Clinical Intelligence Platform:
Leveraging Big Data Technology for Real-Time Clinical Decision Support in the MICU

Madhu Sasidhar, MD

At Cleveland Clinic’s Respiratory Institute, we have built what we believe is the first-ever implementation of a clinical intelligence tool for healthcare using Big Data for decision support.

It is estimated that 90 percent of all data in the world has been created within the last two years. This explosive increase in data, especially on the Internet and mostly in the form of user-generated content, has given rise to new technologies that are loosely referred to as Big Data.

Big Data is characterized by the three Vs: a large volume of data that are rapidly changing (velocity) and comprise a variety of data types such as numbers, dates and unstructured data.

Healthcare has long dealt with problems of volume, velocity and variety in clinical data. Emerging Big Data technologies can be exploited for large-scale storage and rapid analysis of clinical data, which is the basis for the Clinical Intelligence Platform (CIP) that we have developed for the Respiratory Institute.

Also in This Issue

Airway Stenting: Changing Forms to Meet Function
Fibroblast Migration and Transdifferentiation in Pulmonary Fibrosis
Cleveland Clinic Hosts Three World Congresses in Pulmonary Medicine
Dear Colleagues:

Welcome to the Winter 2013 issue of Respiratory Exchange, which highlights some of the latest clinical innovations, emerging research and new treatment modalities within Cleveland Clinic’s Respiratory Institute.

The Respiratory Institute is growing — in the Staff Directory section, you will notice many new faces! Now with more than 70 pulmonologists, allergists/immunologists and critical care specialists, we plan on adding 30 more physicians in the next couple of years. The Respiratory Institute diagnoses and treats a wide range of conditions. We provide an integrative, multidisciplinary approach to patient care that includes close collaboration with specialists from cardiothoracic and vascular surgery, thoracic imaging, and pulmonary pathology.

In this issue, you will learn more about our clinical and research leadership in areas such as leveraging Big Data for real-time clinical decision support, novel approaches to airway stenting, and bronchial artery revascularization in lung transplantation. We also provide updates on separate research programs evaluating the role of bone marrow hematopoietic stem cells and the role of hyaluronan matrices in the pathophysiology of idiopathic pulmonary hypertension, as well as an emerging study of estrogen signaling in portopulmonary hypertension.

In a remarkable span of a little more than 12 months, the Respiratory Institute was honored to host three international medical congresses. We provide highlights from each, including:

• The 17th World Congress for Bronchology and Interventional Pulmonology and the 17th World Congress for Bronchoesophagology

• The 4th International Conference on Beryllium Disease

• The World Association of Sarcoidosis and Other Granulomatous Disorders

We hope you enjoy the articles in this issue of Respiratory Exchange, which illustrates some of our efforts to reduce the gap between today’s laboratory discoveries and tomorrow’s patient care. You can learn more about our ongoing clinical and research activities at clevelandclinic.org/pulmonary (where you can find current and archived issues of Respiratory Exchange) and clevelandclinic.org/thoracic.

Providing nearly 100,000 patient visits annually, the Respiratory Institute has expertise and experience that attract physician referrals from all over the world. As always, we welcome the opportunity to work with you. If you have any questions and/or would like to refer a patient, please contact us at our toll-free number for physicians, 866.CCF.LUNG (866.223.5864).

Sincerely,

Herbert P. Wiedemann, MD, MBA
Chairman, Cleveland Clinic | Respiratory Institute

Our CIP offers real-time integration of admission/discharge/transfer, lab, electronic record, radiology and financial data for MICU patients. A simple interface allows users to create actionable alerts that are delivered through secure email and online sign-out systems.

Since November 2011, we have continuously deployed the CIP for decision support in our 53-bed MICU. The platform, which is based on open-source technologies for real-time decision support, has many practical applications. For example, the CIP helps clinicians identify critically ill patients for early mobilization and physical therapy. While literature clearly points to improved outcomes in patients who are mobilized early during the course of critical illness, implementing a program is made difficult by rapidly changing clinical conditions.

Table 1: The Clinical Intelligence Platform identifies patients who are appropriate for physical therapy intervention using 38 clinical criteria, including variables within these categories.

