PARKER B. FRANCIS
FELLOWSHIP
PROGRAM

Class of 2010

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 770 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 2010.

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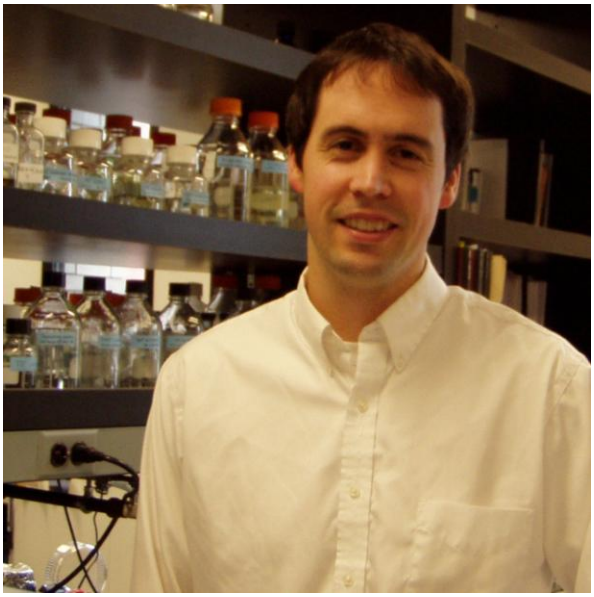
Jonathan K. Alder, Ph.D.

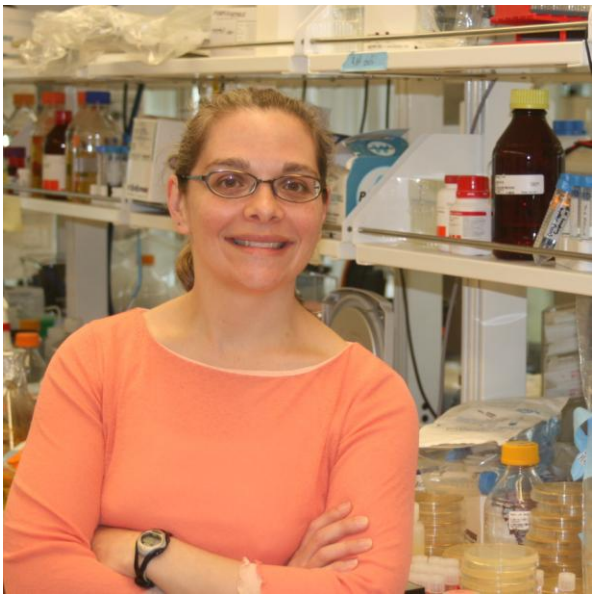


Mentor: Mary Y. Armanios, M.D.
Institution: Johns Hopkins University

The role of short telomeres in COPD pathogenesis

Emphysema is a progressive lung disease and is the fourth leading cause of death in the United States. In general, it is caused by cigarette smoke, although 1 in 5 individuals who are affected are non-smokers. Not all individuals who smoke develop emphysema, but it is clear that age is a very important risk factor. Telomeres are DNA-protein caps that protect chromosomes ends. As we age, telomeres become shorter and eventually prevent tissues from being able to repair after injury. Since every individual has a unique telomere length, this research has the potential to explain why some individuals are more likely to develop emphysema in response to cigarette smoke. A better understanding of how telomeres and aging affect the lung's ability to repair after injury can help define new strategies to treat emphysema.

Amy K. Barczak, M.D.



Mentor: Deborah T. Hung, M.D., Ph.D.
Institution: Massachusetts General Hospital

Chemical genetic approach to cellular mechanisms of M. tuberculosis virulence

Tuberculosis remains a major cause of disability and death globally. Recently, emergence of increasingly drug resistant tuberculosis has put into sharp focus the limitations of current management strategies. The development of new therapeutics will depend on a better understanding of the interaction between the bacterium that causes disease and the human host. Macrophages, one of the cells present in the lungs that take up the bacteria upon infection, play a key role in the course of infection. Using a screen of thousands of small molecules, we have identified several that enhance the macrophages' ability to kill tuberculosis bacteria. Our studies will use these molecules to add to our understanding of how macrophages control or fail to control infection. It is our hope that such studies will provide an important step forward on the path to developing novel and improved drugs to treat tuberculosis.

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Patricia M. George, M.D.

Mentor: Mark T. Gladwin, M.D.
Institution: University of Pittsburgh

HIV-nef and Src kinase signaling in HIV-related pulmonary arterial hypertension

HIV-related pulmonary arterial hypertension is a lung disease that affects at least 1 in 200 HIV infected patients, significantly decreases life expectancy, and is incurable. HIV-PAH is a cancer-like disease of uncontrolled growth of inner and middle layers of blood vessels in the lungs. Scientists have shown that a part of the HIV virus called Nef may play a role in PAH, but how it does so is not known. In other parts of the body, Nef can activate Src kinases, which function as switches that turn on genes and cause cells to multiply and grow. This project will explore how Nef interacts with Src kinases to cause pulmonary artery cells to grow. By furthering our understanding of how HIV *Nef* promotes pulmonary artery cell growth and developing ways to prevent it, our ultimate goal is to develop new treatments in this fatal disease.

Sean E. Gill, Ph.D.

Mentor: William C. Parks, Ph.D.
Institution: University of Washington

The protective role of TIMP3 in acute lung injury

Lung injury that results from trauma, infection, or disease is often made worse by out-of-control inflammation and scarring (or fibrosis). A group of enzymes, called metalloproteinases, and their inhibitors, called the tissue inhibitors of metalloproteinases (TIMPs), normally work together to hold inflammation and scarring to beneficial levels. This enzyme-inhibitor balance is thought to go astray in disease; however, the specific enzymes that are important and whether they promote or restrain inflammation and fibrosis is largely unknown. The goal of these studies is to determine what enzymes TIMP3 controls and what those enzymes do to stimulate inflammation and fibrosis. This project will address fundamental mechanisms of how inflammation and fibrosis are regulated and turned off following injury and will potentially provide information regarding potential therapeutic targets.

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Brian B. Graham, M.D.

Mentor: Rubin M. Tuder, M.D.
Institution: University of Colorado Denver

Schistosomiasis-associated pulmonary arterial hypertension

Schistosomiasis is the third most common parasitic disease worldwide and the number one cause of pulmonary arterial hypertension (PAH), affecting about 10 million people predominantly in under-developed countries. PAH is a devastating condition of progressive shortness of breath and heart failure. We have developed a model of this disease by infecting mice with schistosomiasis. In chronic schistosomiasis infection, the parasite deposits eggs in the intestinal vessels, which can migrate to the lungs. Alterations in the pulmonary vessels may result from the body's immune response to the eggs in the lung and/or the liver. We will study this connection using our mouse model and we will also study the disease in humans by analyzing lung tissue from patients in Brazil who died of schistosomiasis and PAH.

Ramaswamy Krishnan, Ph.D.

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

Physical forces and regulation of pulmonary endothelial integrity

During ALI/ ARDS, pulmonary vascular endothelial cells are the targets of disruption and the sites of increased macromolecular movement, but specific mechanisms are unknown. These studies will focus on the underlying role of physical forces within the epithelial monolayer, specifically high-force junctions which would comprise the likely locus of barrier disruption. Our preliminary studies suggest a radical new hypothesis, namely, the virtual irrelevance of average cellular behaviors in the face of the inordinate importance of a few extreme events. Are these extreme events exaggerated by aberrant physical and biochemical cues, as would occur in ALI/ARDS? If so, what interventions can we design to lower their occurrence and protect the EC barrier from disruption? These are the questions our studies will address.

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Ian P. Lewkowich, Ph.D.

Mentor: Marsha Wills-Karp, Ph.D.
Institution: Cincinnati Children's Hospital

Synergistic role of IL-17 and IL-13 in asthma susceptibility

Currently available treatments are ineffective in controlling disease in patients with severe asthma. Thus, these patients are more likely to die or require hospitalization following an asthma attack. Our preliminary data from a mouse model, and newly emerging data from human studies suggest severe asthma is associated with a combination of Th2 cells and Th17 cells, and their ability to produce a mixture of IL-13 and IL-17A. However, the mechanisms by which these cytokines induce disease are not well understood. The aims of these studies are to identify how the production of IL-17A makes disease more severe than the production of IL-13 alone. A better understanding of how IL-17A promotes severe disease will lead to the development of life-saving therapies to treat severe asthmatics, a population that is underserved by currently available treatments.

Kelvin D. MacDonald, M.D.

Mentor: William R. Skach, M.D.

Institution: Oregon Health & Science University

Activating non-CFTR chloride channels reduces airway epithelial inflammation

Cystic Fibrosis is characterized by thick mucus in the lungs leading to chronic infection, inflammation and pulmonary death. How the airways develop thick mucus is probably related to dysfunction of the CF chloride channel and interaction with other airway channels that maintain salt and water balance. Investigators in both CF and Chronic Obstructive Pulmonary Disease think that therapeutic agents regulating salt and water balance in the airways are highly desirable. One way to accomplish this goal is selectively activate certain chloride secretion channels while inhibiting sodium absorption channels. We have previously shown that lubiprostone activates the airway chloride channel CLC-2 in mice. Our studies will evaluate the effect of these compounds on inhibiting the sodium channels in airway cells as well their impact on airway inflammation signaling.

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Harikrishna Tanjore, Ph.D.

Mentor: Timothy S. Blackwell, M.D.
Institution: Vanderbilt University

Endoplasmic reticulum stress in pulmonary fibrosis

Idiopathic Pulmonary Fibrosis (IPF) is a fatal lung disease that results in respiratory failure and death in most patients within five years of diagnosis. Lung transplantation is the only therapeutic option available. Scarring or fibrosis is characterized by the deposition of extracellular matrix proteins, including collagen, affecting lung architecture and gas exchange. The cells lining the airspaces, alveolar epithelial cells, are involved in proper gas exchange function in the lungs. Repetitive injury to these cells is thought to initiate processes that lead to lung fibrosis. Both genetic and acquired factors could impact the response of epithelial cells to injury. We will perform experiments to better understand the epithelial cell responses to stress and cell injury that impact fibrosis. The goal of these studies is to provide important insights to identify novel therapeutic targets for IPF.

Cory M. Yamashita, M.D.

Mentor: James F. Lewis, M.D.
Institution: University of Western Ontario

The role of MMP-3 in acute lung injury and multiple organ failure

Each year, many thousands of North Americans sustain a severe injury to the lung and will require admission to an ICU. Despite optimal treatment, 30-50% of these patients die, often as a result of multiple organ failure. It has been speculated that mediators generated by the lung in response to the injury are released into the circulation, and subsequently trigger damage in organs. Our studies will focus on a specific enzyme, matrix metalloproteinase-3, which we have recently determined to be generated and released into the circulation by the lung in response to injury. Our preliminary data suggests that this molecule is important in both lung injury and the injury of remote organs. We will employ experimental models of acute lung injury in cultured cells and animal models to confirm our hypothesis that MMP-3 can mediate damage within the lung and also in other organs, with the goal of identifying MMP-3 as a potential therapeutic target.