turn up the "gain" of systemic responses to reduced oxygen. I will test the importance of these pathways in rats acclimatized to hypoxia to determine the efficacy of this approach to enhancing oxygen delivery in hypoxia-intolerant mammals.



## Class of 2014

**Elizabeth F. Redente, Ph.D.**



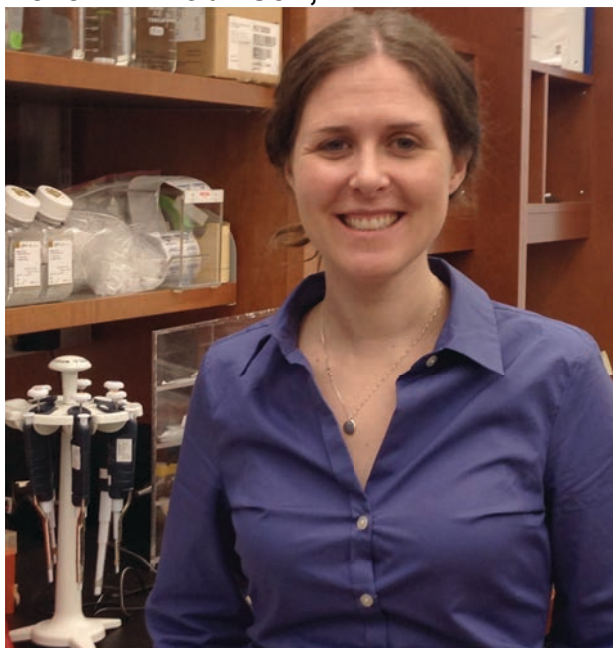
**Mentor:** David W.H. Riches, Ph.D.

**Institution:** National Jewish Health

### **Therapeutic targeting of macrophage DUSP1 in fibroproliferative lung disease**

Pulmonary fibrosis is a serious condition that can lead to long-term scarring of the lungs and impaired lung function in some patients. Little is known about how lung scar formation develops or how to treat patients who develop lung scarring. This grant proposal seeks to address how the functions of the immune system, specifically macrophages can be altered to reduce lung scarring and improve patient outcomes with the longer-term goal of developing novel therapeutic approaches to treat this devastating and often fatal disorder.

**Keven M. Robinson, M.D.**



**Mentor:** John F. Alcorn, Ph.D.

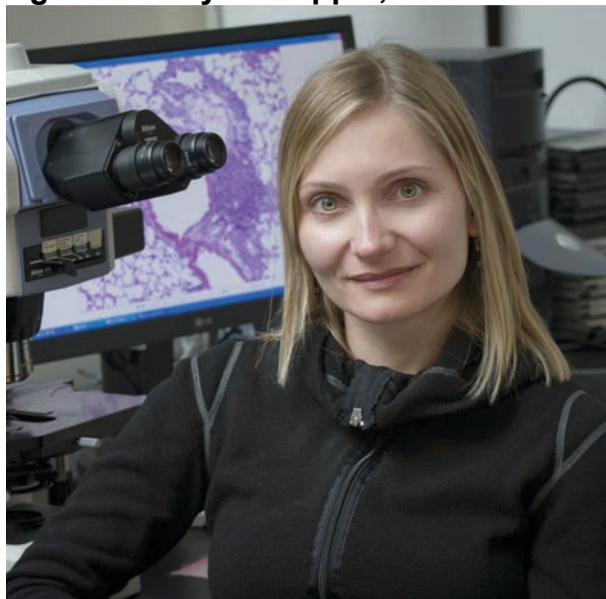
**Institution:** University of Pittsburgh

### **Role of IL-1 $\beta$ in influenza and Staphylococcus aureus co-infection**

Influenza infection is a common respiratory illness that causes seasonal epidemics and sometimes even pandemics. While most cases of influenza do not result in death, secondary bacterial infections, such as Staphylococcus aureus pneumonia, are associated with increased morbidity and mortality. Scientists have shown that the signaling molecules IL-17 and IL-22 are necessary to fight the bacteria S. aureus. Preceding influenza decreases production of these molecules, making the body more susceptible to S. aureus infection. Another signaling molecule, IL-1 $\beta$ , can affect production of IL-17 and IL-22. This project explores the role of IL-1 $\beta$  in viral/bacterial co-infection in mice. These experiments will provide insight into how influenza weakens the immune system, predisposing to bacterial pneumonia, with the goal of developing new drugs to decrease influenza-associated mortality.

