Parker B. Francis Fellowship Program
Class of 2020

Michaela Anderson, MD PhD

Visceral adipose tissue and frailty in idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is an increasingly prevalent chronic lung disease with no cure; frailty affects 50% of IPF patients, and is associated with increased severity of illness in response to acute insults (e.g. internal fat, called visceral adipose tissue (VAT), is a risk factor for frailty and wek propose to investigate potential mechanisms linking VAT and frailty. Better understanding the link between VAT and frailty may identify a modifiable target to improve morbidity and mortality in this growing patient populations. Our findings may lead to novel therapies and clinical trials evaluating the role of existing medications in the prevention and treatment of frailty in IPF.

Mentor: R. Graham Barr, MD PhD
Institution: Columbia University Medical Center

Raghu Chivukula, MD PhD

Analysis of lysosome dysfunction in the pathogenesis of pulmonary fibrosis.

Although it has been long appreciated that epithelial injury and stress can lead to pulmonary fibrosis, no current therapies target this critical step of the disease owing to a limited understanding of underlying biochemical mechanisms. We are interested in the role of specialized cellular “recycling bins” known as lysosomes, which have increasingly recognized roles in pulmonary fibrosis but have not been studied in detail previously due to inadequate experimental tools. Our group has now developed methods which allow exactly such biochemical and genetic characterization. We are focusing our initial efforts on a genetic disease which causes pulmonary fibrosis by disrupting lysosome function and a drug which acts similarly, with the intention to leverage the insights gleaned here to the treatment of patients with more common forms of this deadly disease.

Mentor: David M. Sabatini, MD PhD
Institution: Massachusetts General Hospital

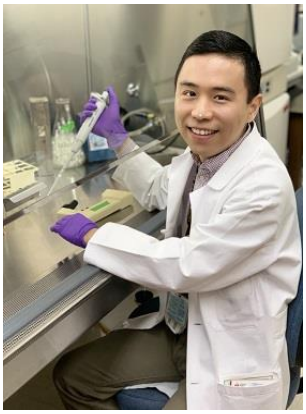
Adam Haber, PhD

Implicating rare epithelial cells in allergic asthma using single-cell analysis

Asthma is a heterogeneous disease involving many cellular factors, but one constant identified across many studies is the central role of airway epithelial cells. These cells comprise a specialized cell population that lines the airways of mammalian lungs. Airway epithelial cells are diverse, with complex delegation of biological functions to specific subtypes. My recent work has shown that even the rarest subtypes can play surprisingly important roles in the regulation of the local immune system, the physiology of the airway surface liquid, and mucosal barrier function. Importantly, the responses of these rare cell-types to environmental exposures are not yet known. Study of these responses by conventional methods is difficult because these cells are extremely rare and protocols to isolate them are not yet in place. To fill these gaps, my proposed project will use single-cell technologies to uncover the specific function of each epithelial cell-type, including the rarest, in mediating airway inflammation. These studies may lead to the discovery of new biomarkers and novel targets for therapies.

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

Chao He, MD PhD

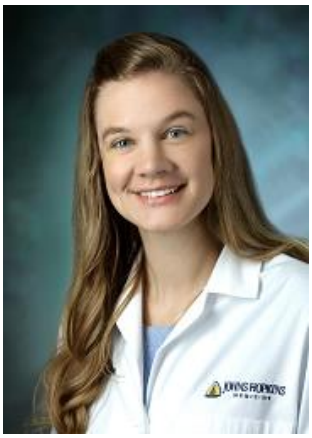


Targeting MCT1-mediated Lactate Intercellular Shuttling in Pulmonary Fibrosis

Pulmonary fibrosis is a class of disease conditions characterized by subacute and chronic progressive scarring of the lungs. The most common form, idiopathic pulmonary fibrosis (IPF), has a survival of 3 to 5 years, which is worse than most cancers. Macrophages, one of the immune cells, promote fibrosis progression by acquiring a phenotype that induces scar formation. The interplay between lung macrophages and the scar-producing fibroblasts is poorly defined. These proposed studies are the first to investigate if lactate, a byproduct of glucose metabolism in fibroblasts, can serve as the signal to worsen fibrosis development. This study uses cutting-edge techniques to understand the changes in macrophage metabolism and will provide potential mechanisms and therapeutic targets to modulate disease progression in IPF.

Mentor: A. Brent Carter, MD MDPhD
Institution: University of Alabama at Birmingham

Megan M. Hosey, PhD



An Early Psychological Intervention for Anxiety Symptoms in Patients with Acute Respiratory Failure

A growing number of patients are surviving a stay in the intensive care unit (ICU) but may experience long-lasting psychological problems. Early psychological treatment to reduce anxiety symptoms in the ICU and hospital may help improve long-term psychological outcomes, but research evaluating such treatment for ICU patients is scant. This is a pilot randomized controlled trial to evaluate the feasibility, acceptability, and potential benefit of an evidence-based psychological intervention for anxiety and associated outcomes for ICU patients.

