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Dear Colleagues:

Welcome to the Winter 2014 issue of Respiratory Exchange, which highlights the latest discoveries and accomplishments of our pulmonary, critical care medicine, allergy and clinical immunology staff in Cleveland Clinic’s Respiratory Institute.

In these pages, you’ll read fascinating accounts of leading-edge methods — including exhaled-breath analysis, three-dimensional printing, and novel methods to enhance EGFR and ALK mutation detection — that are poised to transform our practice of respiratory medicine.

While police officers routinely use devices that check drivers’ breath for evidence of intoxication, the air we expel contains a trove of additional untapped information about a person’s medical state. These exhalation components constitute a unique individual “breathprint,” as revealing as a fingerprint, that could aid health monitoring and disease diagnosis. Cleveland Clinic researchers are working to identify novel exhaled biomarkers for specific diseases and to create sensors that will accurately detect them. Pulmonary Vascular Program Director Raed Dweik, MD, describes his group’s initial successes using breathprints to diagnose and assess the severity of alcoholic hepatitis, and to differentiate between patients with acute decompensated heart failure and those with other cardiovascular problems.

Elsewhere, Thomas Gildea, MD, who heads the Respiratory Institute’s Section of Bronchology, writes about our experience using the emerging capabilities of medical 3-D printing to help a bilateral lung transplant recipient. 3-D printers enable the quick, in-house design and fabrication of highly customized, biocompatible replacement parts — in this case, a silicone airway stent that worked when conventionally made stents proved inadequate.

Joseph Cicenia, MD, and Raymond Tubbs, DO, describe novel methods to test for EGFR and ALK mutations in endobronchial ultrasound samples from lung cancer patients. This promises to reduce the test failure rate.

These are just three of the many ways in which the Respiratory Institute continues to advance patient care. As we grow, we have restructured the institute into three departments: Allergy and Clinical Immunology, Critical Care Medicine, and Pulmonary Medicine. I’m pleased that Robert “Duncan” Hite, MD, formerly of the Wake Forest School of Medicine, arrived in December to become the inaugural chair of the Department of Critical Care Medicine. Also, Robert M. Kotloff, MD, of the University of Pennsylvania, will be joining us in June as the inaugural chair of the Department of Pulmonary Medicine. Drs. Hite and Kotloff join David M. Lang, MD, who heads the Department of Allergy and Clinical Immunology.

To learn more about our clinical and research activities, please visit clevelandclinic.org/pulmonary (where you’ll find current and archived issues of Respiratory Exchange) and clevelandclinic.org/thoracic. As always, use our toll-free number for physicians, 866.CCF.LUNG (866.223.5864), if you have questions or would like to refer a patient. We’re here to help.

Sincerely,

Herbert P. Wiedemann, MD, MBA
CHAIRMAN | CLEVELAND CLINIC RESPIRATORY INSTITUTE
Beyond the Lungs: Utility of Exhaled Breath in the Diagnosis and Monitoring of Systemic Diseases

Raed A. Dweik, MD

As the headspace of the blood, our exhaled breath contains a vast array of substances and molecules that hold great promise for monitoring our health and for diagnosing and managing various lung and systemic diseases. This includes substances we produce endogenously as part of our normal (or disease-related) metabolism, whether this is local in the lung or systemic in origin. Since we are constantly inhaling air from our environment as we breathe in the ambient air, exhaled breath can also reflect our environmental exposure(s). Furthermore, our breath contains volatile compounds produced by our “internal environment”: the bacteria in our gut and mouth. Add to all of those the volatile byproducts generated from our diet, medications, drugs or toxins that we are exposed to and you get a very rich matrix that has great potential to revolutionize and personalize medicine.

With continued advances in technology, essentially anything in the blood that is potentially volatile or has a volatile metabolite can be measured in exhaled breath. Sensor array (electronic nose) devices can be trained to recognize patterns or “smellprints” in exhaled breath that allow identification of certain diseases or disorders. However, this technology is not well-suited to identify the specific compounds that contribute to a recognized pattern. The mass spectrometry approach to breath analysis, on the other hand, allows the identification of specific individual compounds in the breath, but it is not ideal for recognizing patterns commonly seen in disease.

Figure 1. Canonical discriminant analysis using five selected mass scanning ion peaks was performed in a training cohort of 25 acute decompensated heart failure (ADHF) subjects (blue) and 16 controls (red). This ADHF “breathprint” was then used to classify an independent validation cohort of 36 ADHF subjects (green) with no misclassifications.1
In our group, we have used both approaches to analyze breath and have come to recognize their strengths and weaknesses of both approaches. More recently, we have started to use an approach that combines the strengths of both methods. By approaching each compound (or peak) on the mass spectrometry output as its own sensor, we are able to recognize patterns or “breathprints” in mass spectrometry data in a way similar to how the sensor arrays (or electronic noses) recognize smellprints.

Unlike pattern recognition by the sensor array-based systems, the major strength of our approach is that we are able to identify the individual components that contribute to each pattern we recognize.

With this best-of-both-worlds approach, we are able to identify unique breathprints in patients with liver disease (fetor hepaticus) as well as heart and lung disease. We are further able to analyze these patterns to identify single molecules in the breath of these patients and link them to the underlying pathobiology of the disease.

One such example is our recent study,1 in which we set out to investigate and establish a breathprint that distinguishes between patients with acute decompensated heart failure and non-heart failure cardiovascular diagnoses. (Figure 1) Our team evaluated the volatile organic compounds (VOCs) composition of exhaled gas in patients with heart failure (HF) compared with non-heart failure patients admitted to the hospital. All study participants underwent analysis of single breath exhaled gas by selected ion flow tube mass spectrometry (SIFT-MS), including quantification of six preselected VOCs and mass scanning (MS) for H2O+, NO+ and O2+ ion products from 14 to 200 amu. These findings from the training set were tested in a validation set of 36 patients admitted with acute decompensated HF. We observed acetone and pentane were significantly elevated in HF patients vs. controls. Discriminant analysis utilizing preselected VOCs and select MS peaks correctly classified 100 percent of subjects as HF vs. control. Results were validated by the control cohort. Thus, breath analysis demonstrates a signature in HF patients distinct from control patients that may have clinical utility in the diagnosis and monitoring of these patients.

In another study,2 we examined breathprints in patients with liver disease and were able to identify novel breath biomarkers in alcoholic hepatitis (AH). To determine whether the concentration of VOCs in the breath correlates with the diagnosis and severity of liver disease in patients with alcoholic hepatitis, we prospectively recruited patients with liver disease. The study population was divided into two groups: liver cirrhosis with AH (N = 40) and liver cirrhosis with acute decompensation (AD) from etiologies other than alcohol (N = 40). A healthy control group without liver disease was also identified (N = 43). Using SIFT-MS, precise identification of VOCs in the breath in the parts per billion ranges was achieved on all subjects. Of the 14 preselected volatile breath compounds, we identified six compounds that were elevated in patients with liver disease compared with healthy controls. Those compounds included 2-propanol, acetaldehyde, acetone, ethanol, pentane and trimethylamine (TMA). The mean concentrations of TMA, acetone and pentane, in particular, in the exhaled breath were remarkably higher in patients with AH compared with those with AD and with healthy volunteers (all P < 0.001). With the use of an ROC curve, we developed a model for the diagnosis of AH that included the breath levels of TMA, acetone and pentane (TAP model). TAP provided excellent prediction accuracy for the diagnosis of AH (AUC = 0.93) with 97 percent sensitivity and 72 percent specificity for a TAP score of 28. The levels of exhaled-breath TMA moderately correlated with the severity of AH as presented by MELD score. Furthermore, isoprene and ethanol in the breath were associated with transplant-free survival in AH. Thus, our breathprint approach provides a noninvasive method for the diagnosis of AH and may provide independent prognostic value in AH patients.

The long-term goal of our ongoing work is to continue to discover new markers of disease in the breath that will serve as the basis for the eventual development of novel sensors to detect these biomarkers in exhaled breath in a variety of disease states. This will eventually allow us to provide not only leading-edge care for all our patients, but also personalized care for each patient based on his or her unique breathprint.

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References


Case Study: The Role of Bronchial Thermoplasty in the Management of Severe Asthma

Sumita Khatri, MD

A 24-year-old man, a former ice hockey player and nonsmoker, presented to Cleveland Clinic’s Department of Pulmonary, Allergy and Critical Care Medicine for evaluation of severe persistent asthma/aspirin-exacerbated respiratory disease (AERD). Asthma first became a problem for the patient at age 18, when his breathing difficulties resolved only after treatment with albuterol in the emergency department (ED). His symptoms had since worsened.

The patient had a history of aspirin sensitivity and at least one reaction to ibuprofen, as well as a shellfish allergy. His triggers included cold air exposure and sinus infections. At the time of presentation, he worked in an auto body shop with minimal ventilation. He was using rescue treatments more than three times a day and had been to the ED 12 times in the prior year.

Our patient’s other pertinent medical history included sinusitis, nasal polyps and reflux. Medications at the time of initial evaluation included combination high-dose inhaled steroids and long-acting β-agonist, with additional inhaled steroid supplementation, leukotriene antagonist and prednisone (15 mg daily). Spirometry demonstrated a diminished FEV1/FVC ratio of 58 percent, FEV1 of 4.18 L (73 percent) and FVC of 7.17 L (102 percent). Bronchodilator treatment improved FEV1 by 16 percent to 4.83 L.

POOR ASTHMA CONTROL

At initial evaluation, our patient’s asthma control test score was 7, indicating very poor control. His upper airway symptoms of nasal stuffiness and sinus pain were considerable. Therefore, sinus CT imaging was obtained, which showed chronic pansinusitis and prompted referral to ENT rhinology. Functional endoscopic sinus surgery was performed two months later, when our patient’s FEV1 was 67 percent and his exhaled nitric oxide levels were severely elevated at 186 ppb (normal < 35 ppb).

Although our patient’s sinus disease improved, he continued to have upper airway symptoms and reflux. GI evaluation demonstrated ongoing severe reflux, despite optimization of medications. Our patient next underwent ongoing severe reflux, despite optimization of medications. Our patient next underwent laparoscopic Nissen fundoplication. Postoperative follow-up testing showed FEV1 of 71 percent with an 18 percent bronchodilator response, hyperinflation with a total lung capacity of 120 percent and air trapping with residual volume of 150 percent. At times when he was on higher-dose prednisone, our patient’s FEV1 improved to 100 percent.

BRONCHIAL THERMOPLASTY INDICATED

At this point, after management of multiple comorbidities, we pursued bronchial thermoplasty (BT). The Asthma Research Intervention 2 (AIR2) clinical trial, in which the Respiratory Institute participated, previously demonstrated the safety and efficacy of BT to improve disease control out to two years in patients with severe persistent asthma. Recently published longer-term findings from the AIR2 trial extend BT’s safety and efficacy record to at least five years. The AIR2 Trial Study Group reported in August 2013 that one-time, three-session administration of BT resulted in sustained reduction in patients’ severe exacerbations and ED visits for respiratory symptoms. BT patients in the AIR2 trial showed no decrease in lung function (no deterioration of FEV1) and no significant structural changes in airways at five-year outpoints.

Our patient tolerated all three individual BT sessions well. Two months after the procedure, he had effectively been weaned from oral steroids. His rate of exacerbations is reduced, and those that remain may be due to allergies and reflux. He feels that the duration of exacerbations is shorter and recovery is quicker than before BT. Our patient’s asthma control test at last visit was 22 following a short prednisone burst the previous month. In the future we may reconsider aspirin desensitization.

CONCLUSIONS

The care and management of our patient demonstrates the need for concerted and multimodal therapy for those with severe persistent and refractory asthma. Proper management of comorbidities is necessary, and BT used at the appropriate time can help reduce the number of severe exacerbations and improve asthma-related quality of life.

We are pleased to report that our patient has returned to school and is studying to become a respiratory therapist.

Dr. Sumita Khatri is Co-Director of Cleveland Clinic’s Asthma Center. She can be reached at 216.445.1701 or khatris@ccf.org

Reference

Studies of Sleep-Disordered Breathing Open New Avenues to Understanding Atrial Fibrillation

By Reena Mehra, MD, MS

Sleep-disordered breathing (SDB) exposes patients to chronic intermittent hypoxemia and broad swings in intrathoracic pressure. These effects alter autonomic balance, have untoward effects on cardiac preload and afterload, and enhance inflammatory and oxidative stresses, all of which produce a proarrhythmogenic milieu (Figure 1). Animal and human studies have identified potential mechanisms by which SDB directly and indirectly alters the functional and cardiac structural substrate for arrhythmogenesis in atrial fibrillation (AF) (Figure 2).

EPIDEMIOLOGIC EVIDENCE OF A ROLE FOR SDB IN AF

Our group has performed several epidemiologic observational studies that have demonstrated statistically significant associations between SDB and AF (odds ratio point estimates, 2 to 4). These associations remained even after we took into account a host of potential confounding factors such as age, sex, race, body mass index, and self-reported comorbidities such as hypertension, diabetes mellitus, cardiovascular disease and heart failure.\(^1,2\) For example:

- In a study of approximately 600 patients who participated in the Sleep Heart Health Study, we found that those with moderate to severe SDB on overnight polysomnography (PSG) had fourfold higher odds of AF than did patients without SDB.\(^1\)
- In a cohort of almost 3,000 older men, we found a stronger association with AF among those with central sleep apnea than among those with obstructive sleep apnea, even after controlling for confounding factors.\(^2\) In this study, we noted a threshold effect in which patients with moderate to severe SDB (apnea-hypopnea index \(\geq 24\)) had the highest incidence of AF, independent of any self-reported heart failure and cardiovascular disease. Patients who had a central apnea index greater than 3 had a threefold higher incidence of AF, and those with Hunter-Cheyne-Stokes breathing had an almost fivefold higher incidence.\(^2\)
- We also examined the temporal relationships between discrete respiratory events and paroxysms of AF.\(^3\) This investigation involved a novel application of a case-crossover study design, which is well-suited for studying short-lived exposures and outcomes. We found a strong temporal relationship between apneas/hypopneas and paroxysms of AF. Indeed, we noted seventeenfold higher odds of episodic AF during the 90 seconds following an apnea/hypopnea event than after a period of nonobstructed breathing. This finding supports the premise that SDB plays a role in the etiology of atrial arrhythmias.

Figure 1. Atrial fibrillation is demonstrated in the ECG channel in the context of severe repetitive apnea/hypopnea associated with oxygen desaturations during REM sleep.
IMPLICATIONS FOR FUTURE RESEARCH

Now that compelling data have been accumulated regarding aspects of the SDB-AF relationship, future clinical and epidemiologic research should focus on specific areas, including:

- Collection of objective data on cardiac function
- Measurement and analysis of markers of autonomic function, systemic inflammation and oxidative stress
- Examination of both daytime and nocturnal ECGs in an effort to further elucidate pathophysiologic underpinnings
- Reversing SDB pathophysiology to alleviate AF and its associated morbidity and mortality

TWO STUDIES UNDERWAY

To overcome knowledge gaps in these areas, our group is conducting two NIH-funded research studies:

Sleep Apnea and Atrial Fibrillation
Electrophysiology: Biomarkers and Evaluating Atrial Triggers (SAFEBEAT).

This investigation involves examination of paroxysmal AF because it provides an ideal milieu in which to investigate the immediate influences of SDB and to examine its temporal patterns in view of its intermittent nature. In this case-control study, we are comparing 150 patients with paroxysmal AF to 150 controls without paroxysmal AF. Participants are being matched for important confounders such as age, sex, race and body mass index. They will be characterized on the basis of detailed collections of overnight sleep study data, echocardiographic measures, biomarkers and continuous ECG monitoring. With these data in hand, we will have the opportunity to explore the relationships between paroxysmal AF and both obstructive and central apnea. Another goal is to investigate the associations between paroxysmal AF and age in SDB; our earlier work showed that the association of SDB and arrhythmia is stronger in younger patients. Moreover, we are examining diurnal variations in paroxysmal AF in patients with SDB in terms of immediate and chronic SDB-related physiologic stresses (i.e., intermittent hypoxia, intrathoracic pressure alterations and autonomic influences). Finally, we are assessing the effects of SDB treatment on paroxysmal AF to inform future randomized controlled trials in this area.

Sleep-Related Respiratory and Electrophysiological Atrial Fibrillation Predictors.

The primary goal of this study is to identify PSG-based SDB phenotypes that predict incident AF. We will be investigating the relative contributions of central apnea and periodic breathing vs. obstructive apnea, as well as mediation by inflammation and oxidative stress. Another aim is to identify PSG-derived ECG markers of atrial ectopy, conduction delay and autonomic imbalance, and then to evaluate their utility as predictors of incident AF. For parts of this study, we will be collaborating with engineers at Case Western Reserve University. Depending on what we find, the results of this study may lead to a shift in the current clinical paradigm by identifying which PSG-based physiologic indices should be included in standard PSG monitoring to forecast arrhythmias such as AF.

Figure 2. Schematic showing potential mechanisms by which sleep-disordered breathing (SDB) may contribute to atrial fibrillation (AF). Boxes with dashed lines represent the pathophysiologic indices that link SDB and AF (HRV = heart rate variability; HRT = heart rate turbulence; PAC = premature atrial contraction).

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References

Adult Primary Immunodeficiencies: Complex Patients and Growing Needs

By James Fernandez, MD, PhD, and Leonard Calabrese, MD

Adult primary immunodeficiency diseases are being recognized with increasing frequency. At Cleveland Clinic, our team works closely together to manage patients with a wide variety of primary immunodeficiencies. Common variable immunodeficiency (CVID) is the condition we most often see, but we also treat patients with specific antibody deficiency, natural killer cell deficiencies, hyper IgE, idiopathic CD4 lymphocytopenia, complement deficiencies and an array of other immunologic defects.

Figure 1. Chest CTs at the patient’s presentation showing ground-glass opacification and interstitial thickening in both lungs. Atelectasis or scarring is present in the right middle lobe.

Cleveland Clinic is a member of the United States Immunodeficiency Network (USIDNET), a research consortium founded to advance scientific research in primary immunodeficiency diseases. A main goal of USIDNET is to assemble a registry of patients with primary immunodeficiencies to advance understanding of these diseases. We feel strongly that working closely with other academic centers advances our understanding of the biological defects in immunodeficient patients, which ultimately will lead to improved healthcare. These patients frequently incur life-threatening complications above and beyond infections, as the following case demonstrates.

PRESENTATION

A 38-year-old woman presented to Cleveland Clinic’s Immunology Clinic with new-onset severe headache, left-sided numbness and weakness, nausea, vomiting, and an expressive dysphasia. Her long-term history included recurrent sinopulmonary infections and a subsequent diagnosis of CVID based on hypogammaglobulinemia and a lack of specific vaccine responses. She was put on intravenous immunoglobulin replacement therapy at 400 mg/kg in 2004 and switched to subcutaneous immunoglobulin replacement (for greater convenience) in 2008. With regard to her CVID, a chest CT showed granulomatous disease of the lungs (Figure 1), but transbronchial biopsy was nonspecific and there were no signs of infection or other concerning signs.

One month before presenting at the Immunology Clinic, the patient noted two episodes of visual loss lasting approximately 45 minutes each. On both occasions, neuroimaging studies at a local hospital were negative. She described her recent headaches as sharp, constant, bitemporal and retro-orbital, eventually developing into the “worst headache of my life,” with associated difficulty speaking, left-sided weakness, nausea and vomiting. Imaging at this time (Figure 2) revealed a right frontoparietal lobe hemorrhage. Cerebral angiography was normal, and laboratory results — including CBC, ESR, CRP and BMP — were unremarkable.

EVALUATION AND INITIAL MANAGEMENT

Examination revealed an expressive dysphasia, decreased sensation to pinprick on the left side and mild splenomegaly. The patient was started on 40 mg/day of prednisone and experienced improvement in symptoms. She did well with physical and speech therapy until two months later, when she developed right-sided numbness, hemianopia and worsening dysphasia. Repeat imaging of the head showed a large hemorrhage at the left tempo-occipital junction (Figure 3). Biopsy of the temporal lobe showed a perivascular noncaseating granuloma consistent with granulomatous angiitis of the central nervous system (Figure 4).

The patient was started on prednisone and rituximab, with B-cell depletion subsequently documented. After two doses of rituximab, she experienced worsening dysphasia and right-sided weakness, and brain MRI showed progression of her vasculitis. The rituximab was stopped and infliximab was added to her regimen.

FOLLOW-UP

The patient responded well to prednisone and infliximab, as subsequent neuroimaging showed no further progression. Her weakness and dysphasia slowly improved over months. She is currently receiving prednisone 5 mg daily, infliximab 5 mg/kg every eight weeks and weekly subcutaneous liquid immunoglobulin therapy (Hizentra®). She remains free of severe infections, and her neurological deficits are slowly improving.

COMMENT

This case demonstrates the complexity characteristic of primary immunodeficiencies. For example, patients with CVID are
at risk of multiple complications, including autoimmune disease, which develops in 20 to 25 percent of patients. These patients require continued monitoring, not only for infections but granulomatous disease of the lungs, autoimmune disorders, lymphoma, malabsorption and other complications. For these reasons, a team approach is vital to the overall care of our primary immunodeficiency patients.

The Allergy and Clinical Immunology Department works closely with pulmonologists, hematologists, oncologists and gastroenterologists to provide the best care for these patients. We frequently make decisions about care as a team, and constant communication among physicians is a necessity. In the end, patients are better served and appreciate a collaborative effort by multiple physicians with specific expertise in managing primary immunodeficiency and the complications related to it. With a growing number of adult immunodeficiencies being identified, our institute is fully committed to advancing the care of patients and initiating new research projects in this growing and exciting field.

Dr. Fernandez is an associate staff physician in the Department of Allergy and Clinical Immunology in Cleveland Clinic’s Respiratory Institute. His specialty interests include primary immunodeficiency. He can be contacted at 216.444.6933 or fernanj2@ccf.org. Dr. Calabrese is Director of the R.J. Fasenmyer Center for Clinical Immunology in the Department of Rheumatic and Immunologic Diseases. He can be reached at 216.444.5258 or calabrl@ccf.org.

Suggested Reading

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Figure 2. Brain CT at presentation showing a hyperintensity in the subcortical white matter underlying the right supramarginal gyrus with separate patchy hyperintensity in the overlying right frontoparietal lobe. Abnormal hyperintensity is present along the cortex of the right parietal operculum and supramarginal gyrus. No significant mass effect is present.

Figure 3. Brain CT two months after presentation showing a large hemorrhage at the left temporo-occipital junction with surrounding edema. There is a moderate mass effect on the left lateral ventricle. A small subdural hematoma may be present along the left lateral frontotemporal region.

Figure 4. Temporal lobe biopsy findings two months after presentation showing a noncaseating granuloma characterized by lymphocytes, epithelioid histiocytes and a multinucleated giant cell in the leptomeninges adjacent to a small artery. Multiple veins in the meninges show perivascular and intramural lymphocytes. These histologic findings are compatible with a primary vasculitis of the central nervous system.
Therapies for the management of non-small cell lung cancer continue to evolve with advances in early detection (screening), radiation treatment and chemotherapy. The mainstay of the management of early stage lung cancer continues to be surgical resection. To this end, surgical techniques and strategies focus on minimally invasive surgical techniques and lung-sparing operations to preserve pulmonary function while effectively treating early lung cancer. Advances in staging, both radiographic and interventional, have allowed for optimized selection of surgical candidates as have nuances in assessing cardiopulmonary fitness. Consequently, surgeries performed for lung cancer are safer and more effective than ever before.

Technological developments have also significantly impacted surgical management of non-small cell lung cancer. Specifically, improvements in minimally invasive staging of cancer and surgical resection have translated into better outcomes for patients. Endobronchial ultrasound (EBUS) assessment of the mediastinum has allowed for accurate interrogation of central mediastinal lymph node and hilar lymph node involvement and has become an important tool for preoperative staging of lung cancer (Figure 1). When combined with other modalities (PET scan and mediastinoscopy), unsuspected metastatic involvement of local and regional lymph nodes is dramatically reduced, lessening the frequency of futile noncurative thoracotomy. These three staging modalities are collaboratively utilized, and algorithms have been developed to help decide which is necessary for a given patient.

Less invasive operations lead to a shorter hospital stay, less morbidity and more rapid return to full function. Historically, lung cancer operations were performed through extended thoracotomies with division of chest wall musculature and often removal of ribs. This created significant trauma for patients and led to a protracted hospital course and delayed recovery. When possible, thoracotomies are now performed using muscle-sparing techniques and rib preservation. More important, the thoracotomy is being replaced by true minimally invasive techniques, whereby small incisions are created and operations are assisted by video guidance. Video-assisted thoracic surgery (VATS) is now the preferred surgical treatment for early stage lung cancer (Figure 2). Operations performed using VATS account for almost 50 percent of surgeries performed for lung cancer at Cleveland Clinic. Hospital stays and time to resume normal activities are

Figure 1. Endobronchial ultrasound (EBUS) of enlarged mediastinal lymph node.
markedly shortened. Notably, studies have consistently demonstrated that cancer cure rates are equal, if not better, when VATS operations are performed instead of classic thoracotomy. Not surprisingly, patient satisfaction is much greater with these less invasive operations.

Even more recently, robotic technology has joined the therapeutic armamentarium against lung cancer. Over the last two to three years, robotic lung resections (lobectomy) have entered into routine clinical practice at some major academic institutes. These operations are utilized for stage I non-small cell lung cancer and offer all the benefits of VATS surgery with even smaller incisions. The surgeon is stationed at the robot console while his assistants are changing robotic instrumentation at the patient’s bedside (Figure 3). Three or four robotic arms are utilized, and each provides several degrees of freedom within the patient’s thorax to allow for fine movements of the surgeon’s hand to be translated directly to the tips of each instrument (Figure 4). Magnifying cameras are used to further increase visualization, and the surgeon sees a 3-D image (Figure 5). These operations generally take more time to complete, though from a patient standpoint, this appears to be time well spent. Preliminary data suggest that robotic lobectomy is well-tolerated and patient recovery appears to be accelerated when compared with traditional thoracotomy approaches.

Much like other respiratory-related diseases, lung cancer is better diagnosed, better staged and better treated than ever before. Recent advances have come on the technologic front with use of sophisticated techniques, particularly from minimally invasive interventions. Patients likely benefit most from multidisciplinary management of lung cancer, especially when expertise in minimally invasive staging and surgery exists.

Dr. Murthy is the Surgical Director of the Center of Major Airway Disease and a staff thoracic surgeon in the Department of Thoracic and Cardiovascular Surgery, Sydell and Arnold Miller Family Heart & Vascular Institute. He holds joint appointments with the Transplant Center and the Taussig Cancer Institute. He can be contacted at 216.444.5640 or murthys1@ccf.org.

Reference
Three-dimensional (3-D) printing is a hot topic in the news and in the medical community, where the technology is being used to make customizable medical implants. In May 2013, we employed a 3-D printer to fabricate a bioresorbable tracheal splint that saved the life of an Ohio child with congenital tracheobronchomalacia. Computer 3-D rendering, materials science and the ability to construct a device with these 3-D printers are constantly evolving. These are being used in several areas of bronchology.

In the Respiratory Institute’s Bronchoscopy Section, we face complex, unique airway challenges and have been investigating the use of 3-D printers to help address our patients’ needs. Currently, the selection of airway stents is extremely limited in the U.S. market. There are only two basic types: silicone-based tube stents and self-expandable metallic nitinol stents and their hybrids. These have only simple tubular shapes and their size range is very limited. Unfortunately, airway diseases don’t just affect the long airways at the midpoint, where the available stents are relatively easily placed. Even in those accessible locations, they can result in airway kinking, bending, conical shapes and problems at branch points.

Following bilateral lung transplant, one of our patients developed an unusual native airway bronchomalacia above the anastomosis and required an airway stent after fighting recurrent pneumonia with trouble clearing secretions. Over time, the limits of existing stents became clinically problematic:

- The anastomotic line was several millimeters smaller than the native airway, causing granulation from improper fit.
- The proper combination of length and diameter was not available.
- The left main bronchus and new lung were not a simple straight tube shape, but a curve with cone-shaped distal end (Figure 1).

Despite cutting the proximal end of the stent, it still rode over the main carina and may have migrated proximally. The angle from the main carina to the anastomotic line is curved, not straight, and seems to have some space, but the anastomotic line is clearly smaller than the midpoint.

By Thomas Gildea, MD

Figure 1. Coronal CT image of silicone stent in the left main bronchus. Note that there is evidence of poor fit at the arrows.
We initially tried metallic stenting, but these quickly failed due to metal fatigue. We tried standard silicone stents, but they did not sit well and developed a biofilm with severe halitosis. We eventually moved to combinations of differing-sized, modified stents, altered to fit the airway as best we could. Clearly, there is a role for a custom shaped and sized single-airway prosthesis not currently available. For this patient, we needed a longer-than-available stent that tapers distally. We could cut and shape the proximal end as needed. We were able to employ a technique of making a basic mold with a 3-D printer and pressure-injecting the silicone material around a mandrel to make the basic size and shape we needed. Note the tapered diameter on the left (Figure 2).

Another utilization in which 3-D printing has been explored is for medical education. We have identified many respiratory patients with complex anatomical challenges. Printing a 3-D model of each patient’s airway anomaly can provide us an opportunity to try different techniques ex vivo to address the problem. Figure 3 shows a 3-D printed model based on CT scan data. At this point, almost every variation of central airway anomaly can be reproduced except dynamic airway diseases. There are still issues with making 3-D prints from peripheral lung images, as these are subject to the resolution of CT imaging.

We have been collaborating with other institutions to provide these 3-D disease airway models for experimentation with novel materials. Materials scientists can try different deployment systems and techniques to address nonstandard airway shapes and sizes.

Dr. Thomas Gildea, Head of the Section of Bronchology and member of the Advanced Lung Disease Section of the Department of Pulmonary Medicine and Transplant Center, can be reached at 216.444.6503 or gildeat@ccf.org.
Pulmonary arterial hypertension (PAH) is characterized by pathological changes in the pulmonary arteries leading to a progressive increase in pulmonary vascular resistance, with subsequent development of right heart failure. New drugs and therapies, as well as a better understanding of the pathophysiology of the disease, have led to improvements in morbidity and survival in recent years. However, despite recent advancements, survival continues to be low, with three-year survival at 69 percent.\(^1,2\)

Current treatments work mainly by vasodilating the pulmonary vessels. However, a significant cause of disease progression in PAH is the development of right heart failure. In fact, studies have shown that whereas mean pulmonary artery pressure and pulmonary vascular resistance do not correlate well with survival in PAH, right heart function indicators successfully predict mortality.\(^3,4\) Recently, there has been increased interest in tools to monitor right ventricular function and in therapies targeting the right ventricle.

Hypoxia-inducible factors (HIF), the protein complexes that govern the body’s response to low oxygen concentrations, are activated in PAH. HIF signaling leads to alterations in cellular bioenergetics, causing a shift to glycolysis. Expression of HIF is increased in the myocardium of patients with ischemic heart disease, suggesting a role in cardiac function. Cleveland Clinic investigators and others have shown increased HIF expression in the lungs of patients with PAH\(^5-7\) and a parallel increase of glucose uptake in the lungs of patients with PAH compared with healthy controls as determined by 2-deoxy-2\(^{-}\)[18F]fluoro-D-glucose (FDG) positron emission tomography (PET) scan.\(^8\)

To investigate mechanisms of right ventricular failure in PAH, researchers in Cleveland Clinic’s Respiratory Institute, Miller Family Heart & Vascular Institute and Imaging Institute evaluated FDG uptake in the hearts of patients with PAH over time as a marker of HIF activation in the cardiac myocytes.\(^9\) Six healthy controls and 14 patients with PAH were enrolled in the study and underwent FDG-PET under fasting conditions and echocardiogram. Of the PAH patients, 12 had repeat studies at one year. FDG uptake in the right ventricle of patients with PAH was higher than in healthy controls (Figure) and strongly correlated with echocardiographic parameters of right ventricular function. Over time, the changes in FDG uptake continued to be correlated with echocardiographic parameters. Explanted hearts from PAH patients undergoing transplantation had high levels of HIF expression. The study identifies fasting FDG-PET as a
Ongoing studies at Cleveland Clinic continue to focus on the pathophysiology of right heart failure. Overactivation of the sympathetic nervous system is present in right heart failure. This initially occurs to compensate for reduced cardiac output. Various measures of sympathetic activity have been found to be abnormal in PAH patients. Those abnormal measures include elevated plasma norepinephrine, reduced cardiac uptake of meta-iodobenzylguanidine, increased post-ganglionic muscle sympathetic nerve activity, downregulation of the β-adrenergic receptors in the RV, and reduced heart rate variability.

Although β-blockade is a cornerstone therapy in left heart failure and has been shown to reduce morbidity and mortality, its use in right heart failure is controversial. Cleveland Clinic investigators have initiated a study to assess the role of β-blockade in PAH. The randomized, double-blind, placebo-controlled study uses the β-blocker carvedilol in patients with PAH. The PAHTCH (Pulmonary Arterial Hypertension Treatment with Carvedilol for Heart Failure) study currently is enrolling patients. Building on the previous findings using fasting FDG-PET in PAH, patients will have fasting FDG-PET done to monitor RV response to therapy.

Eligibility criteria for study participants are Group 1 PAH, NYHA Class I-III, age 18-65, stable on PAH medications for the past 30 days and not currently enrolled in any other clinical trials. For more information, please contact our study coordinator, Dr. Charles Roach, at 216.445.7706 or roache@ccf.org, or our principal investigator, Dr. Samar Farha, at farhas@ccf.org.
Novel Methods to Test for EGFR and ALK: Innovative Technique Developed at Cleveland Clinic Extends Yield of EBUS Samples

By Joseph Cicenia, MD, and Raymond Tubbs, DO

The advent of molecular profiling and the emergence of targeted therapies in lung cancer have resulted in a radical change in how we classify and approach this disease, especially with regard to adenocarcinoma of the lung. Currently, the U.S. Food and Drug Administration has approved three targeted therapies based on the presence of their corresponding molecular targets in adenocarcinoma cells: erlotinib (Tarceva®) and afatinib (Gilotrif®) as a first-line therapy for patients who harbor epidermal growth factor receptor (EGFR) gene mutations, and crizotinib (Xalkori®) for treating patients who exhibit anaplastic lymphoma kinase (ALK) gene translocations.

All three drugs have shown a significant progression-free survival advantage compared with standard therapy when used in patients who exhibited the presence of their corresponding oncogenes. Recently published guidelines submitted jointly by the College of American Pathologists, the International Association for the Study of Lung Cancer and the Association of Molecular Pathology recommend molecular testing for all patients with lung adenocarcinoma who have advanced (Stage IV) disease, and encourage similar testing in patients with lung adenocarcinoma in earlier stages of the disease (Stages I-III). Furthermore, the organizations recommend a laboratory testing turnaround time (TAT) of five days, with an absolute maximum of 10 days.

Due to the fact that lung cancer most often initially presents as advanced disease, and with the emergence of minimally invasive diagnostic testing (such as endobronchial ultrasound-guided transbronchial needle aspiration, or EBUS-TBNA), more than half of the samples used for molecular testing are derived from needle-based biopsies.

Utilizing methods approved as in vitro diagnostic tests by the FDA and adopted by many reference labs (including our own), there has been a reported test failure rate of as much as 10 percent for EGFR testing and as much as 30 percent for ALK testing. It was our hypothesis that these failures derive from the standard fixation methods used on paraffin-embedded samples and from using tissue processed from cytology cell blocks. Standard fixation typically uses formalin, which has been shown to denature and fragment DNA and thus will increase the failure rate of molecular testing. Further, the nonuniform distribution of tissue within the cytology cell block in addition to the cell block cutting (which may cut through the cell and damage DNA directly) are also hypothesized to increase the failure rate of molecular testing.

Our molecular pathology lab therefore hypothesized that if we performed molecular testing on fresh tissue, the rate of test failures would drop. To that end, our lab began processing EGFR (done via polymerase chain reaction, PCR) and ALK (done via fluorescence in situ hybridization, FISH) testing directly from the cytospun CytoLyt® pellet that was derived from fine-needle aspiration samples preserved in CytoLyt solution (a methanol-based preservative). After creation of the cell pellet by centrifugation of the methanol-preserved sample, the pellet was divided into samples that would go directly to DNA extraction for EGFR testing, and to be made into a ThinPrep® slide for FISH analysis for ALK testing. The rest of the pellet would be sent for cell block preparation, from which immunostaining could be performed, if needed.

Because the FDA-approved regimen for EGFR and ALK testing calls for formalin-fixed, paraffin-embedded tissue, our novel methodology for performing these tests needed to be internally validated based on College of American Pathologists and Clinical Laboratory Improvement Amendments guidelines. Validation of both tests was done with 100 samples for EGFR and 116 samples for FISH, with 98 percent and 98.4 percent agreement on EGFR and FISH testing, respectively. Once validation was completed, all subsequent testing was performed using these novel methods. Data from January 2013 through October 2013 showed a reduction of test failures to 2.6 percent for EGFR and 0.9 percent for ALK. Additionally, our TAT remained within guideline standards, at five working days. To our knowledge, we are the first center to report on these novel methods to test for EGFR and ALK using ThinPrep for testing of slides and DNA extracted for CytoLyt.

This is a perfect example of Cleveland Clinic’s ability to respond to problems that may interfere with patient care: identification of the problem, interdepartmental collaboration to assess the problem, novel ideas to correct the issue, and having the resources to validate and implement the solution. Reducing the test failure rate to less than 3 percent for both EGFR and ALK testing will allow more of our patients to be identified for targeted therapy in a more timely fashion and will significantly reduce the number, and extent, of re-biopsies.

Dr. Joseph Cicenia, a member of the Pulmonary Department, can be reached at 216.445.8606 or cicenij@ccf.org. Dr. Raymond Tubbs, Section Head of Molecular Oncologic Pathology, can be reached at 216.444.2844 or tubbssr@ccf.org.
Cleveland Clinic Respiratory Institute
Selected Clinical Trials

Consider offering your patient enrollment in a leading-edge clinical research trial at our Respiratory Institute. Further information can be obtained by contacting the study coordinator or principal investigator.

CRITICAL CARE MEDICINE

Study of Ganciclovir/Valganciclovir for Prevention of Cytomegalovirus Reactivation in Acute Injury of the Lung and Respiratory Failure (GRAIL)

A NHLBI-supported study to evaluate whether administration of ganciclovir reduces serum IL-6 levels (i.e., reduction between baseline and 14 days post-randomization) in immunocompetent adults with severe sepsis or trauma-associated respiratory failure.

ELIGIBILITY: Selected inclusion criteria include patients age 18 years or older; CMV IgG seropositive; report that patient has previously been tested and found to be CMV seropositive at any time; intubation and requiring mechanical positive pressure ventilation (including acute lung injury/ARDS (EA Consensus Definition); meets criteria for either A.) severe sepsis or trauma-associated respiratory failure.

PRINCIPAL INVESTIGATOR: R. Duncan Hite, MD
STUDY COORDINATOR: Michelle Ferrari, RN, BSN | 216.445.1939

Impact of Aggressive Empiric Antibiotic Therapy and Duration of Therapy on the Emergence of Antimicrobial Resistance During the Treatment of Hospitalized Subjects with Pneumonia Requiring Mechanical Ventilation

The primary objective of this NIAID-sponsored study is to demonstrate a low rate of emergence of antibiotic resistance in P. aeruginosa and Acinetobacter spp during the treatment of hospitalized patients with pneumonia requiring mechanical ventilation treated with PD-optimized meropenem administered as a prolonged infusion in combination with a parenteral aminoglycoside plus tobramycin by inhalation (Group 1) compared with therapy with meropenem alone (Group 2, control arm).

ELIGIBILITY: Selected inclusion criteria include receiveing treatment in an ICU, or in an acute care setting with documented orders to transfer to the ICU; clinical evidence of bacterial infection and a known site of infection; and of the following: currently receiving treatment with antibiotics, WBC > 12,000/mm^3 or < 4,000/mm^3 or bandemia > 10%, platelet counts in the range of > 30,000/mm^3 to < 150,000/mm^3; fever with core temperature of < 36ºC or > 38ºC. Subjects with inflammatory changes due to sepsis defined by receiving vasopressors to maintain mean arterial pressure greater than or equal to 65 mmHg.

PRINCIPAL INVESTIGATOR: Jorge Guzman, MD
STUDY COORDINATOR: Michelle Ferrari, RN, BSN | 216.445.1939

Vitamin C Infusion for Treatment in Sepsis-Induced Acute Lung Injury

The objective of this NIH-supported study is to assess the efficacy of a 96-hour intravenous vitamin C infusion protocol (200 mg/kg per 24 hours) in patients with established acute lung injury (ALI) from sepsis.

ELIGIBILITY: Selected inclusion criteria include patients age 18 years or older with a suspected or proven infection, and meeting 2 out of 4 of the criteria for systemic inflammatory response (SIRS) due to infection, and accompanied by at least 1 criterion for sepsis-induced organ dysfunction (defined as fever > 38ºC (any route) or hypothermia < 36ºC (core temp only), tachycardia heart rate > 90 beats/min or receiving medications that slow heart rate or paced rhythm, leukocytosis: > 12,000 WBC/µL or leukopenia < 4,000 WBC/µL or > 10% band forms. Respiratory rate > 20 breaths per minute or PaCO2 < 32 or invasive mechanical ventilation).

PRINCIPAL INVESTIGATOR: R. Duncan Hite, MD
STUDY COORDINATOR: Michelle Ferrari, RN, BSN | 216.445.1939

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Assess the Safety and Efficacy of ART-123 in Subjects with Severe Sepsis and Coagulopathy

Sponsored by Asahi Kasei Pharma America Corp., this study is designed to determine whether ART-123, when administered to subjects with infection complicated by at least one organ dysfunction and coagulopathy, can reduce mortality, and to assess efficacy of ART-123 in resolution of organ dysfunction.

ELIGIBILITY: Selected inclusion criteria include receiving treatment in an ICU, or in an acute care setting with documented orders to transfer to the ICU; clinical evidence of bacterial infection and a known site of infection; and of the following: currently receiving treatment with antibiotics, WBC > 12,000/mm^3 or < 4,000/mm^3 or bandemia > 10%, platelet counts in the range of > 30,000/mm^3 to < 150,000/mm^3; fever with core temperature of < 36ºC or > 38ºC. Subjects with inflammatory changes due to sepsis defined by receiving vasopressors to maintain mean arterial pressure greater than or equal to 65 mmHg.

PRINCIPAL INVESTIGATOR: Jorge Guzman, MD
STUDY COORDINATOR: Michelle Ferrari, RN, BSN | 216.445.1939

A 26-Week Randomized, Double-Blind, Active Controlled Study Comparing the Safety of Mometasone Furoate/Formoterol Fumarate MDI Fixed Dose Combination vs. Mometasone Furoate MDI Monotherapy in Adolescents and Adults with Persistent Asthma

ASTHMA
**ELIGIBILITY:** To qualify for inclusion, patient must report using one of the following asthma therapies: (a.) ICS or ICS with one or more adjunctive therapies (LABA, LTRA or theophylline) at a stable dose for at least 4 weeks prior to randomization, (b.) leukotriene receptor antagonist (i.e., LTRAs such as montelukast, zafirlukast or pranlukast) OR xanthines (e.g., theophylline) as monotherapy at a stable dose for at least 4 weeks prior to randomization, or (c.) daily albuterol/salbutamol (used on most days) without any other asthma controller, in the 4 weeks prior to randomization. Subject must be able to discontinue his/her current asthma medication (e.g., SABA, LTRA, theophylline, ICS or ICS/LABA) and must report a history of at least one asthma exacerbation between 4 and 52 weeks prior to randomization. Key exclusion criteria include unstable asthma; COPD, cystic fibrosis or other significant, non-asthmatic, lung disease; cumulative history of smoking > 10 pack years; an asthma exacerbation within 4 weeks of randomization; and reporting > 4 separate asthma exacerbations within last 52 weeks.

**PRINCIPAL INVESTIGATOR:**
David Lang, MD

**STUDY COORDINATOR:**
Elizabeth Maierson, RRT | 216.444.2901

### **Severe Asthma Research Program (SARP)**

Sponsored by the NHLBI, this multicenter, 36-month study is designed to evaluate the pathology of asthma longitudinally.

**ELIGIBILITY:** Individuals (6-65 years old) who have been clinically diagnosed with asthma and are prescribed oral corticosteroids or high-dose inhaled corticosteroid and long-acting beta agonist or other controller medication. Participants must demonstrate FEV1 bronchodilator reversibility ≥ 12% or airway hyper-responsiveness reflected by a methacholine PC20 ≤ 16 mg/mL. Exclusion includes smoking history > 10 pack years if ≥ 30 years of age, or smoking history > 5 pack years if < 30 years of age, and no smoking within the past year.

**PRINCIPAL INVESTIGATOR:**
Serpi Erzurum, MD

**STUDY COORDINATOR:**
Marybeth Boyle | 216.445.1756

### **KIA**

Sponsored by the NIH and Brigham and Women’s Hospital, this is a 30- to 34-week, treatment-randomized, double-blind, placebo-controlled study of the effects of cKIT inhibition by imatinib in patients with severe refractory asthma (KIA).

**ELIGIBILITY:** Patients age 18-60 years, diagnosed with asthma for at least one year, ACQ 1.5 at VI and V3, pre-bronchodilator FEV1, 40% predicted, > 80% compliance with PEF recording and diary recording during the run-in period.

**PRINCIPAL INVESTIGATOR:**
Serpi Erzurum, MD

**STUDY COORDINATOR:**
Jackie Sharp, CNP | 216.636.0000

### **A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel Group Study of JNJ-38518168 in Symptomatic Adult Subjects with Uncontrolled, Persistent Asthma**

Sponsored by Janssen Research & Development, this study will evaluate the safety and efficacy of orally administered JNJ-38518168 in subjects with uncontrolled, eosinophilic, persistent asthma that is inadequately controlled despite current therapy compared with placebo over a 32-week treatment period.

**ELIGIBILITY:** Patients, 18 to 75 years of age, with a diagnosis of asthma for > 26 weeks, with blood eosinophil count of ≥ 300/µL or FENO ≥ 35 ppb at screening, inhaled corticosteroid (ICS) dose ≤ 1,000 µg/day fluticasone or its equivalent for at least 12 weeks, be receiving the same dose of ICS ≤ 1,000 µg/day fluticasone or its equivalent alone or in conjunction with LABA and/or montelukast for > 4 weeks and pre-bronchodilator FEV1 equal to 40%–80% predicted recorded at screening. Exclusion criteria include ever having had a life-threatening asthma attack including respiratory arrest, intubation or ICU admission due to asthma, current usage of systemic corticosteroids, oral beta-agonists, cromolyns, leukotriene inhibitors, theophylline, inhaled anti-cholinergic agents and Xolair®; diagnosis of other conditions that could lead to an elevated eosinophil count; having smoked within 3 years of screening or a history of smoking ≥ 10 pack years; and BMI ≥ 40.

**PRINCIPAL INVESTIGATOR:**
Sumita Khatri, MD, MS

**STUDY COORDINATOR:**
Tani Martin, RN, BSN | 216.444.9975

### **Alternate Day Diet (ADD)**

Sponsored by the NHLBI, this study is looking at the effects of a calorie-restricted diet in asthmatics.

**ELIGIBILITY:** Participants must be between the ages of 18 and 65 with a diagnosis of asthma. Healthy individuals will also be enrolled for comparison. Exclusion criteria include diabetes (fasting blood sugar >110 mg/dL), lactose intolerance, BMI > 32 kg/m², pregnancy and inability to maintain ADD diet. Low-calorie “shakes” will be provided to participants.

**PRINCIPAL INVESTIGATOR:**
Serpi Erzurum, MD

**STUDY COORDINATOR:**
Megan Park | 216.445.1756

### **COPD**

**Long-Term Oxygen Treatment Trial (LOTT)**

Sponsored by the NHLBI, this randomized clinical trial is examining supplemental nasal oxygen therapy vs. no oxygen.

**ELIGIBILITY:** Patients age > 40 years, FEV1 < 70% of predicted, FEV1/FVC < .7, smoking history > 10 pack years, resting room air SpO2 = 89%-93% range or resting oxygen saturation > 94% and desaturation during exercise defined as saturation < 90% for at least 10 seconds during the six-minute walk.

**PRINCIPAL INVESTIGATOR:**
James K. Stoller, MD, MS

**STUDY COORDINATOR:**
Richard Rice, Med, RRT | 216.444.1150

### **SARCOIDOSIS AND INTERSTITIAL LUNG DISEASE**

**STX-100 in Patients with Idiopathic Pulmonary Fibrosis**

Sponsored by Stromedix Inc., this randomized, double-blind, placebo-controlled, multiple-
dose, dose escalation study is examining a humanized monoclonal antibody targeting integrin αvβ6 in IPF patients.

**ELIGIBILITY:** Patients age 50-84 years, IPF diagnosis prior to screening via HRCT showing UIP pattern; FVC > 50% of predicted value, DLco > 35% predicted value, oxygen saturation > 90% on room air at rest, residual volume < 120% predicted value, FEV1/FVC ratio 0.65 after use of bronchodilator. Ages 18-49 are eligible if they have a diagnosis of UIP based on surgical lung biopsy.

**PRINCIPAL INVESTIGATOR:** Daniel Culver, DO

**STUDY COORDINATOR:** Tani Martin, RN, BSN | 216.444.9975

### A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of GS-6624 in Subjects with Idiopathic Pulmonary Fibrosis (RAINIER)

Sponsored by Gilead Pharmaceuticals, this is a Phase 2, randomized, double-blind, placebo-controlled study of a subcutaneous monoclonal antibody (simtuzumab), once a week. Simtuzumab is a humanized mAb with an immunoglobulin IgG4 isotype directed against human LOXL2 (lysyl oxidase-like 2), an ECM enzyme that promotes cross-linking of proteins. The primary objective is to determine the effect of simtuzumab on progression-free survival as determined by either a categorical decline in FVC or all-cause mortality.

**ELIGIBILITY:** Patients age 45-85 with definite IPF using HRCT/SLB in past 3 years. However, if dx > 3 years but clinically deteriorating, they can be screened for participation. RA sat ≥ 89% at rest, able to walk > 50 meters, FVC 35%-90% predicted, DLco > 25% predicted. Exclusions include use of supplemental O2 > 6 L with activity; FVC < 90% predicted; history of aortic aneurysm ≥ 3.5 cm in diameter; obstructive lung disease by PFT's OR HRCT; respiratory hospitalization within past 26 weeks; treatment with immunosuppressive, cytotoxic or anti-fibrotic drugs (NAC is OK); chronic use of moderate- or high-dose oral corticosteroids (> 10 mg/day) and being listed for lung transplant.

**PRINCIPAL INVESTIGATOR:** Joseph Parambil, MD

**STUDY COORDINATOR:** Ron Wehrmann, RRT | 216.445.0574

### Safety and Efficacy of a Lysophosphatidic Acid Receptor Antagonist in Idiopathic Pulmonary Fibrosis (SEAL)

Sponsored by Bristol-Myers Squibb, this is a double-blind, placebo-controlled, Phase 2 study of the safety and efficacy of lysophosphatidic acid receptor antagonist (BMS-986020). The primary efficacy outcomes assessment is rate of change in FVC from baseline to week 26.

**ELIGIBILITY:** Patients ages 40-80, 6 months > UIP dx > 48 months, FVC 50%-80% predicted, DLco 50%-80% predicted, able to walk 150 meters. Exclusions include ratio < 80% after administration of BD at screening, + BD response with spirometry, having a family or personal history of long QT syndrome and/or torsades de pointes, QTcF > 450 ms.

**PRINCIPAL INVESTIGATOR:** Daniel Culver, DO

**STUDY COORDINATOR:** Ron Wehrmann, RRT | 216.445.0574

### A Double-Blind, Placebo-Controlled Phase 2 Dose-Ranging Study of the Effects of ARA 290 on Corneal Nerve Fiber Density and Neuropathic Symptoms of Subjects with Sarcoidosis

Sponsored by Aram Pharmaceuticals, the primary objective of this study is to determine the safety and efficacy of 1 mg, 4 mg or 8 mg of ARA 290 administered subcutaneously for 28 consecutive days vs. placebo on corneal nerve fiber density.

**ELIGIBILITY:** Patients ages > 18 and < 70 with neuropathic symptoms and diagnosed with sarcoidosis, who meet both of the following two criteria: score of 4 or greater on BPI and discomfort defined as distal pain/discomfort and either of the following two criteria: corneal nerve fiber density reduced compared with normal or a previous skin biopsy showing a reduced intraepidermal nerve fiber density, BMI ≤ 40 kg/m². Exclusion criteria include abnormal history of physical and mental health, abnormal laboratory results, abnormal ECG, history of serious malignancy or reduce lung function by any of the following criteria: RV/TLC < 80%, or RV > 120% of predicted, or extent of emphysema on HRCT greater than the extent of fibrosis on HRCT; treatment with immunosuppressive, cytotoxic or anti-fibrotic drugs (NAC is OK); history of cancer of any type in the 5 years preceding Screening Visit 1, excluding non-melanomatous skin cancer, localized bladder.

**PRINCIPAL INVESTIGATOR:** Daniel Culver, DO

**STUDY COORDINATOR:** Tani Martin, RN, BSN | 216.444.9975

### Use of Roflumilast to Prevent Exacerbations in Fibrotic Sarcoidosis Patients

Sponsored by Forest Research Institute, the primary objective of this study is to determine the effectiveness and toxicity of roflumilast in treating fibrotic sarcoidosis, including reducing episodes of acute exacerbations.

**ELIGIBILITY:** Patients ages > 18 and < 70 with sarcoidosis, FEV1/FEV ratio < 80%, fibrosis on CXR or HRCT, at least two exacerbations of sarcoidosis in the past year, stable dose of corticosteroids and other agents at least 4 weeks prior to first visit. Exclusion criteria include hypersensitivity to theophylline or pentoxifylline (patients will not be able to take theophylline or pentoxifylline during the time of the study), serum creatinine > 3 mg/dL, moderate or severe liver disease, unstable cardiac disease, noncutaneous malignancy treated in the past 2 years.

**PRINCIPAL INVESTIGATOR:** Joseph Parambil, MD

**STUDY COORDINATOR:** Tani Martin, RN, BSN | 216.444.9975

### FibroGen FGCL-3019-067: Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of FG-3019, a Fully Human, Recombinant DNA-Derived, IgG1 Kappa Monoclonal Antibody that Binds to CTGF in the N-terminal Domain 2.

The primary objective of this study, sponsored by FibroGen Inc., is to determine the effect of FG-3019 on FVC % predicted in patients with usual interstitial pneumonia (UIP).

**ELIGIBILITY:** Patients 40-80 years old with < 48 months dx of UIP; FVC 55%-90% predicted; DLco > 30% predicted. Exclusion criteria include DLco < 30% predicted (corrected); FVC > 90% predicted; evidence of obstructive lung disease by any of the following criteria: RV/TLC < 80%, or RV > 120% of predicted, or extent of emphysema on HRCT greater than the extent of fibrosis on HRCT; treatment with immunosuppressive, cytotoxic or anti-fibrotic drugs (NAC is OK); history of cancer of any type in the 5 years preceding Screening Visit 1, excluding non-melanomatous skin cancer, localized bladder.
cancer, or in situ cervical cancer; upper or lower respiratory tract infection of any type within 4 weeks of Screening Visit 1; planned elective surgery during the study including 4 weeks following the final dose of study drug; body weight > 130 kg; inadequate IV access; listed for lung transplant.

PRINCIPAL INVESTIGATOR:
Daniel Culver, DO
STUDY COORDINATOR:
Ron Wehrmann, RRT | 216.445.0574

LUNG CANCER
The Evaluation of Exhaled Breath in Disease States
The pattern of chemicals (volatile organic compounds) in exhaled breath of people with particular diseases seems to be different than in the breath of those without the disease. Advances in chemical sensing devices allow the detection of these patterns. This study assesses the ability of sensors to detect the presence of a disease by analyzing subjects’ exhaled breath. This stage of the study focuses on breath samples from subjects who are at a high risk of developing lung cancer and those with proven lung cancer.

ELIGIBILITY: Patients ages 40-90 years, ≥ 10 pack year history; untreated, tissue confirmed lung cancer, or high suspicion of lung cancer; evaluation of an indeterminate lung nodule with a maximum diameter of 3-20 mm. Exclusion criteria include any cancers within with maximal dimensions identified by CT scan ≥ 8 mm and ≤ 30 mm. Exclusion criteria include previous nodule diagnostic procedures, nodule detected by previous CT scan 60 days prior to current CT scan, prior diagnosis of any cancer within 2 years of lung nodule detection, except for nonmelanoma skin cancer, and administration of blood product.

PRINCIPAL INVESTIGATOR:
Peter Mazzone, MD, MPH
STUDY COORDINATOR:
Mary Beukemann | 216.445.8651

Early Diagnosis of Pulmonary Nodules Using a Plasma Proteomic Classifier
A prospective, multicenter, blinded observational study to collect blood specimens and clinical data in association with patients with a newly diagnosed lung nodule who have been referred for pulmonary consultation to guide diagnostic decision-making and clinical management. The study, sponsored by Integrated Diagnostics Inc., will explore the clinical hypothesis that the lung nodule test demonstrates performance parameters, such as negative and positive predictive values that would substantiate the test’s use in clinical decision-making for individual patients presenting with new lung nodules.

ELIGIBILITY: Patients age ≥ 40 years, undergoing diagnostic evaluation for a new lung nodule with maximal dimensions identified by CT scan ≥ 8 mm and ≤ 30 mm. Exclusion criteria include previous nodule diagnostic procedures, nodule detected by previous CT scan 60 days prior to current CT scan, prior diagnosis of any cancer within 2 years of lung nodule detection, except for nonmelanoma skin cancer, and administration of blood product.

ELIGIBILITY: Patients age ≥ 40 years, undergoing diagnostic evaluation for a new lung nodule with maximal dimensions identified by CT scan ≥ 8 mm and ≤ 30 mm. Exclusion criteria include previous nodule diagnostic procedures, nodule detected by previous CT scan 60 days prior to current CT scan, prior diagnosis of any cancer within 2 years of lung nodule detection, except for nonmelanoma skin cancer, and administration of blood product.

PRINCIPAL INVESTIGATOR:
Peter Mazzone, MD, MPH
STUDY COORDINATOR:
Mary Beukemann | 216.445.8651

LUNG TRANSPLANT
Immune Mechanism of Rejection in Human Lung Allografts
To determine mechanisms by which pre-existing immune responses to self-Ags increase PGD leading to augmented alloimmune responses resulting in chronic rejection following human LTx, subjects will be recruited who have high PRA percentages prior to transplant. Serum and BAL samples will be collected prior to lung transplant as well as post-transplant. This study is sponsored by the NIH and Washington University in St. Louis.

ELIGIBILITY: Patients awaiting LTx at Cleveland Clinic who undergo desensitization if there is sensitization to HLA and self-Ags using the standard desensitization protocol with rituximab and IVIG.

PRINCIPAL INVESTIGATOR:
Marie Budev, DO, MPH
STUDY COORDINATOR:
Chenett Greer | 216.445.9287

Lung Transplant and Cognitive Impairment
This is a prospective study that is intended to further investigate the incidence, prevalence and risk factors for neurocognitive impairment in a cohort of lung transplant recipients. All patients who agree to participate will undergo a series of selected neurocognitive tests on the day of their standard outpatient post-transplant appointment. Patients will not be asked to come in for a separate appointment or day to participate in the research study. In a confidential, one-on-one testing method in a private exam room, each study participant will undergo the Montreal Cognitive Assessment Test and a series of neurocognitive tests referred to as neurocognitive battery (NB) to evaluate domains of cognitive function/dysfunction.

ELIGIBILITY: Patients 18 or older who are ≥ 12 months from their transplant surgery.

PRINCIPAL INVESTIGATOR:
Marie Budev, DO, MPH
STUDY COORDINATOR:
Chenett Greer | 216.445.9287

LUNG VOLUME REDUCTION
Multicenter, Randomized, Assessor-Blinded Controlled Study of Safety and Effectiveness of the PneumRx Inc. RePneu® Lung Volume Reduction Coil (RePneu LVRC™) System
The objective of this study is to demonstrate the safety and effectiveness of the PneumRx RePneu Lung Volume Reduction Coil (RePneu LVRC) System in a population of patients with emphysema. This is a prospective, multicenter, randomized, controlled study comparing outcomes between the treatment and control groups. Subjects will be block randomized in a treatment (LVRC)-to-control ratio of 1-to-1. The randomization will be stratified by homogeneous vs. heterogeneous emphysema, to support a balance of patients with differing heterogeneity in both the LVRC and control groups.

ELIGIBILITY: Patients ≥ 35 years of age; CT scan indicates bilateral emphysema; post-bronchodilator FEV1 ≤ 45% predicted; total lung capacity > 100% predicted; residual volume (RV) ≥ 225% predicted; marked dyspnea scoring ≥ 2 on mMRC scale of 0-4; stopped smoking for at least 8 weeks prior to entering the study, as confirmed by a cotinine level of < 10 ng/mL; completed pulmonary rehabilitation program within 6 months prior to treatment and/or regularly performing maintenance respiratory rehabilitation if initial supervised therapy occurred more than 6 months prior to baseline testing.

PRINCIPAL INVESTIGATOR:
Atul Mehta, MD
STUDY COORDINATOR:
Yvonne Meli, RN | 216.445.4215
PULMONARY HYPERTENSION

A Phase 2, Placebo-Controlled, Double-Blind, Randomized, Clinical Study to Determine Safety, Tolerability and Efficacy of Pulsed, Inhaled Nitric Oxide (INO) vs. Placebo as Add-On Therapy in Symptomatic Subjects with Pulmonary Arterial Hypertension (PAH)

This study, sponsored by Ikaria, is to determine if inhaled nitric oxide (INO) given through a special delivery device (INOpulse® DS) is safe and efficacious in treating pulmonary arterial hypertension (PAH). The primary endpoint is change in pulmonary vascular resistance (PVR) (dynes·sec/cm-

ELIGIBILITY: IPAH, heritable PAH, anorexigen-induced PAH, associated PAH (APAH) with connective tissue disease (CTD), APAH with repaired simple congenital systemic to pulmonary shunt (i.e., atrial septal defect [ASD], ventricular septal defect [VSD]) and/or patent ductus arteriosus (PDA); complete repair at least 1 year prior to screening) or APAH with human immunodeficiency virus (HIV); age 16-80; receiving at least one approved PAH therapy, on stable dose(s) for 12 weeks and clinically symptomatic from PAH; 6-minute walk test 100-450 m.

ELIGIBILITY: Patients age ≥ 18 and < 70 with confirmed ES by echo, mPAP > 25 mmHg, PCWP < 15 mmHg, PVR > 800 dynes·sec/cm or > 10 Wood units, WHO functional class > II, 6-minute walk test with a minimum distance of 50 m and a maximum distance of 450 m. Exclusion criteria include TLC < 60%; FEV1/FVC < 70%, Down syndrome diagnosis, known coronary artery disease, or if being considered for an organ transplant.

ELIGIBILITY: Patients age ≥ 18 years old; idiopathic or heritable PAH (idiopathic or heritable) NYHA Class II-III over 24 weeks. Age ≥ 18 years old; idiopathic or heritable PAH with WHO II-III performance status; stable on PAH medications for the past 2 months; seronegative for HIV antibody, hepatitis B antigen and hepatitis C antibody.

ELIGIBILITY: Patients age ≥ 18 years, diagnosis of PAH in WHO Functional Class II-IV and belonging to a subgroup of the Dana Point Clinical Classification Group 1, mPAP > 25 mmHg, PVR > 240 dynes·sec/cm, PCWP < 15 mmHg, 6-minute walk test > 150 m. Exclusion criteria include TLC < 60%; FEV1/FVC < 70%; FEV1 < 65%; life-threatening diseases with a life expectancy of < 12 months, recently started or planned cardiovascular rehabilitation program based on exercise; treatment with ERAs, riociguat, IV or subcutaneous prostacyclin or prostacyclin analogs within 3 months prior to Visit 2; CYP3A inducers within 4 weeks prior to Visit 2.

PULMONARY VASCULAR COMPLICATIONS OF LIVER DISEASE-2 (PVCLD2)

Sponsored by Perelman School of Medicine at the University of Pennsylvania as a subcontract of the NHLBI, the purpose of this study is to determine if certain genes, hormones or other factors predict the risk of developing lung vessel disease in patients with liver disease and whether they determine outcome.

ELIGIBILITY: Patients age ≥ 18 years with chronic portal hypertension from intrinsic liver disease or portal vein disease, documented by clinical history or liver biopsy, referral for evaluation for liver transplantation (LT) or portopulmonary hypertension (or a known diagnosis of portopulmonary hypertension). Exclusion criteria include having an active infection, active or recent (< 2 weeks) gastrointestinal bleeding, lung transplant or LT recipients, being pregnant.

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Phase 3 Study to Evaluate the Effects of Macitentan on Exercise Capacity in Subjects with Eisenmenger Syndrome

The primary objective of this study, sponsored by Actelion Pharmaceuticals Ltd., is to demonstrate that macitentan improves exercise capacity in comparison with placebo in subjects with Eisenmenger syndrome (ES).

ELIGIBILITY: Patients age ≥ 18 years old; idiopathic or heritable PAH with WHO II-III performance status; stable on PAH medications for the past 2 months; seronegative for HIV antibody, hepatitis B antigen and hepatitis C antibody.

Hydroxyurea in Pulmonary Arterial Hypertension

Sponsored by the NIH, this study is a nonrandomized, pilot study of hydroxyurea in patients with PAH (idiopathic or heritable) NYHA Class II-III over 24 weeks.

Pulmonary Arterial Hypertension Treatment with Carvedilol for Heart Failure (PAHTCH)

Sponsored by the NIH, this study is a 6-month double-blind, randomized, controlled intervention with three arms preceded by an open-label, 1-week run-in period of the effects of carvedilol in patients with pulmonary arterial hypertension.

ELIGIBILITY: Age 18-65; PAH Class 1 (Dana Point 2008); NYHA/WHO Class I-III; stable on PAH medications for the last 30 days; women of childbearing age must use a double-barrier local contraception till completion of the study.

Instrument Psychometrically Validate the PAH-SYMPACT Instrument

Sponsored by Actelion Pharmaceuticals Ltd., this study is to demonstrate the psychometric characteristics of reliability and construct validity of the PAH-SYMPACT instrument and its ability to detect change.

ELIGIBILITY: Patients age 18-80, diagnosis of PAH in WHO Functional Class II-IV and belonging to a subgroup of the Dana Point Clinical Classification Group 1, mPAP > 25 mmHg, PVR > 240 dynes·sec/cm, PCWP < 15 mmHg, 6-minute walk test > 150 m. Exclusion criteria include TLC < 60%; FEV1/FVC < 70%; FEV1 < 65%; life-threatening diseases with a life expectancy of < 12 months, recently started or planned cardiovascular rehabilitation program based on exercise; treatment with ERAs, riociguat, IV or subcutaneous prostacyclin or prostacyclin analogs within 3 months prior to Visit 2; CYP3A inducers within 4 weeks prior to Visit 2.

Pulmonary Arterial Hypertension with Carvedilol for Heart Failure (PAHTCH)

Sponsored by Ikaria, this is to demonstrate the psychometric characteristics of reliability and construct validity of the PAH-SYMPACT instrument and its ability to detect change.
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• To arrange for a critical care transfer, call 216.448.7000 or 866.547.1467 (see clevelandclinic.org/criticalcaretransport).

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