Hello and Welcome back! We have had a very eventful Fall! As winter begins to seep in, let’s look back on some of the accomplishments and events from September 2019-January 2020. Let’s also look ahead to the upcoming events for Spring and Summer!

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NEW FACES

Neelou Etesami
MD/ PhD Student
Mizgerd Lab

(Susan) Sunhyo Ryu, Ph.D.
Postdoctoral Fellow
Jin Lab

Jake Le Suer
Graduate Student
Hawkins Lab

Taylor Matte
Graduate Student
Hawkins Lab
2019 FALL EVENTS

A look back on some of the fun events from this quarter including, the new Pulmonary CCR Conference, the Jerry Brody Lecture, and more!
Evans Day was a great success thanks to the many posters, oral presentations, and abstracts contributed by our Pulmonary Center.

Congratulations to everyone who won an Evans Day Award!

Kristine Abo
First Place Basic Research (Poster) Award

Anukul Shenoy, Ph.D.
Second Place Basic Research (Poster) Award

Finn Hawkins, M.D.
Evans Junior Faculty Research Merit Award
PULMONARY COMBINED CLINICAL AND RESEARCH (CCR) CONFERENCE

The inaugural season of the Pulmonary CCR Conference is well under way, and it has been a great success so far due to our talented trainees and faculty!

GUEST LECTURE

We had a fun visit from Claire Doerschuk, M.D. this fall!
Nov. 15th 2019
Annual Holiday Party
Dec. 14th

Our annual Holiday Party was an absolute blast! We welcomed friends and family to join the Pulmonary Center for a night of food, dancing, and cheer. It was a truly wonderful way to say goodbye to 2019 and look ahead to the bright New Year!
CONGRATULATIONS!

Congratulations to Faculty Member Jonathon Iaccarino and Pulmonary Fellow Samuel Belok on the new additions to their families!

WILLIAM BASIL IACCARINO

Born Dec. 25th

JUDAH BERLIN BELOK

Born Dec. 18th
We were very excited to bring in Dr. Scott Budinger to speak for this year’s Jerry Brody Lecture! Jerry Brody, his wife Anne, several of his trainees, a few of his old medical school friends, the pulmonary center, and many others were all in attendance. It was wonderful to come together through science and celebrate the life and accomplishments of our dear friend Jerry.

Guest Lecturer: Scott Budinger, M.D.

“Understanding Aging Through the Prism of Alveolar Macrophages”
We are pleased to announce the Jerome S. Brody, M.D., Endowed Fund, to honor our friend and colleague Jerry Brody. Dr. Brody was the longest serving director of the Pulmonary Center. For over 30 years, his vision of multidisciplinary biological research in pulmonary medicine drove tremendous growth and achievement here, while he also served as a renowned and valued advisor to fellows and students. Jerry’s scientific passion focused on lung development. He established foundations for our current knowledge about lung cell and molecular biology, and he made seminal contributions relating to cigarette smoke-induced lung diseases including lung cancer and COPD. Jerry substantially improved the Pulmonary Center and the BU School of Medicine, and he had a huge impact on pulmonary medicine worldwide. This endowment will specifically support pulmonary research at BU, and will convert to the Jerome S. Brody Professorship if and when the professorship target is reached. We hope you will be as excited as we are about this opportunity to honor Dr. Brody!

To make a secure gift on-line in support of the Brody endowment, please go to our development page and click the red box saying “Click Here to Choose a Fund” which will allow you to specify “Jerome S. Brody, M.D. Endowed Fund.” For other opportunities or questions, please contact Suzanne Maselli, Assistant Dean for Development, at 617-358-9530 or smaselli@bu.edu. Your donation is tax-deductible, fully credited as a gift to BU, and helps fight lung disease. Thank you for your support!

Jerry Brody Endowment
http://www.bumc.bu.edu/pulmonarycenter/support/brody-endowment/
Every year *Boston Magazine* announces a list of Boston’s “Top Docs,” we are very proud to have many of our pulmonologists make the 2020 list, including:

George O’Connor  
Liz Klings  
Arthur Theodore  
Fred Little  
Jeffery Berman  
John Berk  
John Bernardo

Dr. Hasmeena Kathuria spoke with the *Boston Herald* on the dangers of unregulated vaping products.