## Class of 2014

### Agnieszka Rynda-Apple, Ph.D.

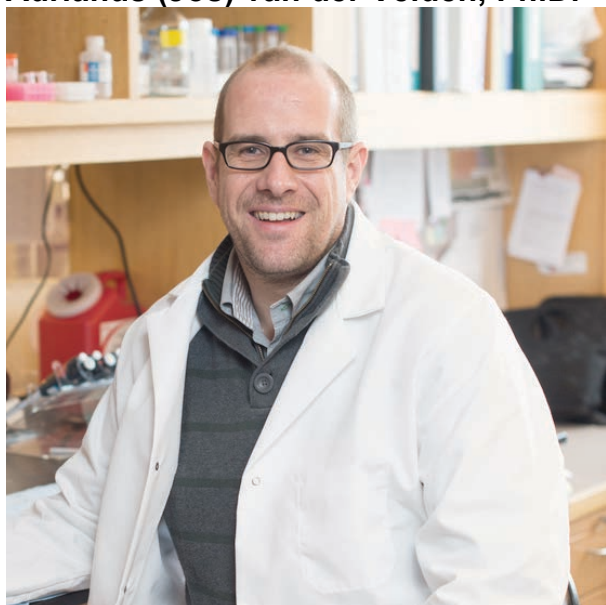


**Mentor:** Allen G. Harmsen, Ph.D.  
**Institution:** Montana State University

#### Utilizing VLPs to understand predisposition to secondary bacterial pneumonia

Post-influenza secondary bacterial infections (superinfections) are the primary cause of deaths during influenza pandemics. In mouse models if bacterial infection occurs 3 days after influenza infection, the mouse immune system is able to resolve bacterial infection, but then loses control over influenza disease. Our preliminary results indicate that this shift in susceptibility to superinfections is determined by a sequence of immunological events, but how these events are regulated is currently unknown. The same time-dependent shift in susceptibility to MRSA infection can be induced when various empty virus capsids (of a virus not related to influenza) is used instead of intact influenza virus, suggesting that this time-dependent shift in susceptibility to bacterial superinfection is pre-determined at the time of the interaction of a virus capsid with immune cells, and that it does not require active infection with the virus. Results from this study will shed insight into how this interaction occurs and how it is regulated and may lead to new therapies for patients with life threatening viral and bacterial infections.

### Adrianus (Jos) van der Velden, Ph.D.



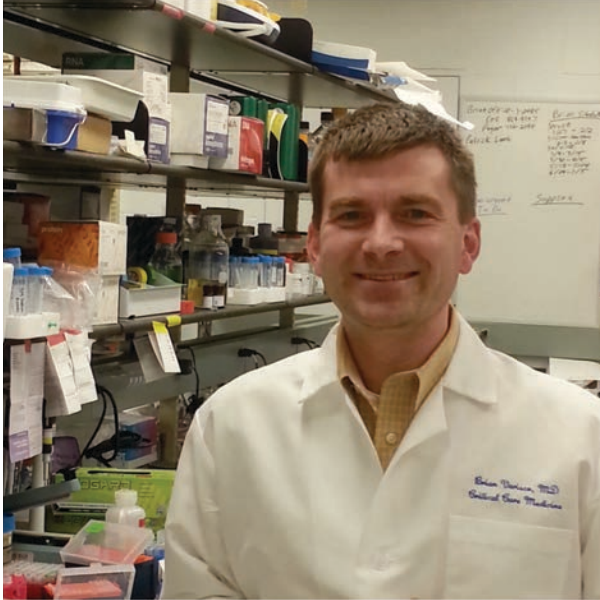
**Mentor:** Yvonne Janssen-Heininger, Ph.D.  
**Institution:** University of Vermont

#### GSTP-catalyzed s-glutathionylation in KRAS<sup>G12D</sup> induced tumorigenesis

Despite many years of investigations no effective treatment exists to date for Non-Small Cell Lung Cancer (NSCLC) and remarkably in spite of incremental advances in lung cancer therapy the 5-year survival rate has remained essentially unchanged over the past 3 decades. Therefore, there is an urgent need to develop novel therapies based on newer understanding of the molecular mechanisms and pathways that participate in lung carcinogenesis for better and improved treatment of patients diagnosed with NSCLC. Completion of this proposal could provide an exciting new molecular mechanism and lead to a new therapeutic approach with an existing drug (TLK199) for patients with Non-Small Cell Lung Cancer.

## Class of 2014

**Brian M. Varisco, M.D.**



**Mentor:** Jeffrey A. Whitsett, M.D.

**Institution:** Cincinnati Children's Medical Ctr

### **Chymotrypsin like elastase-1 links alveolar and microvascular growth**

Many conditions lead to reduced alveolar surface area which causes reduced exercise tolerance and increased susceptibility to pulmonary disease. This proposal tests whether a novel protease, CELA1, regulates remodeling the lung during alveolarization and promotes alveolar blood vessel growth. To test this hypothesis, we will quantitate alveolar and vascular growth after elastase inhibition and CELA1 silencing. To determine how CELA1 promotes blood vessel growth, we will perform a series of activation and inhibition assays to rescue the effects of CELA1 silencing. To determine how CELA1 remodels lung matrix, we will perform a series of imaging and molecular experiments to test where and how CELA1 binds and cleaves elastin. This knowledge will provide the scientific foundation for novel therapies to improve lung growth and function.