INNOVATIVE PROGRAM SUPPORTS NEXT GENERATION OF RESPIRATORY PHYSICIAN AND SCIENTIST INVESTIGATORS – p. 6
At the Respiratory Institute, specialists in pulmonology, allergy and immunology, infectious disease, and critical care medicine work in close collaboration to diagnose and manage the full spectrum of pulmonary and allergic disorders, serving more than 200,000 patients annually. The institute is part of Cleveland Clinic, a nonprofit, multispecialty academic medical center integrating outpatient and hospital care with research and education for better patient outcomes and experience. More than 4,500 staff physicians and researchers provide services through 20 patient-centered institutes. Cleveland Clinic is currently ranked as one of the nation’s top hospitals by *U.S. News & World Report*.

**INSIDE**

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**ON THE COVER** — Mouse macrophages engulfing antibody-coated fluorescent beads. Image from research by T32 SMARRT fellow Erica Orsini. See story on page 6 to learn more about her work and the T32 SMARRT program.
DEAR COLLEAGUES,

These past few years have produced unprecedented challenges, and the COVID-19 pandemic has forever changed healthcare delivery. Much like other large healthcare systems, Cleveland Clinic has had to adapt and innovate, and I’m proud of the Respiratory Institute’s commitment to provide world-class healthcare to all our patients in the midst of these challenging times. Concomitantly, we also remain fully dedicated to advancing care and embracing the challenge of answering “How can we improve this?”

It is with this approach and premise that I am pleased to share with you some of our incredible accomplishments over the past year. Our cover story for this issue of Respiratory Exchange discusses how we will be using a T32 training grant awarded by the National Institutes of Health to supplement the education of postdoctoral trainees with a research training curriculum. The curriculum will give participants the ability to rapidly translate scientific discoveries into better ways to diagnose and treat disease, and it is specifically tailored for MD, PhD or equivalent degrees in the areas of pulmonary, allergy, infectious disease, sleep, or critical care medicine. Our hope is that the participants in this program will go on to become leaders in their fields and in our nation’s scientist workforce.

This is not the only development we are excited about. In the pages that follow, we provide new insights on:

➢ How to optimally use fractional exhaled nitric oxide tests for patients with asthma (p. 4).
➢ The potential of mechanotransduction and excessive extracellular matrix signal processing as new therapeutic options for treating pulmonary fibrosis (p. 16).
➢ How inequalities in critical care management and limited access to healthcare have affected racial and ethnic minorities throughout the COVID-19 pandemic (p. 10).
➢ A new program created by Cleveland Clinic to better understand and treat fibrosing mediastinitis (p. 12).
➢ What the updates to the 2014 “Consensus Document for the Selection of Lung Transplant Candidates” mean for transplant specialists (p. 14).

I hope you find this issue informative and are able to get a sense of our team’s passion and excitement. We’re proud of our accomplishments and the people behind them working as a team of teams to take care of the patients of today as well as the patients of tomorrow. Please be sure to take a look at the expanded list of clinical studies included in this publication and consider offering your patients the opportunity to participate in our research. I look forward to sharing more with you in future publications, and please don’t hesitate to contact me or my colleagues with any feedback.

Sincerely,

RAED DWEIK, MD, MBA
E. Tom and Erika Meyer Professor and Chair
Chair, Cleveland Clinic Respiratory Institute
The fractional exhaled nitric oxide (FeNO) test is a simple test that can be performed in the physician’s office. Patients blow steadily into a tube for a few seconds, and the results are available immediately.

“We’ve known for several years now that nitric oxide is a biomarker for airway inflammation,” says Cleveland Clinic pulmonologist Sumita Khatri, MD. “But there wasn’t a lot of literature available indicating how and when it should be used, or what clinicians should do about high levels. We wanted there to be guidance for clinicians.”

**Recommendations**

The new guideline provides clarity by recommending that clinicians use the test to make treatment decisions for patients already diagnosed with asthma. But the paper stops short of setting hard-and-fast rules about the levels that should trigger treatment. Instead, they recommend that physicians use their clinical judgment along with the test results when making treatment decisions.

“We found there are not enough data to support cut-offs,” Dr. Khatri says. “Instead, it’s like a sliding scale. Each patient is different. If somebody’s nitric oxide is high but they feel fine, you won’t necessarily treat them. But if their nitric oxide is high and they don’t feel well, that justifies ramping up treatment.”

Dr. Khatri, along with her co-chair, Teal S. Hallstrand, MD, MPH, led an international, multidisciplinary panel of 21 experts tasked with writing the consensus document. Panelists narrowed down more than 2,000 scientific papers to focus on 20 key studies from the past five years that addressed using the FeNO test in treating adult and pediatric patients already diagnosed with asthma.

**Findings**

They found that the test made a difference for two key criteria. First, they found moderate evidence that asthma exacerbations (i.e., flare-ups) were less frequent in patients when physicians used nitric oxide measurements to guide treatment. “That was very important, because flare-ups of asthma make people miss work, or they don’t feel well and are not fully present. Plus, asthma flare-ups often cause patients to return to their physician for additional care,” Dr. Khatri notes.

Second, having the test results available was associated with lower rates of oral steroid use by patients — another key positive outcome. Interestingly, however, use of the test did not seem to make a difference in whether patients reported that their asthma was under control. There was also no significant difference in emergency department visits or hospitalizations.
Next steps

Dr. Khatri notes that the American Thoracic Society will be releasing a pocket card with the new guidelines, with the goals of making the recommendations simple as well as easy for clinicians to implement. She says more data are needed to determine whether the FeNO test is helpful when making an initial asthma diagnosis or while monitoring a patient’s response to treatment.