This article, titled “Most nicotine vapes have 6 ingredients: solvent, flavor, sweetener, nicotine, metal and the scariest ingredient – the unknown,” was released in January 2020.

The *ATS Critical Care Assembly* interviewed Dr. Allan Walkey about strategies to address Atrial Fibrillation.

In this “Breathe Easy Critical Perspective” podcast, Dr. Dominique Pepper interviews Dr. Allan Walkey to discuss atrial fibrillation in the ICU (Released January 2020).
Researchers Describe Unique Genetic Identity of Primordial Lung Progenitors

Findings may lead to better stem cell protocols for lung diseases

(Boston)—For the first time, researchers describe the genetic program behind primordial lung progenitors—embryonic cells that give rise to all the cells that form the lining of the respiratory system after birth. They believe this study has long-term implications for the treatment of diseases affecting the respiratory system, such as chronic obstructive pulmonary disease (COPD), alpha-1 antitrypsin deficiency and cystic fibrosis.

Diseases affecting the lungs are not easily treatable and result in significant morbidity and mortality worldwide. Specialized stem cells with the potential to self-renew have been proposed as a critical component of tissue homeostasis for many organs, including the lung. Similar cells can be engineered in vitro and used in the future in cell replacement therapies for respiratory diseases.

Using a genetically modified experimental model, researchers from the Center for Regenerative Medicine (CReM) of Boston University and Boston Medical Center, were able to isolate and describe the genetic program of the earliest lung progenitor cells and understand the signals that instruct them. They then used computational methods that helped them define how similar their engineered lung cells are to the in vivo progenitors.

“Our findings define in great detail a rare, transient cell, namely the primordial lung progenitor. The knowledge generated from this study will be of great value in the derivation of human primordial lung progenitors in culture, since the equivalent stage in human lung development is not accessible,” explained corresponding author Laertis Ikonomou, PhD, assistant professor of molecular and translational medicine at Boston University School of Medicine.

Respiratory system diseases, such as COPD, cystic fibrosis and lung interstitial disease severely affect quality of life. “We hope that our findings will eventually lead to more protocols for, transplantable lung epithelial cells for treatment of such diseases and for drug development,” added Ikonomou.

These findings appear online in the journal *Nature Communications*.

Researchers Build a Better Lung Model

May lead to more personalized treatments for lung diseases

(Boston)—Using a combination of pluripotent stem cells (cells that can potentially produce any cell or tissue type) and machine learning (artificial intelligence that allows computers to learn automatically), researchers have improved how they generate lung cells.

Using this technique, cells can be grown in a laboratory and stored for more than one year without losing their lung identity and used to model lung diseases thereby finding better treatments and cures for lung diseases in the future.

Induced pluripotent stem (iPS) cells are derived from the donated skin or blood cells of adults and, with the reactivation of four genes, are reprogrammed back to an embryonic stem cell-like state. iPS cells can be differentiated toward any cell type in the body and do not require the use of embryos.

Building on previous work from the Center for Regenerative Medicine (CReM) of Boston University and Boston Medical Center, researchers in the CReM, working together with investigators from Carnegie Mellon University (CMU), reprogrammed blood from adults into iPS cells. They then treated these stem cells with growth factors over a period of one month until they became cells which were very similar to adult lung cells.

According to the researchers, often when this type of experiment is performed the resulting cells are not a pure collection of the cell that they aimed to create (target cell) and they do not keep the characteristics of the target cell for prolonged periods of time.

“Therefore, we developed a combination of techniques that examines the gene expression of thousands of single cells combined with DNA barcoding of each individual cell and machine learning to build up a dynamic picture of what factors favor cells that go on to be lung cells in our system. Using this knowledge we were able to improve our methods for generating lung cells so that we can now create more relevant cells that keep their cell identity in a dish for more than one year,” explained Killian Hurley, MD, PhD, researcher at the Royal College of Surgeons in Ireland, who co-authored the study with Jun Ding, PhD, a post-doctoral fellow at CMU.

