CENTER FOR FACULTY DEVELOPMENT

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Introduction

I am a physician researcher in the Division of Pulmonary and Critical Care Medicine at Massachusetts General Hospital (MGH). I specialize in the care of patients with pulmonary fibrosis, in particular those with acute exacerbations requiring hospitalization and critical care. After completing my fellowship training in Pulmonary and Critical Care Medicine in the Harvard Combined Program, I joined the faculty at MGH and Harvard Medical School (HMS), where I conduct research on the mechanisms of fibrogenesis to enhance our knowledge and the quality of patient care as well as provide clinical care and supervise trainees. My goal as a physician scientist is to build a research program focused on studying the role of the endothelium in the development of pulmonary fibrosis, using both animal models and patient lung samples to understand how endothelial dysfunction contributes to fibrosis, and how to use this knowledge to design novel therapeutic strategies to cure fibrotic diseases.

Area of Excellence: Investigator

Pulmonary fibrosis carries significant morbidity and mortality and significant gaps remain in the understanding of the pathogenesis of pulmonary fibrogenesis. In particular, while there is accumulating evidence for endothelial dysfunction in the lungs of IPF patients, the role of the endothelium in the development of fibrosis has been understudied. I began my research in the lab of Dr. Andrew Tager studying the links between lung injury, vascular permeability, and the development of pulmonary fibrosis. By studying Rho kinase, a major regulator of cellular cytoskeleton and vascular integrity, I found that mice haplo-insufficient for Rho kinase were protected from bleomycin induced pulmonary fibrosis, and one of the major mechanisms for this protection was a significant reduction in vascular permeability in the mice which preceded the development of fibrosis. In 2018, I published these findings in an original manuscript entitled "The Rho Kinase Isoforms ROCK1 and ROCK2 Each Contribute to the Development of Experimental Pulmonary Fibrosis" in the American Journal of Respiratory Cell and Molecular Biology. I have continued my research into the role of vascular permeability with support from an NIH K08 award to study two signaling pathways which regulate vascular permeability, Rho kinase and S1P/S1PR1. I recently published a first-author paper in the American Journal of Respiratory Cell and Molecular Biology describing my findings that mice deficient in endothelial S1PR1 have exaggerated vascular permeability and fibrosis after bleomycin injury. I have also published a review paper in Pharmacological Reviews entitled "Rho kinases as critical mediators of multiple pro-fibrotic processes: potential therapeutic targets for pulmonary fibrosis" and another review on the role of vascular permeability in pulmonary fibrosis (last author) in 2020 in the European Respiratory Journal. I have presented my research at international meetings including the American Thoracic Society and the International Colloquium for Lung and Airway Fibrosis. I have also successfully obtained grant funding

from the ATS Foundation, Boehinger Ingelheim, MGH DOM, and the HMS Shore Fellowship to study both Rho kinase and S1P/S1PR1 signaling in the context of pulmonary fibrosis.

In addition, I have participated in the peer-review process, invited twice to serve on the program committee for the Assembly for Respiratory Cell and Molecular Biology for the American Thoracic Society (ATS). As a member of this committee, I review hundreds of abstracts each year to select which ones are presented in each format at the annual ATS meeting. I also serve on ATS RCMB Early Career Professionals Working Group where I work to develop programs and activities to involve young professionals in the RCMB assembly, and I chair the subcommittee on mentorship, matching mentors and mentees within the assembly. I have been invited as an ad hoc reviewer for several journals including the *American Journal for Respiratory and Critical Care Medicine* and *Circulation*.

Due to the COVID-19 global pandemic, my work shifted significantly as I was pulled into the hospital to work caring for the sickest COVID patients in the ICU at MGH. Alongside my colleagues in critical care, we all worked in shifts of five days on and five days off as we expanded into more than five additional ICUs throughout the hospital. The labs were shut down for months in 2020, and my research was put on hold as I utilized my training in pulmonary and critical care to care for mechanically ventilated patients with COVID-19 induced ARDS, including those requiring ECMO. I participated in research which was published in *Critical Care Explorations* studying tools for allocation of resources in the pandemic. In addition, I co-authored an article in the MGH PCCM Fast Literature Assessment and Review (FLARE) on the anticipated rates of post-COVID pulmonary fibrosis.