“Those other two questions are also very important, and we need more research,” she explains. “We need more rigorous clinical trials — evaluating specific subgroups, such as pediatrics versus adults, checking nitric oxide levels sequentially and characterizing what type of asthma the patient has — so we can come up with additional and practical consensus guidelines.”

REFERENCE


**Sumita Khatri, MD**

**ABOVE:** Dr. Khatri discusses the results of the FeNO test with her patient. One of the benefits of the test is that the results are available right away.
**INNOVATIVE PROGRAM SUPPORTS NEXT GENERATION OF RESPIRATORY PHYSICIAN AND SCIENTIST INVESTIGATORS**

The SMARRT program, developed through a T32 grant from the NIH, promotes an entire program of scholarship, training and mentoring for participants.

After being awarded a prestigious T32 training grant from the National Institutes of Health (NIH), Cleveland Clinic’s Respiratory Institute, in collaboration with the Lerner Research Institute, has developed an innovative program to supplement the education of postdoctoral trainees with a research training curriculum.

The program, titled “Supporting Multidisciplinary Achievement in Respiratory Research Training (SMARRT),” is specifically tailored for MD, PhD or equivalent degrees in the areas of pulmonary, allergy and critical care medicine, supporting research in heart, lung, blood and sleep-related disorders. This curriculum will give participants the ability to rapidly translate scientific discoveries into better ways to diagnose and treat disease.

ConsultQD had a chance to sit down with Raed Dweik, MD, principal investigator of the T32 grant and Chair of the Respiratory Institute, and Wayne Tsuang, MD, staff physician in the Respiratory Institute and one of the program’s collaborators, to learn more about the program, its development and its next steps.

**Can you please give a brief overview of the grant award and the SMARRT program that’s been created from it?**

The Respiratory Institute, in collaboration with the Lerner Research Institute, was awarded a selective and prestigious T32 training grant from the NIH. This $1.6 million grant will enhance the recruitment and training of early scientists who will become future leaders in their fields. While most NIH funding supports a specific scientist or small group of scientists, what makes this grant special is that it supports an entire program of scholarship, mentoring and training for selected trainees.

**Why did you see a need for this kind of program?**

The U.S. has seen a 30% increase in respiratory-related mortality over the past 20 years. This statistic is from before the onset of the COVID-19 pandemic and is now likely higher. The pandemic clearly highlighted a need for physician and scientist leaders to be in laboratories rapidly developing vaccines, in hospitals quickly facilitating clinical trials or in public health forums creating policies to guide communities.

In response to this need, the NIH, in coordination with the U.S. Congress, has long supported the training of early scientists so that there is a continuous pipeline of bright and capable investigators to lead our nation’s medical workforce. Given the long history of collaboration, the many shared resources between the Respiratory Institute and Lerner Research Institute, and Cleveland Clinic’s mission of scholarship, we felt we were ideally positioned to answer the call to train leaders and independent scientists.
Cleveland Clinic has long had a commitment to training both clinical and basic science investigators, starting with our research-focused medical school and including our highly successful NIH KL2 program for junior faculty. This T32 SMARRT program fills a critical gap in our research training portfolio. As we designed our program, we borrowed best practices from our existing innovative and highly successful medical school, residency program, research education programs and KL2 junior faculty program. We have also incorporated proven strategies from published national studies on mentorship and approaches recommended by these studies to attract and retain promising young trainees.

Trainees will stay in the program for two to three years. The goal is to prepare them to obtain independent research grants and to become leaders of research teams. Ultimately, PhD, MD or MD/PhD scientists will learn to work with each other, rely on each other for expertise, and use cutting-edge tools from both clinical and research areas to develop novel approaches to address patients’ respiratory, critical care and allergy problems. The curriculum is broad, offering training that spans the entire spectrum of research — including fundamental discovery science, early translational research, clinical investigations and population science research — thereby moving fundamental discoveries into clinical and public health practice in real-world settings. Trainees will be engaged in experimental approaches, form mentor-trainee relationships and gain additional research experience needed to enhance their competitiveness for subsequent independent research and career development awards.

Who was involved with securing the grant and developing the SMARRT curriculum?

We had close collaborations with Serpil Erzurum, MD, Chief Research and Academic Officer of Cleveland Clinic; Christine Moravec, PhD, Director of Research Education and Training for the Lerner Research Institute; Mitchell Olman, MD, Professor of Medicine and Pulmonary Staff in the Respiratory Institute; Mark Aronica, MD, Vice Chair of Allergy and Immunology in the Respiratory Institute; and Rendell Ashton, MD, Pulmonary and Critical Care Medicine Fellowship Director.

What makes SMARRT different from similar programs?

SMARRT collaborates closely with other T32 training programs here at Cleveland Clinic, including those for molecular medicine, digestive diseases and kidney medicine. We are unique in our focus on respiratory diseases, critical care and allergy medicine. Trainees have access to resources, mentors and collaborators across the Cleveland Clinic enterprise.
The program currently has two participants enrolled. What kinds of projects have they been working on?

Erica Orsini, MD, is a graduate of the Respiratory Institute’s Critical Care Medicine Fellowship Program. She is working with Rachel Scheraga, MD, on translational work investigating the interaction between Pseudomonas aeruginosa virulence factors and immune cell mechanoreceptors to better understand the mechanisms of lung injury from bacterial pneumonia. She is enrolled in the PhD program at the Lerner Research Institute.

Catherine Heinzinger, DO, is a graduate of the Neurological Institute’s Sleep Medicine Fellowship Program, and she is working with Reena Mehra, MD, on discovering biomarkers of sleep-disordered breathing and sleep disruption as preventive targets and mechanistic players in the development of atrial fibrillation. She is writing a proposal for a translational project investigating the impact of sleep-disordered breathing on heart tissue and metabolomics. She is enrolled in the Master of Science in Clinical Research program at Case Western Reserve University.