The researchers believe this study will improve their ability to model lung disease and treatments in the laboratory for diseases including idiopathic pulmonary fibrosis, chronic
obstructive pulmonary disease (COPD), alpha-1 antitrypsin deficiency and neonatal respiratory distress or early-onset interstitial lung disease.

Millions of people in the United States and around the world have severe lung diseases, often without good treatments or cure. Some of these diseases may even require lung transplantation which is a complex and high risk surgery with the need for donor organs always exceeding the supply.

“The machine learning methods we developed for this study can also be applied to studies of other tissues and organs,” said Ding. “We hope that our newly developed techniques for generating a pure, unlimited supply of cells using patients-derived stem cells can make possible new treatments or cures for diseases. These developments would prolong lives and improve the quality of those lives.”

“The key hurdle to understanding what goes wrong with an individual patient’s lung cells has been our inability to access those cells or to grow them in the laboratory. This approach allows us to now engineer from any individual patient those very finicky cells and to introduce bar codes into those cells that allow us to track and understand each cell and all their progeny over time in the laboratory dish. The result is an inexhaustible source of new lung cells that can be prepared from any patient of any age,” added co-corresponding author Darrell Kotton, MD, David C. Seldin Professor of Medicine and Director, CReM, who led the work together with Ziv Bar-Joseph, PhD, the FORE Systems Professor of Computer Science at CMU.

These findings appear online in the journal Cell Stem Cell.


[January 28th 2020]

Pneumonia Recovery Reprograms Immune Cells of the Lung

These findings may lead to new strategies for preventing or curing pneumonia.

Researchers have determined that after lungs recover from infection, alveolar macrophages (immune cells that live in the lungs and help protect the lungs against infection) are different in multiple ways and those differences persist indefinitely.

How the lungs protect themselves when they are at their healthiest, like in young adult humans, is complex and only beginning to be understood. BUSM researchers propose that the new alveolar macrophage biology resulting from prior experiences with infections is one of the elements helping to protect the lungs of young adults against pneumonia.

“We have determined that these immune cells have a memory of their prior experiences and that memory influences how they will respond to any subsequent challenges like later infections,”
explained corresponding author Joseph Mizgerd, ScD, professor of medicine, microbiology and biochemistry.

Worldwide, pneumonia remains a serious public health burden. Each year more than one million children under the age of five die from pneumonia and associated complications. In the U.S., pneumonia is the most common reason for the hospitalization of children and accounts for nearly half of the infectious disease-related hospitalizations and deaths of older adults.

In this study, experimental models were infected with a bacteria called pneumococcus, which is a normal experience for humans during childhood, and then allowed to recover. Another set of models were never infected. The researchers then compared the alveolar macrophages in the lungs of these two different groups, including the receptors on the cell surfaces, the genes being expressed by these cells and the metabolites inside of these cells. The alveolar macrophages in the models which had recovered from pneumonia had a new baseline in all these read-outs. In addition, their alveolar macrophages responded differently to subsequent infections, compared to the alveolar macrophages in lungs without a history of infections.

According to the researchers, young children are extremely susceptible to pneumonia, but multiple types of lung defense develop during childhood and protect against pneumonia, persisting through young adulthood. “The combination of aging, poor living habits and disease degrade these lung defenses so that pneumonia susceptibility increases again in later years,” added Dr. Mizgerd.

By working to elucidate the naturally acquired defenses against pneumonia in young healthy adults the researchers hope to find better ways of identifying those most at risk for developing pneumonia and to devise new strategies for preventing or curing pneumonia.

These findings appear online in the *JCI Insight*.


[December 11th 2019]

**Novel Respiratory Cell Changes Identified from Cigarette Smoke Exposure**

*Changes may result in therapies to prevent the development of lung cancer.*

Cigarette smoking changes the types of cells that are present in the respiratory track and some biological processes necessary for detoxification of cigarette smoke are restricted to specific types of cells.