In addition to my recent publications described above, I am involved in several active projects which are nearing publication. Through a funded R33 collaboration with Dr. Peter Caravan in MGH Radiology, I am preparing data for 2 separate papers on molecular probes to identify active fibrogenesis in pre-clinical models of fibrosis. I am also co-mentoring a post-doctoral fellow with my mentor, Dr. Medoff, on a project exploring the role of S1P/S1PR1 signaling in the development of post-viral fibroproliferation. We are preparing a manuscript demonstrating a clear link between endothelial S1PR1, vascular permeability, and fibroproliferation after influenza infection. I am finishing a manuscript on myofibroblast specific targeting of anti-fibrotic drugs using nanoparticles in pre-clinical models of pulmonary fibrosis; this work began with my former mentor, Dr. Tager, on cell-specific targeting of Rho kinase signaling in epithelial cells and fibroblasts. Lastly, I have recently received funding from Boehringer Ingelheim to study the phenotype which is emerging from recent single cell RNA sequencing data in IPF patients, that there is an unexplained expansion of bronchial vessels in the fibrotic lung.

Teaching

As an attending physician on the Pulmonary Consult service, I teach fellows and residents with an emphasis on interstitial lung diseases including the prototypical fibrotic lung disease, idiopathic pulmonary fibrosis (IPF). I supervise and teach the fellows skills, such as bronchoscopy and thoracentesis, during this rotation. I also attend in the MGH Medical Intensive Care Units where I supervise and teach medical and surgical fellows, residents, and nurse practitioners in the critical care setting. In the laboratory setting, I am co-mentoring 2 post-doctoral fellows on projects: Dr. Patricia Brazee on her studies on S1P signaling in post-viral fibroproliferation and Dr. David Ziehr on his studies on glycolytic enzymes and lactate utilization in the context of pulmonary fibrosis. I also teach two to four research technicians animal surgery, molecular biology tools such as qPCR and Western blotting, and animal and human cell culture models of fibrosis.

Supporting Activity: Clinical Expertise

As a pulmonary and critical care attending physician, I work in the MICU overseeing teams of residents and fellows, caring for critically ill patients. I am particularly interested in both interstitial lung disease (ILD) and acute respiratory distress syndrome (ARDS) and many times these patients overlap in our ICU. I have expertise in ARDS management, including mechanical ventilation, prone positioning, and ECMO management. This past year I have cared for many patients with COVID-19 ARDS in our MICU. I also have expertise in ILD management, including acute exacerbations and new presentations of

connective-tissue associated ILD, such as myositis associated ILD. In addition to the MICU, I work in the Respiratory Acute Care Unit (RACU), where I have developed expertise in the care of patients on long term mechanical ventilation and have expertise in tracheostomy management. Lastly, I work on the MGH Pulmonary Consult service, where I have expertise on the diagnosis and management of a wide variety of pulmonary diseases, including COPD, asthma, ILD, vasculitis, organizing pneumonia, and lung cancer. In this role, I also have expertise in bronchoscopy and thoracentesis.

Summary

As an HMS Instructor in Medicine, I conduct basic and translational research on mechanisms of pulmonary fibrogenesis and provide clinical care for patients with pulmonary fibrosis. My goal is to define the role of the pulmonary vascular endothelium in the development of fibrosis, and to use the insights I find to develop novel therapeutic strategies to improve the quality and longevity of life for patients with pulmonary fibrosis. I plan to extend these findings into other fibrotic diseases, including fibroproliferation after ARDS, which has become especially important in the context of the COVID-19 pandemic.