Mentor: Dale M. Needham, MD PhD
Institution: Johns Hopkins University

Crystal M. North, MD

Are people living with HIV more susceptible to air pollution associated lung disease?

People living with HIV (PLWH) may be more susceptible to air pollution-associated lung disease, the leading environmental cause of death globally. This proposal focuses on understanding how HIV serostatus modifies relationships between air pollution exposure, systemic immunologic biomarkers and lung function. This work will provide important insights into chronic inflammatory pathways and lung function among PLWH and may help us understand the mechanistic underpinnings of other HIV-related non-communicable diseases. As the world's air quality continues to deteriorate and the global population living with HIV ages, we must understand how these risks influence respiratory health in order to design effective interventions to improve health outcomes. If our hypotheses are correct, then targeted environmental health interventions could have outsized health impacts among the 38 million PLWH worldwide.

Mentor: David C. Christiani, MD MPH
Institution: Massachusetts General Hospital/Harvard Medicine School

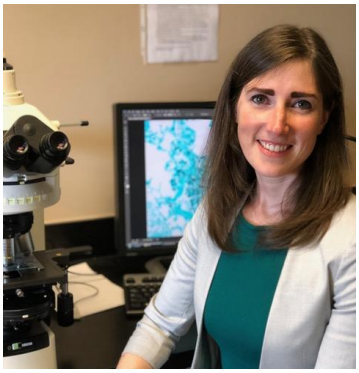
Lokesh Sharma, PhD

Molecular Mechanisms of Fibrosis Induced Antiviral Response

Influenza virus infects hundreds of millions of people and kill almost half million people every year. In the US, influenza killed approximately 80,000 people in 2018 (most lethal infectious disease). Current therapies are inadequate and only effective if administered early enough during the infection. New therapies are urgently needed. We recently found that mice with pre-existing pulmonary fibrosis are protected from influenza viral infection. Upon dissecting the mechanisms, we found that these mice have upregulation of an interferon receptor on the lung epithelium, a cell type that is infected by influenza. Here we propose to further study these mechanisms and use them in mouse models and human cells to understand if this can provide a novel strategy to enhance viral clearance and decrease mortality.

Mentor: Charles S. Dela Cruz, MD MPH
Institution: Yale University

Kelly Shepardson, PhD



The role of IFNAR2 in regulation of damage during A. fumigatus lung infection

Damage occurring during lung infection can result in physical harm to the lungs through increased inflammation and tissue destruction. This can lead to organ impairment and death. Interferons are secreted molecules that can increase inflammation during infection. Interferon interacts with lung cells through specific receptors located on the cells surface to drive inflammation. We found that infection outcome is determined by which portion of the receptor interferons interact with. This interferon-regulated damage response is not pathogen-specific as similar damage occurs during infection with either the fungus Aspergillus fumigatus or influenza virus. Results from this study will allow us to better understand how the host regulates damage during infection, which could guide the rational design of therapies for patients with life threatening infections.

Mentor: Agnieszka Rynda-Apple, PhD
Institution: Montana State University

Dragos M. Vasilescu, PhD

Comprehensive multi-resolution investigation pathology

Idiopathic Pulmonary Fibrosis (IPF) is a rare, chronic, progressive lung disease of unknown cause that affects mostly older adults and has a worse diagnosis than many cancers. IPF is difficult to diagnose, frequently misdiagnosed and patients have a median survival time of 2-3 years from diagnosis. Using a multi-resolution imaging approach that enables ultra-resolution to visualize the IPF lung, the goal of this study is to not only improve diagnosis, but to characterize the changes that occur in the IPF lung to develop new therapeutic treatments.

Mentor: James C. Hogg, MD PhD
Institution: University of British Columbia

Xiaoyi Yuan, PhD

miR-147 Controls Macrophage Lipopolysaccharide-Induced Inflammatory Responses

Acute respiratory distress syndrome (ARDS) is characterized by inflammation and fluid builds up in the lung and results in high mortality and morbidity in patients. So far there is a lack of effective treatment for ARDS. MicroRNAs are small molecules that can inhibit gene expression in the cells. Here, we identified microRNA147 (miR-147) to be a crucial small molecule to reduce lung inflammation in ARDS. MiR-147 is increased in ARDS patients and mice with acute lung injury. Increase miR-147 level in lung reduces inflammation. Here, we will study how miR-147 reduces lung inflammation during ARDS. We will also test whether increasing miR-147 level in the lung will improve ARDS outcomes. Our studies are designed to find novel therapeutic targets to treat ARDS. o test whether increasing miR-147 level in the lung will improve ARDS outcome. Our studies are designed to find novel therapeutic target to treat ARDS.

Mentor: Holger K. Eltzschig, MD PhD
Institution: The University of Texas Health Center at Houston