“Our study describes novel respiratory cell changes that result from cigarette smoke exposure that may be associated with the development of pre-cancerous tissue,” explained
corresponding author Jennifer Beane, PhD, assistant professor of medicine at BUSM. Specifically, the researchers have identified a novel type of cell present in current smokers that remains active even after smoking cessation. Genes expressed by these cells have also been detected in both pre-cancerous lung tissue and lung tumors. Further study of these cells may result in therapies to prevent the development of lung cancer or ways to measure risk of developing lung cancer.

Cigarette smoking is a major risk factor for the development of lung cancer. Lung cancer is the leading cause of cancer death in the U.S. While studies have shown that smoking alters bronchial epithelial function and form, its precise effects on specific cell types and overall tissue composition have been unclear.

Never and current smokers underwent a medical procedure called a bronchoscopy to collect cells from their respiratory tract. Lead author, Grant Duclos, explains “Using a breakthrough approach referred to as single-cell genomics’, the cells sampled from each subject were isolated and the expression of their genes were measured to identify distinct types of cells and characterize differences in the distribution of the cells between never and current smokers.” The results were then confirmed by looking at these differences in tissue sampled from additional never and current smokers.

The researchers believe that a detailed understanding of the molecular consequences of drivers of deadly lung diseases – smoking in particular – will enable them to understand the transition from healthy, normal states to pathological conditions. “We hope that this study and the work that follows it will lead to effective strategies for early detection, prevention and reversal of smoking-associated lung diseases,” added co-corresponding author Joshua Campbell, PhD, assistant professor of medicine at BUSM.

These findings appear in the journal Science Advances.


[December 2nd 2019]

**Advancement Made in the Visualization of Large, Complex Datasets**

*This may lead to the discovery of novel cell types to therapeutically target diseases.*

An improvement to the premier data visualization tool t-distributed Stochastic Neighborhood Embedding (t-SNE), called optimized-t-SNE (opt-SNE), shines new light on researchers’ ability to view exactly what is in their datasets.

opt-SNE is an advancement of the widely used t-SNE created nearly 10 years ago. While t-SNE can accurately analyze approximately half a million cells in any given sample, in recent years, single cell datasets have become much larger. With opt-SNE, researchers can now visualize data from samples containing tens of millions of cells with unprecedented resolution.
The development of opt-SNE was led by Anna Belkina, MD, PhD, assistant professor of pathology and laboratory medicine.

In addition to its capacity to properly process big datasets, opt-SNE was also able to successfully visualize very small, distinct populations of cells in the blood samples tested (with each cell in these groups as rare as one in a hundred thousand of the total number of cells in the sample). Prior to opt-SNE, this accurate, large-scale visualization with simultaneous magnification of miniscule populations was not possible. “t-SNE was originally a “one-size-fits-all” algorithm, but opt-SNE computations are tailored to each individual dataset and this allows both a birds-eye and up-close view of what is in your sample. With opt-SNE, both the haystack and the needles within it can be seen,” explained Dr. Belkina, the corresponding author of the study. “It is a particularly valuable tool for the investigation of cytometry and single cell transcriptomics data”.

The visualization of different populations within a sample of 20 million human blood cells using t-SNE (left) and opt-SNE (middle, right)

opt-SNE allows researchers to pinpoint previously undetectable features that distinguish diseased samples from controls. This new lens into disease states may reveal novel targets for therapies as well as new biological phenomena. This approach is already in use by multiple research groups due to Dr. Belkina’s ongoing collaborations with developers of major single cell data analysis platforms who enabled opt-SNE implementation into the Omiq.ai cloud analysis platform (Christopher Ciccolella, MS) and FlowJo software (Josef Spidlen, PhD and Richard Halpert, PhD) and co-authored the manuscript. An open-source opt-SNE package has also been released.

Additional co-authors of the study, which appears online in Nature Communications, include Rina Anno, PhD and Jennifer Snyder-Cappione, PhD.

Researchers Discover How Lung Cells Respond to Bacteria

This study has implications for preventing and treating pneumonia.