What are the next steps for the program?

There are three overarching goals:

1) To provide early scientists with multidisciplinary didactic research training coupled with a team-mentored research experience.

2) To enhance the ability of young scientists to work as part of an integrated multidisciplinary team by helping them develop a knowledge base and skills in research methods, communication skills, professionalism, the ethical conduct of research, and rigorous analysis of reproducible findings.

3) To recruit, retain and accelerate the independent career development of a pool of early investigators with the multidisciplinary skills necessary for an independent research career in basic, clinical, translational or population health research.

Our hope is that the participants in this program will go on to become leaders in their fields and in our nation’s scientist workforce. They will have the knowledge and skills to pursue outstanding cutting-edge research careers and will be able to recognize the importance of different research paradigms, ranging from molecular medicine to public health sciences, for rapidly translating scientific discoveries into better clinical diagnostics and therapeutics.

Applications for the program are accepted annually in the spring for start dates on July 1. Please reach out to dweikr@ccf.org.

Wayne Tsuang, MD, MHS
RESPIRATORY EXCHANGE PODCAST

A Cleveland Clinic podcast for healthcare professionals exploring timely and timeless clinical and leadership topics in the disciplines of pulmonary medicine, critical care medicine, allergy/immunology, infectious disease and related areas.

Hosted by
Raed Dweik, MD, MBA | Chair, Cleveland Clinic Respiratory Institute

2022 EPISODES

Lung Transplant as Therapy for COVID Fibrosis and COVID ARDS
Co-hosts: Marie Budev, MD
Medical Director, Cleveland Clinic Lung Transplant Program
Kenneth, McCurry, MD
Surgical Director, Cleveland Clinic Lung Transplant Program

Environmental Impact on the Lung
Guest: Sumita Khatri, MD
Vice Chair, Cleveland Clinic Respiratory Institute

Treating Food Allergy with Oral Immunotherapy (OIT) and Early OIT
Guest: Sandra Hong, MD
Director, Cleveland Clinic Food Allergy Center of Excellence

Lung Cancer Screening: It's More Than a CT Scan
Guest: Peter Mazzone, MD
Director, Cleveland Clinic Lung Cancer Screening Program

Lung Transplant A-Z: From Referring a Patient to the Impact of COVID-19
Guest: Marie Budev, MD
Director, Cleveland Clinic Lung Transplant Program

Highlights of the 2021 World Association of Sarcoidosis and Other Granulomatous Diseases Conference (WASOG)
Host: Daniel Culver, MD
Chair, Cleveland Clinic Department of Pulmonary Medicine
Guest: Manuel Ribeiro
Director, Cleveland Clinic Sarcoidosis Center

Penicillin, Aspirin and Vaccine Allergies: New Hope for Patients
Guest: David Lang, MD
Chair, Cleveland Clinic Department of Allergy and Immunology

For more episodes, go to clevelandclinic.org/respiratoryexchangepodcast
The COVID-19 pandemic further illustrated this trend. In urban centers, minority groups and individuals are more likely to have decreased access to timely intervention, an inability to maintain social distancing due to work-related demands, language barriers and larger household sizes. To better understand the implications of these effects, Cleveland Clinic researchers examined whether race and ethnicity were associated with inequalities in critical care management of COVID-19 within the Northeastern Ohio community. These findings recently appeared in the *Journal of Racial and Ethnic Health Disparities*.1

The retrospective cohort study focused on 2,064 patients who tested positive for COVID-19 and were admitted to the ICU at Cleveland Clinic. The primary outcome analyzed mortality, and the secondary outcome was length of hospital stay. The study’s authors hypothesized that patients who identify as Black or Hispanic in Cleveland, Ohio, may have been more susceptible to poorer COVID-19 outcomes following ICU admission, including increased length of stay and increased mortality rates, as compared to non-Hispanic white patients.

Higher comorbidities among racial and ethnic minorities

Of the patients studied, 41.8% were female, 33% identified as Black, and 6.7% identified as being nonwhite or non-Black race. The Black cohort was slightly younger than the white cohort (66 vs. 77 years old). Black patients had a significantly higher prevalence of asthma (26.3% vs. 20.4%, \( P = 0.003 \)), chronic kidney disease (CKD) (48.6% vs. 36.7%, \( P < 0.001 \)) and diabetes (68.1% vs. 56.0%, \( P < 0.001 \)) as compared with white patients. Black patients had a lower prevalence of malignant neoplasm (37.3% vs. 45.0%, \( P = 0.0001 \)). Hispanic patients had a
significantly higher prevalence of liver disease (32.6% vs. 22.2%, \( P = 0.022 \)). There were no significant differences between Black and white patients for chronic cardiac disease, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), dementia, high blood pressure (HTN), hematologic malignancy, solid organ and bone marrow transplant, malnutrition, liver disease, or immunodeficiency. Median APACHE II (Acute Physiology and Chronic Health Evaluation) scores, a predictor of ICU mortality, were fairly similar for Black and white patients (54 and 55, respectively \( P = 0.40 \)).

“In our study, Black patients had a higher prevalence of asthma, diabetes, chronic kidney disease and hypertension, while Hispanic patients had a greater incidence of liver disease,” explains Abhijit Duggal, MD, a critical care physician in Cleveland Clinic’s Respiratory Institute and principal author of the study. “Nationally, Black and Hispanic patients are at a higher risk of COVID-19 infection and death from the virus because of inequalities in chronic disease prevention and management. These conditions are risk factors for more severe cases of COVID-19.”

Differences in care

During their ICU stays, a similar percentage of Black and white patients required intubation (41.9% and 42.7%, respectively, \( P > 0.05 \)). The mean intubation times for both groups were also comparable (7.0 and 8.2 days, respectively). Although the median length of time in the hospital was similar for Black patients and white patients (10.6 and 11.5 days, respectively, \( P = 0.056 \)), the median length of ICU stay was statistically different between the two groups (3.4 and 4.4 days, \( P = 0.003 \)). The authors found that certain factors were statistically significant in regard to mortality: APACHE II score at ICU admission (odds ratio [OR] = 1.02; 95% confidence interval [CI], range 1.01–1.02), CKD (OR = 1.34; 95% CI, range 1.05–1.71), malignant neoplasm (OR = 1.28; 95% CI, range 1.05–1.71), antibiotic use (OR = 1.69; 95% CI, range 1.04 to 2.73), vasopressor requirement (OR = 3.97; 95% CI range 3.12 to 5.05) and age (OR = 1.06; 95% CI range 1.04 to 1.07). After adjustment for underlying disease conditions and severity of disease, there was no difference in mortality based on race or ethnicity.

Outcomes

Based on their findings, the authors concluded that in a healthcare system that was not stressed at the height of the COVID-19 pandemic, race and ethnicity were not associated with COVID-19-related mortality. This study also highlights the significant disparities in pre-ICU pathophysiology and underlying comorbidities based on race and ethnicity, which along with the severity of disease as measured by the APACHE II score, were independently associated with mortality.

Early in the pandemic, Cleveland Clinic implemented several strategies to care for patients with COVID-19. These included ensuring available care at its main campus and several regional hospitals, using an ICU operations team to improve care and standardize best practices, offering training modules to all ICU providers, and providing multidisciplinary care.

“At the end of the day, expanding healthcare access should be a major goal for providers,” says Dr. Duggal. “The effects of access inequality are twofold — not only does access affect how patients are cared for when they are sick, but it also affects their future health. These effects are compounded by situations that increase demand and deplete resources, such as a pandemic. We believe this work demonstrates that equitable healthcare not only is possible, but with a standardized approach, it can be achieved. This is especially important for patients who are traditionally disadvantaged racial and ethnic minorities.”

REFERENCE

Fibrosing mediastinitis (FM) is a rare condition that may develop as a consequence of another disorder, usually infection or inflammation. The most common cause in the U.S. is believed to be an endemic fungal infection, histoplasmosis, which is very common in the Ohio, Missouri and Mississippi River Valley regions.

The condition is characterized by mediastinal lymph node enlargement that eventually leads to an intense immune reaction. The lymphadenopathy and conglomerate mediastinal tissue may get calcified and compress vital structures. Historically, there has been no treatment for the condition.

In order to understand and better treat FM, Cleveland Clinic created a multidisciplinary center focused on the condition. “Often pulmonologists are puzzled by the condition of FM,” explains Francisco Aécio Almeida, MD, MS, a pulmonologist in the Respiratory Institute and one of the leaders spearheading the development of the center. “That’s why we created this center. We want to improve the management of patients with FM and provide them with potential options,” says Dr. Almeida. “The latter would include innovative medical therapies,
endobronchial or intravascular procedures, and the latest surgical interventions. The center will also provide a platform for education and research.”

Exploring fibrosing mediastinitis

“Infection of histoplasmosis can present in many ways,” says Dr. Almeida. “Most of the time it is a mild infection and recognized incidentally as a dormant lung nodule or a calcified lymph node. Occasionally, the calcification can also involve the spleen or the liver.”

In the past, treatment focused on relieving compressions via stent placements in the airway or dilating the esophagus. However, these treatments have potentially long-term side effects, especially when airway stents are required. Sometimes surgical procedures are essential to relieve compression of a large vital mediastinal structure. In some instances, part of the lung or the entire lung may need to be removed. For other patients, disease progression may result in the area becoming so scarred that nothing more can be done.

“Eventually the disease gets to a point where there is exuberant scarring of the mediastinum, and all treatment efforts will be futile,” says Dr. Almeida. “I have a patient who has such chronic occlusion of a great vessel resulting in the development of collaterals, which is a desperate bodily response. In cases where the mediastinum is so densely fibrotic, any surgical intervention is challenging and a great deal of expertise is required. We take the decision to perform a biopsy or a therapeutic procedure very seriously as the risk of complications is high.”

Advancing the research

Dr. Almeida notes that a recent report on FM indicated that the drug rituximab could possibly decrease the activity of B lymphocytes and may decrease inflammation as well as the burden of lymphadenopathy and tissue damage. He explains that although the study size was small, the participants responded well to rituximab. The researchers suggested that a positron emission tomography (PET) scan may help guide the selection of patients who are likely to respond to the therapy.

Dr. Almeida says that one of the goals of the center would be to further expand on these findings. “We would like to explore the therapeutic value of rituximab and similar agents,” he says. “It is still an off-label use of the medication, but our goal is to create a database of potential treatments and patient responses to them that is beneficial to our patient population. This is indeed a rare disease, and eventually, we would like to partner with other centers in creating a registry and research protocols.

A multidisciplinary approach

One of the aspects of the center that Dr. Almeida is excited about is its multidisciplinary approach. The center will bring together a group of providers who have experience with and an interest in this condition to brainstorm how they can advance the management of these patients. The team will include pulmonologists, infectious disease specialists, an interventional radiologist, a cardiologist and pulmonary hypertension specialists. “We hope to grow our expertise as we go,” says Dr. Almeida. “Some people already have plenty of expertise, while others have a basic awareness of the condition. We’re looking into building the knowledge base so that we can grow together and improve the welfare of these patients.”

Because Cleveland Clinic is geographically close to the Ohio River Valley, where histoplasmosis infection is frequent and FM is relatively common, it is a prime location for the center.

Dr. Almeida explains, “We want to centralize the care of patients with FM within Cleveland Clinic so that a group of experts will see the majority of these individuals. We want to get to the point where we can act as internal consultants to caregivers and help them provide comprehensive care to these patients.”

Francisco Almeida, MD, MS
The document used by the U.S. and international lung transplant community as a guide in the evaluation of candidates for lung transplantation has been updated to reflect the most contemporary thinking to date about how the transplant field intersects with science and health equity. It also removes some previously hardline contraindications, favoring instead a more nuanced assessment of multiple risk factors.

The updates to the 2014 “Consensus Document for the Selection of Lung Transplant Candidates” were published in July 2021 in Journal of Heart and Lung Transplantation. The document exists to help healthcare providers who treat patients with pulmonary disease and to provide guidance for transplant centers as they make difficult decisions regarding the selection of candidates for transplants.

“A major addition to the document is a new section that acknowledges inequity in healthcare,” says Maryam Valapour, MD, MPP. “In addition, with more flexibility in the selection of candidates, we believed that it was important to introduce an ethical framework so that physicians have boundaries around how to make these really difficult organ allocation decisions.”

Valapour, a transplant physician with policy and ethics expertise, is Director of Lung Transplant Outcomes at the Respiratory Institute. A major focus for the team in her research program is the study of alternative organ allocation systems to provide patients timely access to transplant and to achieve the best possible outcomes. She is also Senior Investigator for Lung Transplantation for the U.S. Scientific Registry of Transplant Recipients, where she oversees analysis of U.S. lung transplant data and advises transplant policymakers in this area.

The consensus document represents the work of 24 transplant physicians and surgeons chosen from the international community of transplant experts who reviewed current research to distill important new findings in the area of lung transplantation. Panel members voted on all changes, and recommendations required 80% approval to be adopted.

Updates include the elimination of age cutoffs for lung transplant recipients. Instead, the guidelines delineate ages at which patients may be at higher risk. Similarly, contraindications were removed for many cancers — an acknowledgment of how far cancer treatments have advanced.

“The 2021 document acknowledges that transplant medicine has advanced, and it has removed a lot of the absolutist contraindications,” says Maryam Valapour, MD, MPP. “In addition, with more flexibility in the selection of candidates, we believed that it was important to introduce an ethical framework so that physicians have boundaries around how to make these really difficult organ allocation decisions.”

One of the major goals of the new statement is to encourage physicians to involve transplant specialists earlier in the management of all diagnoses that may go on to require a lung transplant so that all options can be considered.

“Often, clinicians will not refer a patient because they think they’re too old, or because the person had cancer 10 years ago,” says Dr. Valapour. “As
“While long-term survival remains a key selection criterion, the new guidelines clarify that it cannot supersede factors such as health equity and respect for individuals.”

“As we were writing this, the science was already changing, so it was hard for us to make recommendations,” she says. “But a new indication for lung transplantation has emerged because of COVID-19.”

Overall, the consensus document reflects advances in lung transplant science on a number of fronts, says Dr. Valapour. “We have gotten better at donor management, we’re doing more lung transplants, and we are improving post-transplant management to increase survival and patient well-being.”

REFERENCE

Maryam Valapour, MD, MPP
IPF is considered secondary to an abnormal wound healing response to numerous subclinical micro-injuries. This results in deposition of excessive extracellular matrix (ECM) and leads to scar formation. At some point, the scarred lung ECM begins to trigger the accumulation of fibroblasts and activation of fibroblasts into myofibroblasts. These scar-producing cells create a feed-forward mechanism that perpetuates fibrosis and disease progression. These ECM signals also affect the function of immune cells and have been shown to play a role in the progression of inflammatory lung diseases such as acute lung injury and acute respiratory distress syndrome (ARDS).

We have known for many years that soluble cytokines and growth factors (e.g., transforming growth factor beta [TGF-β], interleukin-1 beta [IL-β] and tumor necrosis factor alpha [TNF-α]) secreted by both parenchymal and immune cells can drive progression of fibrosis and/or inflammation. Emerging evidence now supports the idea that ECM microenvironmental signals, including the particular composition of ECM components, the architecture of the ECM (linear vs. randomly arranged) or the stiffness of the ECM, can drive the accumulation and activation of fibroblasts. While current anti-fibrotic therapies target the effects of cytokines and growth factors, they only slow fibrosis progression (they do not stop or reverse it), and they do not take into account the interactions of fibroblasts with the underlying matrix. There are currently no specific therapies that are effective for ARDS. But increased understanding of how ECM microenvironmental cues influence cell behavior and perpetuate fibrosis and inflammation is leading to a paradigm shift in the understanding of the pathogenesis of pulmonary disease that will likely lead to novel therapeutic strategies that can target these cell-matrix interactions.

Targeting the mechanical signal in the lungs

The primary focus of our laboratories is understanding how immune cells and fibroblasts interact with the ECM. We study how the ECM stiffness signal is translated into a biochemical signal, a process known as mechanotransduction, and its effect on cellular processes involved in fibrosis and inflammation. We look at how mechanotransduction can promote pulmonary disease progression, in an attempt to develop new therapeutic targets to halt or reverse the disease process. Many published studies have utilized cells plated on glass or plastic, which is 1 million times stiffer than the lung. In contrast, our studies have found that utilizing conditions that resemble normal and fibrotic lung ECM stiffness yields results that differ substantially from prior work.
The role of TRPV4 in pulmonary fibrosis

In 2014, the Olman lab published a first-of-its-kind study showing that the mechanosensing signal in fibroblasts is mediated by the transient receptor potential vanilloid 4 (TRPV4) channel — a surface membrane cation (calcium) channel that responds to changes in matrix stiffness.1 Using complementary in vitro and in vivo methods, we showed that targeting the TRPV4 channel can inhibit the ECM stiffness-mediated activation of fibroblasts and protect mice from experimental pulmonary.

In 2019, the Olman lab, spearheaded by Lisa Grove, PhD, published more detailed insights on the mechanism of TRPV4 signaling.2 We showed that TRPV4 is translocated to the cell surface, where it acts as a mechanosensor/mechanotransducer that generates myofibroblasts through its interaction with a protein called phosphoinositide 3-kinase gamma (PI3Kγ). These data are exciting because blocking the interaction of TRPV4 and PI3Kγ could provide a specific target that does not completely impede the actions of TRPV4 or PI3Kγ, some of which may be beneficial. Furthermore, both TRPV4 and PI3Kγ inhibitors have reached clinical trial status, suggesting potential for rapid bench-to-bedside translation of our results. Ongoing work in this area involves characterizing the specific interacting components of the two molecules in order to design a specific therapeutic that can target this unique pro-fibrotic interaction.

The role of TRPV4 in pulmonary inflammation

In 2016, Dr. Scheraga led work in the TRPV4 field by showing that mechanosensing through TRPV4 also regulated macrophage ingestion of bacteria in the context of increased ECM stiffness, such as that seen in animal models of acute lung injury and infection.3 In contrast to the detrimental actions of TRPV4 in pulmonary fibrosis, Dr. Scheraga showed, using complementary methods, that TRPV4 is required for the induction of anti-inflammatory/pro-resolution cytokines, in vivo and in vitro macrophage ingestion of bacteria, and the consequent reduction in Pseudomonas aeruginosa-associated lung injury in mice. In this context, TRPV4 in macrophages appears to be beneficial, and stimulating TRPV4 could reduce lung injury and increase bacterial clearance, thereby resolving infection-associated ARDS.

Dr. Scheraga published some exciting work in 2019 that demonstrated that the mechanism of TRPV4’s regulation of macrophage activity in a mechanosensitive manner occurs through intracellular signals involving the mitogen activation protein kinase (MAPK) pathway.4 As mentioned above, targeting these specific molecular mechanisms downstream of TRPV4 could modulate the response in various disease states without affecting the overall function of TRPV4. These findings may have broad impact, as TRPV4 and macrophage activation functions are implicated in other inflammatory lung diseases including bronchiectasis, chronic obstructive pulmonary disease and granulomatous lung diseases, as well as in vascular and malignant diseases.

The role of nonmuscle myosin II in pulmonary fibrosis

Many clinical trials in pulmonary fibrosis tend to focus on individual soluble mediators or isolated pathways that play a role in fibrosis and have failed in the clinical setting. Identifying a potential therapeutic strategy that targets a molecule, such as non-muscle myosin II (NM-II),
that is downstream and common to multiple fibrosis pathways could represent a significant paradigm shift in the treatment of patients with IPF and other fibrotic disorders.

Dr. Southern published novel work in 2016 on the role of fibroblast NM-II in responding to ECM cues such as stiffness and architecture. This work demonstrated that when fibroblasts encounter normal lung ECM, NM-II is activated in the periphery of the cell. This limits its lateral protrusive activity and helps the cell establish polarity, and it effectively promotes fibroblast migration. When the fibroblast encounters the stiff fibrotic lung, it becomes immobilized, and NM-II becomes activated diffusely throughout the cell, resulting in increased contractility and differentiation into a fully active myofibroblast.

Since then, Dr. Southern has focused on ways to manipulate the NM-II pathway in fibroblasts and has identified a protein that regulates NM-II movement within the cell. Blocking this protein restricts NM-II from localizing to central stress fibers in the fibroblast and prevents myofibroblast differentiation, as well as pulmonary fibrosis in mice. This work is currently being submitted for publication, and it has the potential to shift the paradigm of treatment by focusing on manipulation of a common final pathway in fibrotic disorders that involves fibroblast matrix interactions.

**New directions**

Through the above work and that of a number of other labs, the understanding of the role of mechanotransduction and processing of other ECM signals has become an integral part of studying pulmonary diseases. Laboratory methods often must account for the stiffness of the substrates on which they studies are performed, as many of these proteins only respond to a finely-tuned range of stiffness, such as that seen in both normal and fibrotic lungs.

Culturing cells and organoids under pathophysiologic ECM conditions is an example of techniques that labs around the world have incorporated. Clinical trials that specifically target matrix stiffness (e.g., lysyl oxidase-like [LOXL] inhibitors) and mechanosensing pathways (e.g., rho kinase [ROCK] inhibitors) are becoming more common. As we begin to elucidate how immune cells and fibroblasts respond to signals in their natural environment, the paradigm for understanding what drives progressive fibrosis or inflammation will continue to shift, and therapeutic options for patients with inflammatory or fibrotic lung disorders will continue to expand.

**REFERENCES**


Consider offering your patients enrollment in a leading-edge clinical research trial at our Respiratory Institute. Contact the study coordinator or principal investigator for more information.

**ALLERGY**

Food Allergy Center of Excellence Registry  
*Principal Investigator:* Sandra Hong, MD  
*Study Coordinator:* Sheffa Almahd, RRT | 216.287.0906

A multicenter, randomized, double-blind, placebo-controlled Phase 3 study of remibrutinib (LOU064) to investigate the efficacy, safety and tolerability for 52 weeks in adult chronic spontaneous urticaria patients inadequately controlled by H1-antihistamines  
*Principal Investigator:* David Lang, MD  
*Study Coordinator:* Sheffa Almahd, RRT | 216.287.0906

**COPD**

Roflumilast or Azithromycin to Prevent COPD Exacerbations (RELIANCE)  
*Principal Investigator:* Umur Hatipoglu, MD  
*Study Coordinator:* Kiran Ashok | 216.538.9139

**CRITICAL CARE MEDICINE**

A Protocol Comparing Temporary Transvenous Diaphragm Pacing to Standard of Care for Weaning from Mechanical Ventilation in ICU Patients (RESCUE 3)  
*Principal Investigator:* Tarik Hanane, MD  
*Study Coordinator:* Connery Brennan | 216.445.3960

Cooling to Help Injured Lungs (CHILL) Phase IIb Randomized Controlled Trial of Therapeutic Hypothermia in Patients with ARDS  
*Principal Investigators:* Abhijit Duggal, MD; and Rachel Scheraga, MD  
*Study Coordinator:* Connery Brennan | 216.445.3960

A PETAL Network Multi-Center Phase 2b Randomized Double-Blinded Placebo-Controlled Trial of Two Different Pharmacologic Therapies (Intravenous Vitamin C or Intravenous Acetaminophen)  
*Principal Investigator:* Abhijit Duggal, MD  
*Study Coordinator:* Kiran Ashok | 216.538.9139

Center for Sepsis Driven Immunodeficiency  
*Principal Investigators:* Rachel Scheraga, MD; and Vidula Vachharajani, MD  
*Study Coordinator:* Margaret Jeng | 216.219.4679

**CYSTIC FIBROSIS**

A Phase 4 Study to Compare US Marketed Creon® Drug Product with Drug Product Manufactured with a Modernized Process at an Alternate Manufacturing Site, in Subjects with EPI due to Cystic Fibrosis  
*Principal Investigator:* Elliott Dasenbrook, MD  
*Study Coordinator:* Donna Lach, RN | 216.218.4997

Cystic Fibrosis Foundation (CFF) Care Center and Patient Registry  
*Principal Investigator:* Elliott Dasenbrook, MD  
*Study Coordinator:* Cassie Best | 216.630.5281

SIMPLIFY-IP-19: To test the impact of discontinuing chronic therapies in people with cystic fibrosis on highly effective CFTR modulator therapy  
*Principal Investigator:* Elliott Dasenbrook, MD  
*Study Coordinator:* Donna Lach, RN | 216.218.4997

A Prospective Study Evaluating Maternal and Fetal Outcomes in the ERas of ModulatorS (MAYFLOWERS)  
*Principal Investigator:* Elliott Dasenbrook, MD  
*Study Coordinator:* Cassie Best | 216.630.5281

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DIFFUSE PARENCHYMAL LUNG DISEASE
Chronic Fibrosing Interstitial Lung Disease with Progressive Phenotype Prospective Outcomes (ILD-PRO) Registry
Principal Investigator: Daniel Culver, DO
Study Coordinator: Sue Gole, RRT | 216.401.5257

SARCOIDOSIS
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study in Participants with Sarcoidosis-Associated Pulmonary Hypertension (SAPH) to Assess the Efficacy and Safety of Oral Selexipag
Principal Investigator: Joseph Parambil, MD
Study Coordinator: Mofetoluwa Oluwasanmi | 216.308.5111

ACTHAR Gel for Cutaneous Sarcoidosis
Principal Investigator: Manual Ribeiro, MD
Study Coordinator: JoAnne Baran-Smiley, BSN, RN | 216.469.2855

Routine Cardiac Screening in Sarcoidosis Patients (PAPLAND)
Principal Investigator: Daniel Culver, DO
Study Coordinator: Shweta Josh | 216.445.7291

Prospective Registry of Outcomes in Myocardial Sarcoidosis (PROMyS). This is a prospective multicenter registry of incident cases of confirmed or suspected cardiac sarcoidosis.
Principal Investigator: Manual Ribeiro, MD
Study Coordinator: Shweta Josh | 216.445.7291

INTERVENTIONAL PULMONOLOGY
A Sham Controlled Prospective Randomized Clinical Trial of the RejuvenAir® System for the Treatment of Moderate to Severe Chronic Obstructive Pulmonary Disease with Chronic Bronchitis (SPRAY-CB)
Principal Investigator: Thomas Gildea, MD
Study Coordinator: Yvonne Meli, RN, BC, CCRP | 216.445.4215

Transbronchial Biopsy Assisted by Robot Guidance in the Evaluation of Tumors of the Lung (TARGET)
Principal Investigator: Michael Machuzak, MD
Study Coordinator: Yvonne Meli, RN, BC, CCRP | 216.445.4215

LUNG CANCER
DECAMP 1 PLUS Proposal: Prediction of Lung Cancer Using Noninvasive Biomarkers
Principal Investigator: Peter Mazzone, MD
Study Coordinator: Brian Smith | 216.904.7198

DNA Evaluation of Fragments for Early Interception - Lung Cancer Training Study (DELFi-L101 Study)
Principal Investigator: Peter Mazzone, MD
Study Coordinator: Brian Smith | 216.904.7198

Nodify XL2 Classifier Clinical Utility Study in Low to Moderate Risk Lung Nodules (ALTITUDE)
Principal Investigator: Peter Mazzone, MD
Study Coordinator: Brian Smith | 216.904.7198

Détermination and Validation of Lung EpiCheck: A Multianalyte Assay for Lung Cancer Prediction
Principal Investigator: Peter Mazzone, MD
Study Coordinator: Susan Charme | 216.318.5687

CFMEDIP-SEQ Assay Multicenter Prospective Observational Validation for Early Cancer Detection, Minimal Residual Disease, and Relapse (Camperr)
Principal Investigator: Peter Mazzone, MD
Study Coordinator: Samantha Goode | 216.440.7733

Detecting cancers Earlier Through Elective plasma-based CancerSEEK Testing – Ascertainment Serial Cancer patients to Enable New Diagnostic II (DETECT-ASCEND 2)
Principal Investigator: Peter Mazzone, MD
Study Coordinator: Samantha Goode | 216.440.7733
LUNG TRANSPLANT

Improving Frailty with a Rigorous Ambulation Intervention in Lung Transplant Patients (iFRAIL)
Principal Investigator: Marie Budev, DO, MPH
Study Coordinator: Rijuta Singh | 216.894.3826

A Phase III, Prospective, Multicenter, Randomized, Controlled Clinical Trial to Demonstrate the Effectiveness and Safety of Liposomal Cyclosporine A (L-CsA) Inhalation Solution Delivered via the PARI Investigational eFlow® Device plus Standard of Care versus Standard of Care Alone in the Treatment of Bronchiolitis Obliterans Syndrome in Patients post Lung Transplantation (BOSTON-1 and BOSTON-2)
Principal Investigator: Marie Budev, DO, MPH
Study Coordinator: JoAnne Baran-Smiley, BSN, RN | 216.469.2855

Cleveland Clinic Lung Transplant Biorepository
Principal Investigator: Maryam Valapour, MD
Study Coordinator: Erin McNamee | 216.210.8616

Technology Enabled And Molecular Monitoring of the Allograft and Transplant rEcipient (TEAMMATE)
Principal Investigator: Marie Budev, DO, MPH
Study Coordinator: JoAnne Baran-Smiley, BSN, RN | 216.469.2855

RARE LUNG DISEASES

ALPHA-1 ANTITRYPSIN DEFICIENCY
Alvelestat (MPH996) for the Treatment of ALpha-1 ANTitrypsin Deficiency (ATALANtA)
Principal Investigators: Umur Hatipoglu, MD; James Stoller, MD
Study Coordinator: Erica Corrao, RRT | 216.444.0843

A Multi-center, Single-Dose and Repeat-Dose Over Eight Weeks, Sequential Cohort Study to Evaluate Safety and Tolerability as well as Pharmacokinetics of Two Different Doses of Alpha1-Proteinase Inhibitor Subcutaneous (Human) 15% Administered Subcutaneously in Subjects with Alpha1-Antitrypsin Deficiency
Principal Investigator: Vickram Tejwani, MD
Study Coordinator: Erica Corrao, RRT | 216.347.4515

BRONCHIECTASIS

Clinical Effectiveness of High Frequency Chest Wall Oscillation (HFCWO) in a Bronchiectasis Population
Principal Investigator: Elliott Dasenbrook, MD
Study Coordinator: Sheffa Almahd, RRT | 216.287.0906

ARISE - A Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Multicenter Study to Validate Patient-Reported Outcome Instruments in Adult Subjects with Newly Diagnosed Nontuberculous Mycobacterial (NTM) Lung Infection Caused by Mycobacterium avium Complex (MAC)
Principal Investigator: Elliott Dasenbrook, MD
Study Coordinator: Sheffa Almahd, RRT | 216.287.0906

ENCORE - A Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Multicenter Study to Evaluate the Efficacy and Safety of an Amikacin Liposome Inhalation Suspension (ALIS)-Based Regimen in Adult Subjects with Newly Diagnosed Nontuberculous Mycobacterial (NTM) Lung Infection Caused by Mycobacterium avium Complex (MAC)
Principal Investigator: Elliott Dasenbrook, MD
Study Coordinator: Sheffa Almahd, RRT | 216.287.0906

ASPEN - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Assess the Efficacy, Safety, and Tolerability of INS1007 Administered Once Daily for 52 Weeks in Subjects with Non-Cystic Fibrosis Bronchiectasis
Principal Investigator: Elliott Dasenbrook, MD
Study Coordinator: Sheffa Almahd, RRT | 216.287.0906

PULMONARY HYPERTENSION

A Phase 3, Randomized, Placebo-controlled, Double-blind, Adaptive Study to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Patients with Pulmonary Hypertension due to Chronic Obstructive Pulmonary Disease (PH-COPD) – (PERFECT)
Principal Investigator: Joseph Parambil, MD
Study Coordinator: Mirha Mahmood | 216.308.6864

A Study to Evaluate Efficacy and Safety of Macitentan 75 mg in Inoperable or Persistent/Recurrent Chronic Thromboembolic Pulmonary Hypertension (MACITEPH)
The primary objective of this Arena-sponsored study is to compare the effect of ralinepag versus placebo in subjects with standard of care or PAH-specific background therapy on disease progression and achievement of a satisfactory clinical response in subjects with WHO Group 1 PAH.
Principal Investigator: Gustavo Heresi, MD
Study Coordinator: Mirha Mahmood | 216.308.6864
LYMPHANGIOLEIOMYOMATOSIS

Multicenter International Durability and Safety of Sirolimus in LAM Trial (MIDAS) Clinical Study

Principal Investigator: Joseph Parambil, MD
Study Coordinator: JoAnne Baran-Smiley, BSN, RN | 216.469.2855

PULMONARY ALVEOLAR PROTEINOSIS

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Once-Daily Inhaled Molgramostim Nebulizer Solution in Adult Subjects with Autoimmune Pulmonary Alveolar Proteinosis aPAP (IMPALA 2)

The goal of this study is to investigate the efficacy of molgramostim, an inhaled form of the recombinant human granulocyte macrophage colony stimulating factor (rhGM-CSF) in subjects with aPAP.

Principal Investigator: Leslie Tolle, MD
Study Coordinator: Sue Gole, RRT | 216.445.5836

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