



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 2016**

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 840 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 2016.

## Class of 2016

### Christopher M. Cielo, M.D.



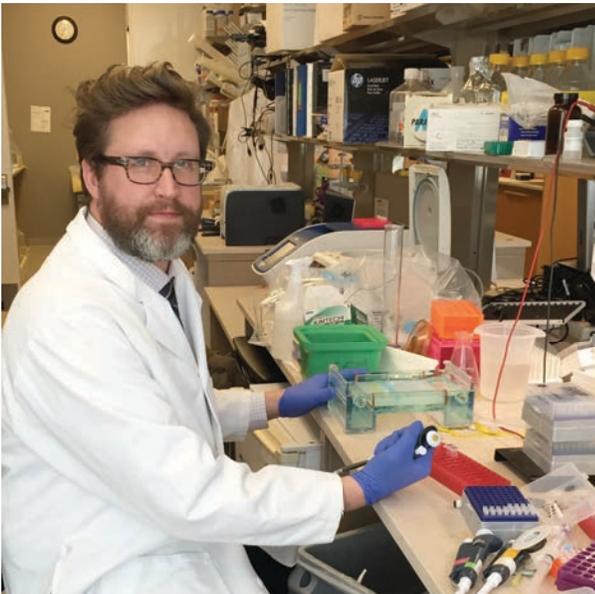
#### **Mechanisms of obstructive sleep apnea syndrome in infants with micrognathia**

Obstructive sleep apnea syndrome (OSAS) is a condition common in children where there are pauses in breathing during sleep. Babies born with a defect causing their jaw to be small (called micrognathia) puts them at high risk for OSAS. It is likely there are multiple factors that put these babies at risk for OSAS and also cause them to have difficulty with growth, but these are not well understood. This study will use a variety of procedures including sleep studies, MRIs, and measurement of the calories consumed to determine which infants are at increased risk and which benefit most from surgical correction of micrognathia. The results will improve the care of these highly vulnerable patients.

**Mentor:** Carole L. Marcus, M.D.

**Inst:** Children's Hospital of Philadelphia

### David B. Frank, M.D., Ph.D.



#### **Wnt-responsive progenitor cells in alveolar development, repair, and regeneration**

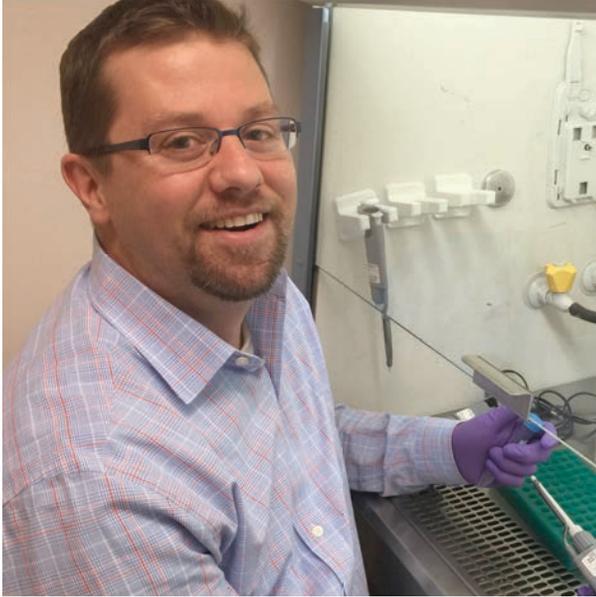
Lung disease in the newborn period can be a significant health burden and can lead to serious complications. With the improved care for premature infants, there has been an increase in the number of premature newborns with bronchopulmonary dysplasia (BPD), a lung disease marked by a disruption in the normal development of the lung. Currently, there is no cure for BPD. We have identified a group of specialized lung epithelial cells, called Axin2<sup>+</sup> type 2 alveolar epithelial cells (AEC2s), that have the Wnt growth factor pathway activated. The Wnt growth factor pathway is involved in stem cell maintenance and differentiation in many different organs in the body. Preliminary studies suggest that Axin2<sup>+</sup> AEC2s have enhanced stem cell properties and could regenerate lung tissue in BPD.

**Mentor:** Edward E. Morrisey, Ph.D.

**Inst:** Children's Hospital of Philadelphia

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### Jason W. Griffith, M.D., Ph.D.



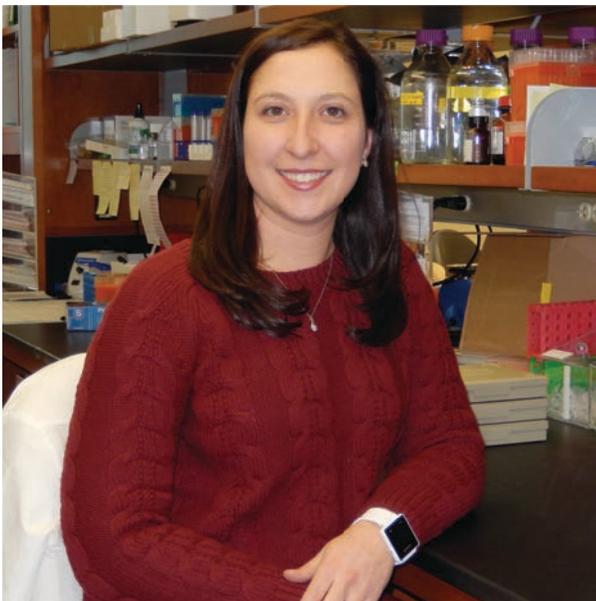
#### **The distinct function and control of regulatory T cell subsets during influenza**

Regulatory T cells critically enhance survival to influenza infection by modulating the inflammatory response to the virus. This proposal focuses on understanding how regulatory T cells form distinct subsets during influenza infection and how these subsets may play non-redundant roles in modulating different parts of the host immune response. A better understanding of the factors that control these distinct regulatory T cell responses to influenza could provide novel therapeutic pathways allowing for specific inhibition of the damaging host immune response without compromising immune control of virus replication.

**Mentor:** Andrew D. Luster, M.D., Ph.D.

**Inst:** Massachusetts General Hospital

### Michelle L. Manni, Ph.D.



#### **The role of IL-22Ra2 in allergic airway disease**

Asthma is a chronic inflammatory disorder of the airways that is a significant health problem worldwide. This heterogeneous disease has no preventions or cures and distinct molecular pathways regulate disease pathogenesis. The need for new models that mimic complex human disease is evident. Research has shown that interleukin (IL-22) may have an immunoprotective role in asthma. The soluble receptor for IL-22, IL-22Ra2, is a newly discovered antagonist of IL-22 activity, but the role of IL-22Ra2 in the lung has not been explored. This novel work will examine the role of IL-22Ra2 in allergic airway disease in modulating proteinase production and IL-22 signaling in the lungs using mouse models of severe asthma. Targeting of IL-22Ra2 could present a novel approach in treating chronic lung disease.

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

**Inst:** University of Pittsburgh

## Class of 2016

### **Bhakti K. Patel, M.D.**



**Mentor:** Gokhan M. Mutlu, M.D.  
**Inst:** University of Chicago

#### **Impact of early mobilization on insulin resistance and ICU acquired weakness**

Patients in critical condition on ventilators often develop a muscle weakness out of proportion to what is expected from bed rest alone. Patients with weakness have enduring physical disability even with rehabilitation. This weakness may be caused by inflammation, high blood sugars, and immobility. We have shown that early exercise for patients on ventilators is safe and improves strength and blood sugars. However, how activity during critical illness decreases blood sugars and inflammation are unknown. The proposed research will study how exercise improves weakness when patients are critically ill. By identifying how weakness develops and is improved with early exercise, we can discover medications that prevent weakness and help patients not just survive the intensive care unit, but to thrive in their recovery without physical disability.

### **Francesca Polverino, M.D.**



**Mentor:** Caroline A. Owen, M.D., Ph.D.  
**Inst:** Brigham and Women's Hospital

#### **Recombinant club cell protein 16 (CC16): A novel disease-modifying therapy for COPD?**

In the USA, COPD is the fourth leading cause of death, and we lack effective therapies that stop its progression. Club cell protein 16 (CC16) is a protein produced by healthy airway cells. CC16 is known to have protective activities in lung diseases other than COPD. We showed that CC16 blood and lung levels are decreased in COPD patients. CC16 protects the lungs of mice from damage caused by cigarette smoke (CS). We will assess whether delivering CC16 protein to the lungs of mice limits CS-induced lung damage, and how CC16 protects these cells from the damaging effects of CS. These studies could help us advance CC16 protein therapy into clinical trials to assess whether CC16 protein therapy stops the progression of human COPD.

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**Seppo T. Rinne, M.D., Ph.D.**

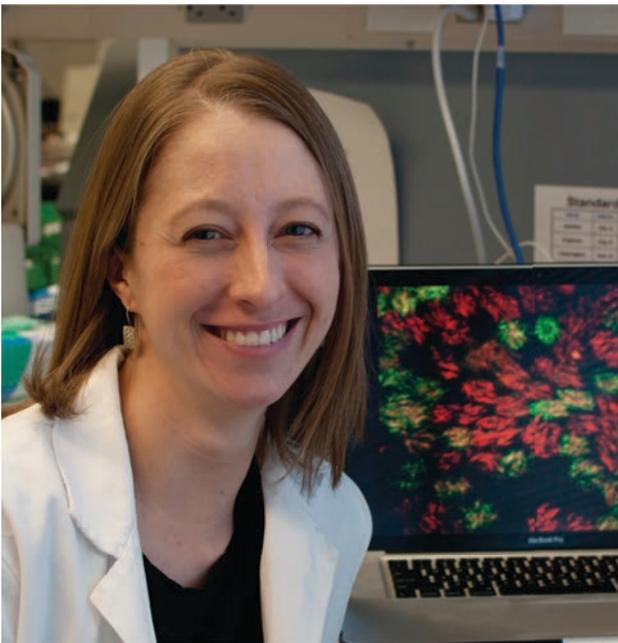


**Mentor:** Lori A. Bastian, M.D. M.P.H.  
**Inst:** VA Connecticut Healthcare System

### **Improving multidisciplinary teamwork for COPD: A mixed methods study**

Patients with chronic obstructive pulmonary disease (COPD), a common lung disease, tend to have many healthcare providers involved in their care, but we do not know the best way to organize these providers into teams or how providers can use teamwork to deliver better care. For this proposal, I will do two studies. First, I will use a large database from the Veterans Affairs Healthcare System (VA) to examine the teams that form in caring for patients with COPD and identify team characteristics that lead to better care. Second, I will interview providers at different VA clinical sites to identify how providers effectively use teamwork to care for patients with COPD. This research has the potential to improve healthcare delivery for patients with COPD.

**Margaret A. Scull, Ph.D.**



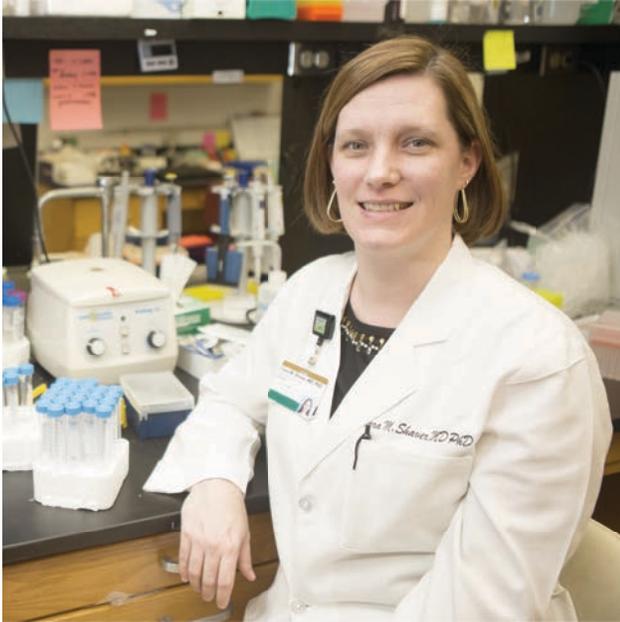
**Mentor:** Charles M. Rice, Ph.D.  
**Inst:** Rockefeller University

### **Dissection of the airway epithelial antiviral response in 3D**

Despite the frequency and severity of respiratory virus infections across the entire human population, antivirals and vaccines are either not available or limited in efficacy. Airway epithelial cells are the first line of defense against, and primary target of, respiratory viruses, yet much remains unknown about their response to infection. We will define the host response across multiple respiratory viruses in a model of human airway epithelium using an unbiased, comprehensive genomics approach. Applying tools to identify and isolate individual cells from infected epithelial cultures, we will further unveil the role of specific cell types in this response. Together, these data will provide novel insight into respiratory virus pathogenesis and identify host factors that mediate infection across diverse viruses and may represent novel therapeutic targets.

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**Ciara M. Shaver, M.D., Ph.D.**



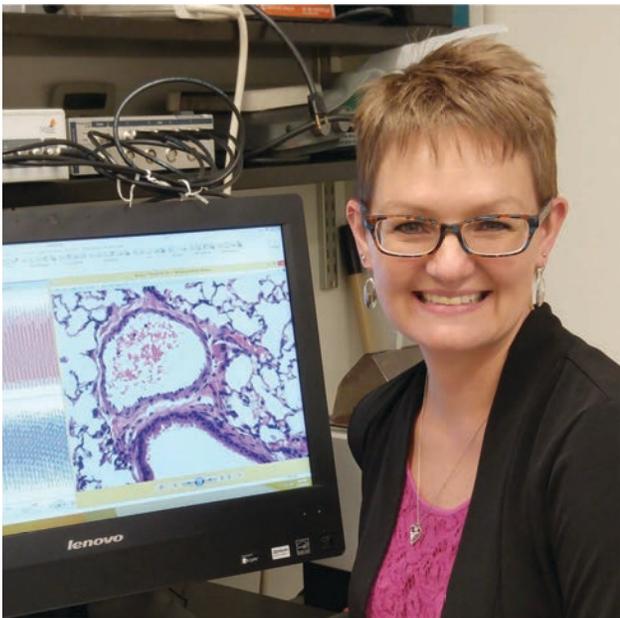
**Mentor:** Lorraine B. Ware, M.D.

**Inst:** Vanderbilt University

### **Cell-free hemoglobin, heme, and macrophage-mediated lung inflammation in ARDS**

Many patients with severe lung injury (ARDS) die despite getting state-of-the-art intensive care. Our goal is to understand why this happens and to develop new therapies to help save lives. We recently reported that many patients with ARDS have high levels of extracellular hemoglobin in the airspaces. In this study, we will try to determine which cells and proteins are involved in causing lung inflammation from hemoglobin using experiments in mice, cell culture, and samples from human lungs. We will also test whether lowering the amount of hemoglobin in the lung will limit the amount of lung injury. We hope that these studies will lead to new clinical trials in patients with ARDS in the near future.

**Kimberly A. Smith, Ph.D.**



**Mentor:** Paul T. Schumacker, Ph.D.

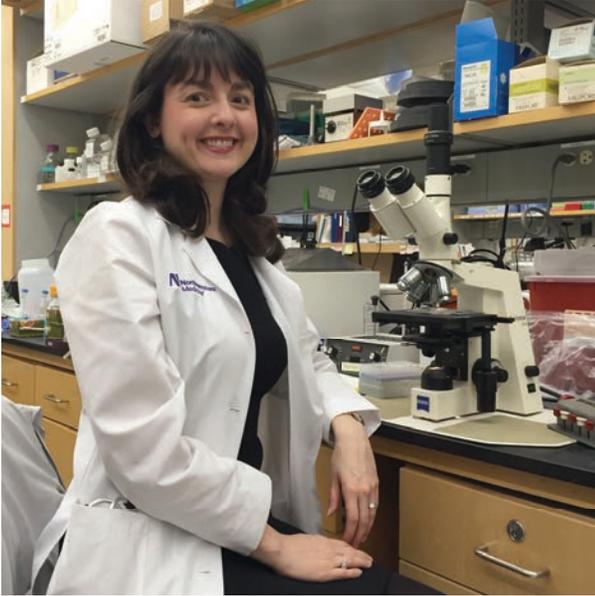
**Inst:** Northwestern University

### **ROS and HIF-1 $\alpha$ in right ventricular hypertension in pulmonary hypertension**

Pulmonary hypertension (high blood pressure in the lungs) is associated with hypoxia (low oxygen levels) in lung cells. Patients with pulmonary hypertension develop thickening of the right heart wall. We have previously shown that inhibition of a HIF-1 $\alpha$ , a protein important during hypoxia, in lung blood vessels prevents pulmonary hypertension, but does not block right heart wall thickening. We propose that HIF-1 $\alpha$  is directly involved in right heart wall thickening during the development of pulmonary hypertension. This project will investigate the role of HIF-1 $\alpha$  in right heart wall thickening in pulmonary hypertension in order to better understand how this disease develops. If true, then emerging drugs to limit HIF activity could prove useful in the treatment of this disease.

## Class of 2016

### Whitney W. Stevens, M.D., Ph.D.



#### Pathogenesis of severe aspirin-sensitive asthma with nasal polyposis

Aspirin Exacerbated Respiratory Disease (AERD) is a severe form of asthma associated with chronic sinus disease with nasal polyps (CRSwNP) and the inability to tolerate medications such as aspirin. Patients with AERD, on average, are more likely to require oral steroids than typical asthmatics and have more severe sinus disease, necessitating repeated sinus surgeries when compared to patients with CRSwNP alone. While AERD is associated with a large socioeconomic burden and negative quality of life, it is unclear what causes this disease and why it is so severe. This proposal aims to first establish a large group of patients with AERD and then to study the role certain immune cells, in particular eosinophils, may play in nasal polyp growth and the inflammation seen in AERD.

**Mentor:** Robert P. Schleimer, Ph.D.

**Inst:** Northwestern University

### Christine U. Vohwinkel, M.D., Ph.D.



#### Alveolar epithelial carbohydrate metabolism during acute lung injury

The lung has about 300 million alveoli that facilitate gas exchange between inhaled air and blood to maintain respiration. Perturbations that injure and weaken alveoli can lead to lung collapse resulting in respiratory distress and possible death. Excess inflammation is a hallmark of acute lung injury. In response to acute lung injury, the mucosal lining of the lung reacts by altering the metabolism to control excess inflammation. However, very little is known about the interplay between inflammation and metabolism. HIF1A (hypoxia inducible factor) is a crucial regulator of those protective mechanisms by increasing gene expression of specific metabolic enzymes. This project will provide further understanding of those innate protective pathways. Harnessing those protective mechanisms will provide innovative therapeutic approaches for treatment of acute lung injury.

**Mentor:** Holger K. Eltzschig, M.D., Ph.D.

**Inst:** University of Colorado