Previous research has shown that recovery from bacterial pneumonia hugely improves our defense against further infections by seeding the lungs with immune cells called lung resident memory T (T\textsubscript{RM}) cells, but how these cells actually protect the lungs against future bacterial infections has been unknown until now.

Researchers have discovered that T\textsubscript{RM} cells tell surrounding lung cells to send out a signal to recruit bacteria killers called neutrophils. These finding show that immunity within the lung tissue is what provides the most protection for preventing pneumonia.

Worldwide, pneumonia remains a serious public health burden. Each year more than one million children under the age of five die from pneumonia and associated complications. In the U.S., pneumonia is the most common reason for the hospitalization of children and accounts for nearly half of the infectious disease-related hospitalizations and deaths of older adults.

Using experimental models BUSM researchers developed ways to deplete T\textsubscript{RM} cells to determine how specifically it affected the lung’s response to infection. “Because we found that the lung-lining cells changed their behavior when T\textsubscript{RM} cells were missing, we studied those lung-lining cells in culture, including how they responded to T\textsubscript{RM}-derived signals to generate neutrophil-recruiting signals,” explained corresponding author Joseph Mizgerd, ScD, professor of medicine, microbiology and biochemistry at BUSM. It was Dr. Mizgerd and his team who first identified that recovery from bacterial pneumonia changes lung tissue that was previously infected.

According to the researchers, this study was designed to generate knowledge about the immune components that are useful for fighting pneumonia. “Over the long-term, our study has implications for preventing and treating pneumonia which is important for keeping people out of the hospital and for preventing hospitalized patients from progressing to the intensive care unit and even worse outcomes.”

Dr. Mizgerd envisions a future in which clinicians can measure and report a person’s lung immunity and pneumonia susceptibility status. “Interventions could be developed to improve an individual’s lung immunity in order to prevent pneumonia, and lung immunity is manipulated, triggered, or mimicked in pneumonia patients to accomplish a cure against drug-resistant organisms or microbes for which no drugs have yet been developed.”

The study appears online in the journal Mucosal Immunology.

PULMONARY OUTREACH

Drs. Fred Little and Paul Maglione represented the Pulmonary Center at the Immune Deficiency Foundation Community Walk on Oct. 6th, 2019.

AWARDS AND ACCOMPLISHMENTS

Finn Hawkins, M.D.
Assistant Professor of Medicine

New Grant
Cystic Fibrosis Foundation Stem Cell Consortium Award
**UPCOMING VISITS**

**Carla Kim, Ph.D.**  
Boston Children’s Hospital Stem Cell Program  
Harvard Medical School, Department of Genetics  
March 4th, 2020

**Bob Dickson, M.D.**  
University of Michigan  
Assistant Professor of Medicine  
Pulmonary Diseases, Internal Medicine, Critical Care Medicine  
March 25th, 2020

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**2020 GORDON L. SNIDER, MD, MEMORIAL LECTURE:**

**Naftali Kaminski, M.D.**  
Yale School of Medicine  
Boehringer Ingelheim Pharmaceuticals, Inc.  
Professor of Medicine (Pulmonary)  
Section Chief, Pulmonary, Critical Care & Sleep Medicine  
April 1st, 2020

**Rachel Zemans, M.D.**  
University of Michigan  
Associate Professor of Medicine  
Pulmonary Diseases, Internal Medicine, Critical Care Medicine  
July 8th, 2020
Notable news from Pulmonary Center alumni and former faculty includes…

Former faculty member Wellington Cardoso had a nice publication, led by former Pulmonary Center postdoctoral fellow Munemasa Mori, this quarter:


Former faculty member Xingbin Ai had an exciting publication with current faculty members Alan Fine and Matt Jones this quarter.


Professor Darrell Kotton caught up with former Pulmonary Center Trainees and star Irish pulmonologists Anto O’Regan and Ross Morgan at this year’s meeting of the Irish Thoracic Society.

Nov. 25th, 2019
Congratulations to the Pulmonary Center members for the following publications this quarter:


