PARKER B. FRANCIS
FELLOWSHIP
PROGRAM

Class of 2008

The Parker B. Francis Fellowship provides funding to outstanding young lung researchers in the US, Canada and Mexico. Since its inception in 1976, the PBF Fellowship program has supported the work of more than 700 fellows in the fields of lung biology and respiratory disease. 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 fill leadership positions in prominent professional organizations throughout the world.

We are proud to present the class of 2008.

Dr. Zoulfia Allakhverdi

The role of epithelial cell-derived cytokines in allergic diseases
The incidence and morbidity of allergic diseases including asthma, rhinitis and atopic eczema have been steadily increasing over the last three decades. These diseases result from a genetic predisposition to react aberrantly to normal components of the environment. It is currently thought that these diseases arise from an abnormal interaction between the epithelial barrier separating the organism from the external world and the immune system. We will explore the role of epithelial cell-derived molecules capable of activating cellular components of the immune system and initiating allergic inflammation.

Mentor: Professor Guy Delespesse
Institution: CHUM Research Center, Montreal, Quebec

Dr. Diego F. Alvarez

Infusion of endothelial progenitor cells promotes repair of the pulmonary microvascular barrier following *Pseudomonas aeruginosa*-induced lung injury. Acute lung injury (ALI) is a major cause of mortality in critically ill patients. A hallmark of ALI is the disruption of the microvascular endothelium, a cellular barrier that protects against excessive movement of fluid from the blood into the lung tissue itself. While restoration of this barrier is essential for resolving ALI, cellular factors that promote such barrier repair are unknown. The goal of this project is to examine whether cell-based therapy utilizing lung-derived endothelial progenitor cells is effective in restoring the microvascular endothelial barrier during ALI. Further, we seek to determine whether a protein known as nucleosomal assembly protein-1 is responsible for the potential capacity of endothelial cells to repair the microvascular barrier.
Mentor: Professor Troy Stevens
Institution: University of South Alabama, Mobile, Alabama

Dr. Xiaoyong Bao

Innate immune response to human metapneumovirus
About 12% of all respiratory tract infections in children are caused by hMPV. This is second only to RSV, indicating that hMPV represents a tremendous pulmonary disease burden. hMPV infection causes pulmonary inflammation and anti-viral responses via the inducible expression of chemotactic factors and interferon. Our laboratory research is focused on respiratory virus-host interactions relevant to live vaccine vector development. In this project, we propose to investigate how airway epithelial cells and primary innate immune cells respond to hMPV infection and how viral proteins regulate these responses in the course of infection.
Mentor: Professor Roberto P. Garofalo
Institution: University of Texas Medical Branch at Galveston, Texas

Dr. Natalie Bauer

Pulmonary microvascular endothelial response to acute hypoxia: RhoA/Rho kinase signaling and microparticles Stress on the respiratory system from diseases such as acute respiratory distress syndrome or high altitude pulmonary edema, can cause endothelial cells that line the pulmonary blood vessels to release small intact vesicles called microparticles. Each microparticle is just 1 micrometer – about 1/25,000 of an inch – in diameter, and carries molecular signals to cells downstream, often leading to detrimental changes. The focus of this project is to understand how microparticles are generated by the parent cell, what molecular signals they carry, and how they damage downstream vasculature, contributing to the pulmonary edema characteristic of these conditions.
Mentor: Professor Ivan F. McMurtry
Institution: University of South Alabama

Dr. Kevin J. Cummings

5-HT disruptions and reflex control of heart rate: implications for SIDS SIDS occurs in infants between 2 and 4 months of age, probably from a failed cardio-respiratory or arousal response to physiological stress (*e.g.* hypoxia) during sleep. Newborns have a strong lung inflation reflex that wanes with development, as well as a strengthening carotid body chemoreflex. It has been proposed that SIDS occurs in part from a developmental imbalance between these reflexes, compromising the cardio-respiratory response to changes in blood gases. Interestingly, a considerable number of SIDS victims display disruptions in the medullary 5-HT (serotonin) system. Our experiments using neonatal rats and mice with disrupted 5-HT systems address the physiological plausibility that SIDS results from a deleterious interaction between lung reflexes, the carotid body chemoreflex and a disrupted 5-HT system.
Mentor: Professor Eugene E. Nattie
Institution: Dartmouth Medical School, Hanover, NH

Dr. Charles S. Dela Cruz

The role of cigarette smoke exposure and respiratory infections in emphysema Only a fraction of cigarette smokers end up developing clinically relevant airway obstruction. Additional events seem to be required to induce chronic obstructive pulmonary disease (COPD). The frequency of COPD exacerbations has been correlated with disease progression and worsening of lung function. These exacerbations are often due to respiratory infections. This proposal is aimed at understanding the cellular and molecular mechanisms by which respiratory pathogens interact with cigarette smoke in regulating inflammatory and airway remodeling responses in the lung.
Mentor: Professor Jack A. Elias
Institution: Yale University, New Haven, CT

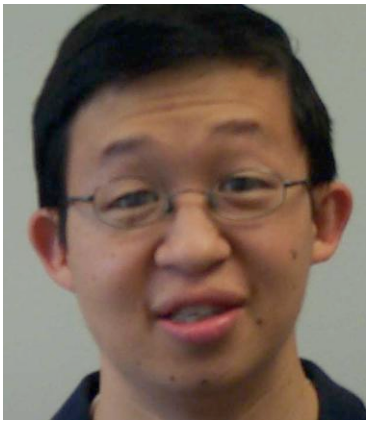
Dr. Elena A. Goncharova

RhoA GTPase modulates cell proliferation in lymphangioleiomyomatosis (LAM) LAM is genetic disorder characterized by unusual growth of smooth muscle-like cells within the lung, which leads to pulmonary disability and death. LAM is associated with loss of function mutations of tumor suppressors tuberous sclerosis complex 1 (*TSC1*) and *TSC2*, which results in constitutive activation of mTOR/S6K1 and abnormal cell proliferation. Recently, we found that loss of TSC2 function leads to aberrant activation of RhoA GTPase, a known regulator of cell proliferation. The goals of our research are to establish a role of RhoA in TSC2-related cell proliferation and to investigate the benefits of the combined treatment of TSC2-deficient cells and tumors with mTOR inhibitor rapamycin and Rho GTPase inhibitors, statins.
Mentor: Professor Reynold A. Panettieri, Jr. (PBF Fellow 1989 – 1991)
Institution: Univ. of Pennsylvania Sch. of Medicine, Philadelphia, PA

Dr. Naveen Gupta

Cell based therapy for experimental acute lung injury
Acute Lung Injury (ALI) and the Acute Respiratory Distress Syndrome (ARDS) are the most common forms of hypoxemic respiratory failure among critically ill patients. Despite the best supportive care, the mortality remains high at approximately 40%, and new treatments are needed. Recent studies have demonstrated that mesenchymal stem cells (MSC) have unique immunomodulatory properties that have beenshown to be beneficial in a variety of organ injury models, including acute renal failure and myocardial infarction. This project is focused on investigating the therapeutic and mechanistic effects of MSC in experimental models of ALI with the goal of potentially translating cell based therapy to clinical ALI/ARDS.
Mentor: Professor Michael A. Matthay
Institution: University of California, San Francisco, California

Dr. Stephen Huang



Epigenetic Regulation of the E Prostanoid 2 Receptor Gene in Fibrotic Lung Fibroblasts Idiopathic pulmonary fibrosis (IPF) is a devastating lung disease of unknown etiology with no effective therapies. Fibroblasts, which deposit extracellular matrix, are thought to be the principle players in the process of fibrosis. The activity of lung fibroblasts is inhibited by prostaglandin E_2 (PGE_2), an inflammatory mediator. We have shown that fibroblasts obtained from patients with IPF and from animal models of fibrosis exhibit resistance to the inhibitory effects of PGE_2 due to diminished expression of EP2, the receptor responsible for PGE_2 signaling. We will examine the role of epigenetic regulation in EP2 downregulation/PGE_2 resistance, as well as the role of epigenetic regulation in the pathogenesis of pulmonary fibrosis in general.
Mentor: Professor Marc Peters-Golden
Institution: University of Michigan, Ann Arbor, MI

Dr. Guillaume Lenormand

Why is the asthmatic airway refractory to deep inspirations?
Of all known agencies of bronchodilation, the single most effective is a simple deep inspiration. During a spontaneous asthmatic attack, however, this potent agency fails. The central hypothesis that I propose to test is that the cytoskeleton of the airway smooth muscle cell fails to become fluid in response to a deep inspiration, and that this failure results in a breakdown of the underlying homeostatic balance between cytoskeleton fluidization on the one hand and cytoskeleton reinforcement/contraction on the other.

Mentor: Professor Jeffrey Fredberg
Institution: Harvard School of Public Health, Boston, MA

Dr. Peter M. MacFarlane

Serotonergic modulation of spinal NADPH oxidase is necessary and sufficient for intermittent hypoxia-induced phrenic long-term facilitation. Acute repetitive bouts of mild hypoxia stimulates breathing and initiates a persistent augmentation of breathing long after the hypoxic stimulus has been removed. This form of respiratory plasticity, known as long-term facilitation (LTF), is attributable to more efficient neural transmission of the drive to breathe. LTF requires hypoxic-induced release of the neurotransmitter serotonin, which could be acting to stimulate formation of reactive oxygen species (ROS) in the brainstem and spinal cord. The primary goal of my research is to investigate the mechanisms of serotonin-induced ROS formation and the signaling role that they play in respiratory plasticity.
Mentor: Professor Gordon S. Mitchell
Institution: University of Wisconsin, Madison. WI.

Dr. Brian Mitchell

The generation and maintenance of directed mucus flow.
Cilia are hair-like structures projecting from cells in the respiratory tract that work together to propel mucus out of the airways. To function properly cilia must all beat in the same direction. My work aims to understand, at the molecular level, how cilia become oriented in a partiular direction and how they work together to generate directed mucus flow. We use the ciliated epithelium of the *Xenopus* larval skin as an experimentally pliable model for understand the relationship between cilia function and directed flow in the hopes of understanding how this relationship is disturbed during respiratory disease.

Mentor: Professor Chris Kintner
Institution: The Salk Institute, La Jolla, California

Dr. Laura M. Palermo

Screening of antiviral compounds and characterization of their effect on paramyxovirus infection in the respiratory tract. Parainfluenza virus 3 infection is the predominant cause of croup in young infants and a common agent of bronchiolitis and pneumonia. Most vulnerable are babies born prematurely or with congenital abnormalities, as well as patients of all ages, who can develop life-threatening pneumonia as a result of this infection. There are no vaccines yet for the parainfluenza viruses, and any vaccine is unlikely to protect the very youngest infants and the immunocompromised. This project aims to identify novel small-molecule inhibitory compounds to prevent or treat parainfluenza infection. Proposed inhibitory molecules will be tested using an *ex vivo* model of the human respiratory system that represents the biology of the human lung.

Mentor: Professor Anne Moscona

Institution: Cornell Univ./ Weill Cornell Medical College, NYC, NY.

Dr. Jordi B. Torrelles

Influence of the human lung hydrolases on Mycobacterium tuberculosis infection The World Health Organization estimates that one person is infected with *Mycobacterium tuberculosis* (*M.tb*, the causative agent of tuberculosis) every 4 seconds and one dies every 18 seconds. *M.tb* infection results from airborne transmission to the alveoli of the lungs. The lung contains homeostatic hydrolytic enzymes that are released to the alveolar space. We hypothesize that these enzymes are critical in determining the nature of *M.tb* infection. We propose to define how enzymes in the lung environment modify the *M.tb* cell envelope and ultimately regulate its metabolism, intracellular survival and the host immune response. This study will be critical in enabling us to develop novel treatment strategies and vaccines at the site of infection.

Mentor: Professor Larry S. Schlesinger

Institution: Ohio State University, Columbus, Ohio

Dr. Phuoc T. Tran

Investigations on the differential oncogene-dependency of MYC versus K-Ras murine primary lung tumor model systems Lung cancer is the leading cause of cancer death worldwide. New treatments directed against cancer-causing "oncogenes" are dramatically changing lung cancer treatment. "Oncogene-addiction" is a phenomenon whereby targeting a single oncogene causes dramatic shrinkage of lung tumors. However, few lung cancers demonstrate addiction to a single oncogene, likely because multiple oncogenes are active simultaneously. Finding and targeting these additional oncogenes concurrently could improve treatment. We are using mouse lung cancer model systems to find and target multiple oncogenes. The ultimate goal of this proposal is to force lung tumors to exhibit oncogene-addiction after simultaneous targeting multiple oncogenes.

Mentor: Professor Dean W. Felsher

Institution: Stanford University School of Medicine, Palo Alto, CA

Dr. Jieru Wang

Influenza A virus induces innate immune response in differentiated adult human alveolar type II cells and macrophages
Influenza A viral pneumonia is characterized by severe lung injury and high mortality. Alveolar epithelial cells are one of the primary targets for viral pneumonia. Recently, we developed an *in vitro* system to culture and maintain differentiated human alveolar type II (ATII) cells. In the proposal we will study the innate immune response of primary ATII cells and alveolar macrophages from the same individual to influenza A infection. The focus of this project will be to understand and enhance the local innate immune system to limit viral production and lessen the inflammatory response and cellular injury.
Mentor: Professor Robert J. Mason
Institution: National Jewish Medical and Research Ctr, Denver, CO

Dr. George R. Washko

Computed tomographic imaging in COPD
COPD is a heterogeneous lung condition characterized by progressive loss of lung function causing increasing breathlessness and loss of quality of life. This condition is due to an unpredictable admixture of emphysema and airway disease indiscernible by conventional spirometric measures of lung function and has necessitated the recruitment of very large numbers of subjects for clinical investigation. We are working to define and validate new CT-based markers of both airway and airspace disease in subjects with COPD that can be used to define more homogeneous study populations and may define useful interim clinical study endpoints.
Mentor: Professor John J. Reilly (PBF Fellow 1988 – 1991)
Institution: Brigham and Women's Hospital, Boston, MA

Dr. Timothy Eoin West

Pulmonary Host Defense in Melioidosis
Melioidosis is a lethal tropical infection caused by the bacteria *Burkholderia pseudomallei* that often presents as pneumonia. Successful host defense against pneumonia requires activation of the innate immune system. We are studying the mechanisms of innate immune signaling in melioidosis using mouse models of airborne infection and by examining how variations in human immune genes influence susceptibility to disease. A better understanding of these mechanisms may lead to new approaches to treating this and other bacterial respiratory infections, leading causes of illness throughout the world.

Mentor: Professor Shawn J. Skerrett
Institution: University of Washington School of Medicine, Seattle WA