<table>
<thead>
<tr>
<th>SELECTED CATEGORIES OF PHYSICAL THERAPY INTERVENTION VARIABLES</th>
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<tbody>
<tr>
<td>• Length of stay in ICU for two days or more</td>
</tr>
<tr>
<td>• Stable respiratory status, not on high PEEP or FiO2 or with high respiratory rate or minute ventilation</td>
</tr>
<tr>
<td>• Hemodynamic stability, not on high doses of vasopressors or ionotropes</td>
</tr>
<tr>
<td>• Awake and able to follow commands, not comatose, not excessively agitated</td>
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<tr>
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Table 1: The Clinical Intelligence Platform identifies patients who are appropriate for physical therapy intervention using 38 clinical criteria, including variables within these categories.
The CIP identified patients daily based on 38 different prespecified clinical criteria (Table 1), and scored patients based on how well they matched these preselected criteria. Physical therapy and medical team members were then electronically notified to evaluate patients and to intervene when appropriate.

At baseline, we found that only 52 percent of patients admitted to the ICU received an initial evaluation by Physical/Occupational Therapy during the course of their ICU stay. Of these patients, a significant proportion were not appropriate for PT/OT and therefore did not receive follow-up treatment. After institution of computerized decision support, there was a 79 percent increase in the average number of PT treatments per patient (2.8 visits/patient at baseline, five visits/patient with computerized decision support). We believe that the appropriate identification of patients with decision support results in the ability to allocate resources to the right patients and therefore leads to a demonstrable improvement in outcome.

Early results indicate that functional status in survivors of critical illness has improved since we started using the CIP (Figures 1 and 2). We have since expanded the use of decision support to include hospital-acquired infections, renal injury and acute lung injury and to screen for clinical trials. We anticipate additional clinical applications in the future for this real-time, practically focused tool.

Dr. Madhu Sasidhar is Head of the Section of Respiratory Therapy. His special interests include critical care medicine and general pulmonary medicine. He can be reached at 216.445.1838 or sasidhm@ccf.org.
Airway Stenting: Changing Forms to Meet Function

CUSToMIZED MODIFICATIoN ADDRESSES CLINICAL PROBLEMS

Thomas R. Gildea, MD, MS, Michael S. Machuzak, MD, and Atul C. Mehta, MD

Stenting the tracheal bronchial tree is one of the more complex procedures in interventional pulmonary medicine, both technically and from a longitudinal management standpoint. While once purely a palliative option for those with inoperable malignant central airway obstruction, early stenting is now used to facilitate therapy with curative intent, as a temporary solution for surgical problems, and as part of a larger management process for complex nonmalignant airway disease and in inoperable patients for whom a surgical procedure may not be feasible.

A limited number of approved airway stents with the characteristics required for various clinical needs is available on the U.S. market. An ideal stent would be easily placed, be easily removed or repositioned, have a high airway-to-wall thickness ratio, mold to fit into noncylindrical spaces, allow accommodations for airway branching, not cause granulation, not migrate, not suffer from fatigue, be resistant to infection, be able to transmit mucus and secretions without plugging, not develop a biofilm, and be inexpensive and available in an infinite number of diameter/length and wall-stiffness combinations. Clearly, no such device exists.

As part of the American College of Chest Physicians Quality Improvement Registry, Evaluation, and Education (AQuIRE) multicenter database registry, we have been tracking our use of airway stents since 2009. We presented our data for several different clinical scenarios in June 2012 at the 17th World Congress for Bronchology and Interventional Pulmonology and 17th World Congress for Bronchoesophagology, which was hosted by Cleveland Clinic's Respiratory Institute.

We reported two aspects of our complex airway management data and specifically discussed our experience with silicone Y stents and lung transplant airway issues. We shared one of the world’s largest experiences with the Novatech Dumon™ tracheobronchial Y stent (Boston Medical Products, Westborough, Mass.) and the use of stent modification techniques in lung transplant recipients.

Between March 2009 and October 2011, we placed a total of 72 Y stents in 50 patients for central airway obstruction (CAO). The patients had either malignant or benign airway disease, and the stents were placed by one of our interventional pulmonologists. Twelve patients (average age 47.3 years) had nonmalignant conditions such as excessive dynamic collapse, relapsing polychondritis, papillomas, vascular ring, and complications related to airway fires and airway stent placement. In these 12 patients, a total of 32 Y stents were

Case 1

Figure 1. Left main stem stenosis with occlusion at the LMSB anastomosis. Completely occluded left upper lobe (LUL) and left lower lobe (LLL).

Figure 2. Planned modification of hourglass silicone stent for placement into LLL; notch cut for LUL orifice.

Figure 3. View through stent beyond stenosis. Stent modification highlighted, allowing passage to left upper lobe.
deployed, with an average of 2.67 stents per patient. The mean time to stent removal was 117.8 days. All patients received follow-up.

Thirty-eight patients (average age 60.7 years) had malignant CAO: primary lung cancer (25), metastases from other organs (7), tracheoesophageal fistula (3), tracheomediastinal fistula (2) or lymphoma (1). A total of 40 Y stents were placed, with an average of 1.05 stents per patient. The mean time to stent removal was 125.6 days for the 12 patients who had follow-up. The rest were lost to follow-up and presumed to be deceased.

Mechanical ablation, cryotherapy and balloon dilation were frequently used prior to airway stenting in both types of diseases. Thermal ablative techniques, including argon plasma coagulation and laser therapy, were almost exclusively used with malignant CAO and avoided in nonmalignant CAO.

Complications due to stent placement were infrequent. One patient with vascular ring was referred to us from another institution for a stent-related complication. Three patients had their Y stents revised just after deployment due to airway-stent size discrepancy. One stent was removed due to mucous plugging. Granulation tissue formation leading to airway obstruction was common in patients with nonmalignant disease (8/12) compared with the incidence in those with malignant CAO (3/12). No death was directly related to airway stenting complications.

Based on our data, we concluded that when performed by experienced thoracic endoscopists, Y stent placement is both safe and effective in palliating or relieving central airway obstruction. The silicone stents are relatively easily inserted and removed, and are well-tolerated and very efficacious in relieving respiratory symptoms caused by extrinsic and mixed airway compression. Complication rates are low, but when complications do occur, they could be life-threatening.

In addition to the above data, we also have recently described modifying silicone stents in order to palliate the most complex anastomotic complications in lung and heart-lung transplant patients. Although only a small percentage of lung transplant patients develop anastomotic complications, these complications can be devastating.

Using a multidisciplinary approach and drawing on one of the world’s largest transplant experiences here at Cleveland Clinic, we have devised several novel modifications for the most complex of these complications. Several examples follow.

**CASE 1**

A 53-year-old patient with cystic fibrosis had a bilateral sequential lung transplant at an outside hospital and presented with dyspnea approximately five months after the transplant. He was found to have an 80 percent stenosis of his left stem bronchus and underwent multiple procedures, with no relief. We were able to relieve his airway complication with the placement of a modified hourglass silicone stent. The stent has since been removed, and he is doing well with no signs of recurrence.

**CASE 2**

A 59-year-old female with interstitial lung disease initially presented with dyspnea four months after a bilateral sequential lung transplant. She was found to have a perianastomotic left main stem bronchus stenosis. She was managed at her transplant center for approximately three years, with repeated procedures performed every one to two months. After an initial dilation, we carefully placed a modified carinal stent. This was a novel approach insofar as a stent was placed in the opposite orientation from what is typical. The modifications in this instance allowed for proper seating with no migration. The patient is currently stent-free and doing well.
Case 3

A 50-year-old male transplanted for interstitial lung disease who was on ECMO at the time of transplant presented with left main stem bronchial stenosis with multiple segmental strictures. The strictures were dilated repeatedly, with recurrence every one to two weeks. Eventually, a silicone stent was modified and three separate stents were placed in the segmental airways, leading to relief of the strictures and a dramatic improvement in the patient’s overall clinical status. His stents are still in place; he is doing well and recently restarted working full time.

Airway stenting is a complex procedure that requires a significant degree of expertise in managing patients over the duration of their illness. In Y stenting, we find that early stenting for very symptomatic patients with malignant disease may expedite treatments and improve clinical status to allow patients to undergo definitive therapy. Although we approach stenting as an option of last resort, many stents eventually are removed based on the clinical context.

In the lung transplant population and in the majority of benign airway disease cases, it is clear that customized stenting/modification allows the flexibility to address clinical problems and extend the range and value of current stent technologies. Until there is a way to make custom stents in a real-time, cost-effective manner, we will continue to innovate and find solutions for our patients with all our available tools.

Dr. Thomas Gildea, Head of the Section of Bronchology and member of the medical staff in the Advanced Lung Disease Section of the Department of Pulmonary, Allergy and Critical Care Medicine and Transplant Center, can be reached at 216.444.6503 or gildeat@ccf.org. Dr. Michael Machuzak, Medical Director, Center for Major Airway Diseases, and member of the medical staff in the Advanced Lung Disease Section of the Department of Pulmonary, Allergy and Critical Care Medicine and Transplant Center, is available at 216.444.2718 or machuzm@ccf.org. Dr. Atul Mehta is a member of the medical staff in the Advanced Lung Disease Section of the Department of Pulmonary, Allergy and Critical Care Medicine and Transplant Center. He can be reached at 216.444.6503 or mehtaa1@ccf.org.

Figure 1. Left main stem bronchus with complete occlusion of all lobar and segmental bronchi due to necrosis.

Figure 2. Silicone stent cut and modified; this was placed in the orifice of the left lower lobe, as well as two others like it in the lingula and LUL.

Figure 3. After balloon dilation and modified stent placement with several segments and lobes reclaimed.

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Emergent Evaluation and Lung Transplant with Bronchial Artery Revascularization

ADVANCED TRANSPLANT CAPABILITIES AT CLEVELAND CLINIC

Marie M. Budev, DO, MPH

A 21-year-old female with cystic fibrosis was referred to Cleveland Clinic’s Lung Transplant Program. The patient had generally been doing well until contracting influenza A one month prior to admission to the Cystic Fibrosis Center in her local area. Prior to this infection, she had been admitted to the hospital at least twice a year for routine respiratory care but had stable lung function and did not need supplemental oxygen therapy. As a result of the respiratory influenza, the patient was hospitalized for three weeks; when finally discharged, she needed supplemental oxygen.

At the patient’s first outpatient appointment following hospitalization, she was noted to have an FEV1 of 17 percent prednisone and had lost 10 pounds, despite having received tube feeds via a PEG tube. Soon thereafter, she was readmitted to the local Cystic Fibrosis Center’s ICU for rising PaCO2 and impending respiratory failure. She required BIPAP (NIPPV) nearly continuously.

Lung Transplant Indicated

The decision was made to transfer her to Cleveland Clinic for lung transplant evaluation. When Cleveland Clinic’s Critical Care Transport Team arrived at the outside ICU, the patient was in significant distress. The team determined it would be unsafe for her to travel without a protected airway. The patient was then intubated to facilitate the transfer.

Upon arrival at Cleveland Clinic’s MICU, the patient required respiratory support. Within the next 48 hours, she was evaluated for lung transplant, and a tracheostomy was performed to facilitate airway clearance and rehabilitation. Bronchoscopy performed during placement of the tracheostomy revealed significant left main stem bronchus narrowing, which could preclude bilateral sequential transplantation.

In this particular case, a tracheal anastomosis would be necessary for a successful transplant. However, performing a tracheal anastomosis for a double lung transplant has largely been abandoned because of the risk of dehiscence of the anastomotic line due to poor vascular supply. A viable tracheal anastomosis could be possible only with a heart-lung transplant due to the coronary circulation or with a surgical technique called bronchial artery revascularization.

Seventy-two hours after her arrival at Cleveland Clinic, the patient was emergently listed for a double lung transplant with the plan for bronchial artery revascularization with Gösta Pettersson, MD, PhD, Vice Chair of Thoracic and Cardiovascular Surgery.

Surgery Successful

Thirteen days after her arrival at Cleveland Clinic, the patient underwent a successful double lung transplant with bronchial artery revascularization and was weaned off ventilatory support within a few days of her transplant. Four weeks after her referral and admission to Cleveland Clinic, the patient was discharged on no supplemental oxygen. She had a rapid recovery, and within a few weeks she returned home.
Lung transplant with bronchial artery revascularization is practiced by only a few centers and cardiac surgeons worldwide.

**DISCUSSION: EMTERENT EVALUATION AND TRANSPLANT OF A VENTILATOR-DEPENDENT PATIENT**

Over the past three decades, lung transplantation has evolved to being considered the standard of care for select patients with advanced lung disease. Listing for transplantation should be considered when the lung disease has advanced to a disabling and potentially life-threatening stage. Although early referral to a transplant center is encouraged so that families as well as the patient can familiarize themselves with the transplant team and process, this may not always be possible. Cystic fibrosis in particular can have a rapid clinical trajectory, leading to a potentially life-threatening stage, as with this patient.

In this patient's case, ventilatory support was necessary to bridge the patient to lung transplantation. Ventilator dependence before transplantation has long been recognized as a risk factor for increased short-term post-transplant mortality, although it does not appear to adversely impact outcomes beyond the first year. Transplantation of ventilator-dependent patients in the ICU was previously discouraged, but the new lung allocation system in the United States has allowed transplant centers to reconsider this philosophy and has assigned high lung allocation scores to patients who are maintained on ventilatory support as a bridge to transplant.

**BRONCHIAL ARTERY REVASCULARIZATION**

Lung transplant with bronchial artery revascularization is practiced by only a few centers and cardiac surgeons worldwide, but prospective studies from Cleveland Clinic and Copenhagen have demonstrated that the procedure is feasible, successful and well-tolerated. Success of the bronchial artery revascularization ensures normal airway healing. Current evidence suggests that bronchial artery revascularization may lower early biopsy rejection grades, postpone the onset of bronchiolitis obliterans syndrome and improve long-term survival. Further experience and research will be necessary to clarify the role of bronchial artery revascularization in lung transplantation.

Dr. Marie Budev is Medical Director, Lung Transplantation. Her other specialty interests include gender-specific pulmonary issues. She can be reached at 216.444.3194 or budevm@ccf.org.

**Recommended Reading:**


Respiratory Institute Joins Consortium to Study Estrogen Signaling in Portopulmonary Hypertension

Gustavo Heresi, MD, and Raed Dweik, MD

Cirrhosis afflicts nearly 3 million people in the United States, and complications of cirrhosis are the fourth-leading cause of death in people aged 45 to 65 years. One complication is portopulmonary hypertension (PPHTN), or pulmonary arterial hypertension (PAH) in the setting of portal hypertension.

Cleveland Clinic has joined the first large, multicenter study of PPHTN. The project's ultimate goal is to identify mechanisms of — and therapeutic targets for — the condition.

With an estimated 170,000 Americans diagnosed with PPHTN, the condition is considered a rare or “orphan” disease. PPHTN, one of the most common causes of PAH, is found in approximately 6 percent of patients evaluated for liver transplantation (LT). PPHTN significantly increases mortality and the risks of LT.

Why PAH occurs in the setting of portal hypertension is poorly understood. Defining the pathobiology of PPHTN could translate into novel treatment strategies applicable to diverse forms of PAH, which could make a meaningful clinical impact. Unfortunately, there have been limited mechanistic studies of PPHTN and no clinical trials of therapy for PPHTN. Recent research has demonstrated that variations in genes linked to estrogen signaling — aromatase (CYP19A1) and estrogen receptor α (ESR1) — and higher estradiol levels significantly increased the risk of PPHTN in patients with advanced liver disease. However, the mechanistic link between estrogen signaling and PPHTN remains unknown.

Animal model-based therapeutic studies and human studies have shown that patients with PAH have increased endothelial progenitor cells in the bone marrow, in circulating endothelial precursor cells (CEPs) and in the remodeled pulmonary vasculature. Estradiol stimulates CEP mobilization via the estrogen receptor α (ERα), and ERα blockade reduces CEP colony formation and endothelial growth. Estradiol is metabolized by cytochrome P450 (CYP) enzymes to metabolites that have both pro-angiogenic (16α-OHE1 via ERα) and anti-angiogenic (2-OHE, 2-methoxyestradiol [2-ME]) effects.

The rs1800440 single nucleotide polymorphism (SNP) in CYP1B1 produces a higher urinary 16α-OHE1/2-OHE ratio, and both the SNP and urinary ratio are risk factors for heritable PAH. Therefore, researchers have hypothesized that genetic determinants of estrogen activity and metabolism lead to increased levels of CEPs (indicating greater angiogenesis) and the development of PPHTN.

The PPHTN research project organized by the University of Pennsylvania with five other participating centers — including Cleveland Clinic — aims to determine whether variation in the rs1800440 SNP in CYP1B1 is associated with a risk of PPHTN; to define the link between estrogen signaling, CEPs and PPHTN; and to determine whether inhibition of estrogen signaling via ERα affects PPHTN.

As the first large, multicenter study of PPHTN, this project will have a significant impact on the understanding of this and many other forms of pulmonary vascular disease.

If the study finds that CYP1B1 variants increase the risk of PPHTN via 16α-OHE1/2-OHE, clinical trials using 2-ME could be pursued.

If we find that CEPs mediate the link between estrogen signaling and PPHTN, trials using tyrosine kinase inhibitors would be the next step. Finally, downregulation of CEPs by fulvestrant — an ERα inhibitor — would identify ERα blockade as another approach.

As the first large, multicenter study of PPHTN, this project will have a significant impact on the understanding of this and many other forms of pulmonary vascular disease. The Pulmonary Vascular Program in the Respiratory Institute at Cleveland Clinic will be recruiting patients into this study and will provide expertise on the measurements of CEPs.

Dr. Gustavo Heresi-Davila, Associate Staff in Pulmonary, Allergy and Critical Care Medicine, can be reached at 216.636.5327 or heresig@ccf.org. Dr. Raed Dweik is Director of the Pulmonary Vascular Program. He can be reached at 216.445.5763 or dweikr@ccf.org.
NIH-Supported Study to Focus on the Lung Matrix in Pulmonary Hypertension
Raed Dweik, MD, and Vincent Hascall, PhD

The National Institutes of Health's National Heart, Lung, and Blood Institute recently awarded six Programs of Excellence in Glycosciences (PEG) project grants to institutes across the United States. Each seven-year PEG grant funds a unique research and training program, with the grants encompassing a multitude of research projects and technology cores.

Cleveland Clinic’s PEG program, which is led by Vince Hascall, PhD, in the Department of Biomedical Engineering, focuses on hyaluronan (HA) matrices in vascular biology.

Raed Dweik, MD, Director of the Pulmonary Vascular Program at Cleveland Clinic’s Respiratory Institute, is the principal investigator on a project studying HA matrices in pulmonary hypertension (PH). The research team has shown that the pathological HA matrix is central to the aberrant vascular angiogenesis that occurs in patients with idiopathic pulmonary arterial hypertension (IPAH). Abnormal proliferation of pulmonary smooth muscle cells is a major component of the remodeling process that is driving this disease. Thus, the goal of the study is to determine the mechanisms involved in the synthesis of the pathological HA matrix by pulmonary smooth muscle cells isolated from lungs of patients compared with those isolated from normal lungs.

Dr. Dweik’s work builds on his novel discovery that pulmonary artery smooth muscle cells (PASMCs) from patients with IPAH spontaneously produce high levels of HA compared with cells from controls (Figure 1). Furthermore, the HA produced by PASMCs from PH patients appears to have major roles in inflammation and vascular remodeling.

The overall goal of Cleveland Clinic’s PEG program led by Dr. Hascall is to explore the central role of the HA-based extracellular matrix synthesized in vascular pathologies and its dialogue with inflammatory cells. One of the main missions of the PEG is to train four to five scientist participants per year on glycoscience topics affecting heart, lung and blood research. A unique focus of this training program will explore the physiological roles of HA and proteoglycans and will include formal didactic courses, resources core training, formal workshop training and a visiting scholar program.

Drs. Dweik and Hascall are planning an Inter-PEG Workshop for investigators from all the PEGs. The workshop will be coordinated with the Pulmonary Hypertension Summit 2013 and 9th Annual PH Symposium taking place at Cleveland Clinic, April 10-13, 2013. The workshop and summit will focus on the research advances by the PEGs and the integration of glycobiology research in the pathobiology of pulmonary vascular disease.

Figure 1. HA production and secretion by PASMCs from IPAH and control lungs. Low nitric oxide (NO) levels in culture and/or in the environment of the IPAH lungs cause PASMCs to produce high levels of HA and HA cables that are capable of binding inflammatory cells. Low NO levels are also associated with fragmentation of HA into smaller pieces that stimulate cell proliferation and inflammation.
In this special feature, we take a behind-the-scenes look into the work being done in the laboratories of three of our staff members here in the Respiratory Institute.

Study Shows Causal Role of Bone Marrow Hematopoietic Stem Cells in Pulmonary Arterial Hypertension

Kewal Asosingh, PhD, and Serpil C. Erzurum, MD

The origin of the cells inducing vascular endothelial injury and in situ thrombi in pulmonary arterial hypertension (PAH) is unknown. Distinct or indolent myeloid abnormalities are present in the bone marrow of the majority of, if not all, patients with PAH and even in unaffected family members in familial cases of the disease.

Physiologically, bone marrow-derived hematopoietic CD133+ stem cells support vascular health but also can participate in pathologic vascular remodeling. In our study published in August 2012 in The American Society of Hematology’s journal, Blood, we showed human PAH CD133+ cells are enriched in myeloid-colony-forming cells. CD133+ common myeloid progenitors proliferate and differentiate into bipotent common megakaryocyte-erythroid progenitors, and into multipotent monocyte/granulocyte progenitors. These lineage-restricted myeloid progenitors differentiate into mature blood cells via unilineage-committed intermediate precursors. The hierarchy of proliferation and differentiation is at each bifurcation strictly regulated by lineage-specific transcription factors. In line with the data from the colony-forming assays, PAH CD133+ cells showed increased expression of myeloid-erythroid-specific transcription factors GATA-1 and EKLF.

Engraftment of human stem cells into NOD SCID mice is a standard in vivo assay to evaluate hematopoietic stem cell function. In our study, compared with healthy control CD133+ cells, PAH cells had a higher NOD SCID engraftment, indicating increased proliferation of these cells in PAH. Unexpectedly, the PAH CD133+ xenograft led to lung endothelial injury and widespread in situ thrombosis in NOD SCID mice, in addition to right ventricular hypertrophy and morbidity or death. Altogether, the findings strengthen the case for a causal role of bone marrow hematopoietic stem cells in PAH (Figure 1).

Most important, the results of this study indicate that targeting CD133+ cells in PAH may reduce the ongoing endothelial cell damage and thromboses that lead to progressive remodeling of the pulmonary vasculature — and, ultimately, heart failure and death.

Dr. Kewal Asosingh is a Staff Scientist in the Department of Pathobiology and a Scholar of the International Society for Advancement of Cytometry. He can be reached at 216.445.6625 or asosink@ccf.org. Dr. Serpil Erzurum, Pathobiology Department Chair and Co-Director of the Asthma Center, can be reached at 216.445.7191 or erzurus@ccf.org.

Recommended Reading


Fibroblast Migration and Transdifferentiation in Pulmonary Fibrosis

Mitch Olman, MA, MD

Our laboratory-based research is focused on the pathogenesis of the fatal and untreatable disorder idiopathic pulmonary fibrosis (IPF). The general approach we adopt is to investigate pulmonary fibrosis at the molecular level, in cells and animal models, and to validate the newly discovered pathways using patient samples. We focus on the fundamental biology of scar formation by fibroblasts and fibroblast-like cells.

Our recent work has focused on the processes of fibroblast migration and transdifferentiation. We have shown that a naturally occurring inhibitor of integrin-dependent signaling, focal adhesion kinase-related nonkinase, can block TGF-beta-induced myofibroblast differentiation and the development of pulmonary fibrosis in vivo.

In ongoing work, we also have shown that the cell surface receptor for the fibrinolytic protease, urokinase, interacts with integrins in primary human lung fibroblasts, thereby enhancing the integrin-dependent functions of fibroblast attachment and migration. Recent work has focused on the mechanotransduction signal responsible for myofibroblast differentiation. We are in the process of defining the pathway by which such a complex signal travels.

At the bedside, I have been privileged to co-chair a nationwide, National Institutes of Health-sponsored, multicenter clinical trial of the anticoagulant warfarin in idiopathic pulmonary fibrosis. The rationale for this trial was based on solid laboratory observations demonstrating that inhibition of coagulation factors, acting through coagulation factor-receptor signaling, or by blocking alveolar fibrin formation, can ameliorate pulmonary fibrosis in animal models. This approach, while initially promising, did not prove to be beneficial. However, it remains to be seen, and important to evaluate, whether specific inhibition of other coagulation factors (e.g., with heparin or direct thrombin inhibitors, etc.) will be beneficial in IPF.

We are actively enrolling participants in clinical trials for idiopathic pulmonary fibrosis. If you are interested in enrolling patients with IPF in national trials, please contact me or Daniel Culver, DO; Joseph Parambil, MD; or Brian Southern, MD.

Dr. Mitch Olman is a Staff Physician in the Respiratory Institute with a primary appointment in the Department of Pathobiology. Contact him at 216.445.7191 or olmanm@ccf.org.

Recent work has focused on the mechanotransduction signal responsible for myofibroblast differentiation. We are in the process of defining the pathway by which such a complex signal travels.
The World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) North America conference took place Oct. 3-6, 2012, and drew more than 200 attendees from five continents.

The major theme of the meeting was interdisciplinary collaboration, with featured sessions covering cardiology, neurology, ophthalmology, immunology and hepatology topics. Major sessions at the conference included symposia on neurosarcoidosis and cardiac sarcoidosis.

The WASOG meeting was held in conjunction with a patient education conference that took place on Oct. 5. All told, 270 patients from 29 states and Puerto Rico attended that conference. The agenda featured updates on the etiopathogenesis of sarcoidosis and management of common patient symptoms as well as organ-specific breakout sessions led by world-renowned sarcoidosis experts.

**SCIENTIFIC HIGHLIGHTS:**

- Preliminary data showing the efficacy of a novel immunomodulating compound, ARA 290 (an erythropoietin receptor agonist), in the treatment of small fiber neuropathy due to sarcoidosis
- Results of a genomewide association study in U.S. patients that suggested a possible role for the NOTCH4 gene in sarcoidosis susceptibility
- Presentation on the crystal structure of the antigen-presenting groove in chronic beryllium disease
- The role of amyloid A protein in sarcoidosis granulomas
- Data implicating mycobacteria in sarcoidosis pathogenesis
- Latent tuberculosis as a model for Th1 pulmonary immunity
- Presentation on genetic associations with sarcoidosis outcomes from the European Genotype-Phenotype Relationships in Sarcoidosis consortium

**THEMES:**

- The need for enhanced collaboration was recognized among investigators, the pharmaceutical industry, patient advocacy organizations, the National Institutes of Health and regulatory agencies.
- The absence of commonly accepted clinical endpoints was identified as a major barrier for clinical research. In this regard, the dearth of large, well-phenotyped cohorts is a major hurdle for developing rigorous clinical endpoints. Some participants suggested that other syndromes, such as vasculitis or lupus, may be useful models for the development of sarcoidosis clinical networks and research metrics.

**WASOG PROJECTS AT THE CONFERENCE:**

- Working session to further refine a set of potential clinical endpoints for pulmonary sarcoidosis, cutaneous sarcoidosis, sarcoidosis-related fatigue, sarcoidosis-associated pulmonary arterial hypertension and phenotyping of sarcoidosis
- Presentation of a revised schema for defining organ involvement in patients with established sarcoidosis, as an update to the ACCESS organ involvement instrument

Dr. Daniel Culver is Director of the Sarcoidosis Program and a Staff Physician in the Department of Pulmonary, Allergy and Critical Care Medicine. He can be reached at 216.444.6503 or culverd@ccf.org.

Dr. Joseph Parambil is Director of the Hereditary Hemorrhagic Telangiectasia (HHT) Center and a Staff Physician in the Department of Pulmonary, Allergy and Critical Care Medicine. He can be reached at 216.444.7567 or parambj@ccf.org.
The 4th International Conference on Beryllium Disease was held on Cleveland Clinic’s main campus in October 2011. More than 100 participants came from 16 states and four countries to hear presentations by about 30 speakers.

**Scientific Highlights:**

- The only placebo-controlled trial in chronic beryllium disease (CBD) conducted with an anti-TNFα Ab (infliximab) demonstrated a significant improvement in SF-36® mental score, but there was no change in rest and exercise A-a gradient, FVC and FEV1, or chest radiograph.

- HLA-DP2 transgenic mice develop a Be-specific adaptive immune response to inhaled beryllium oxide exposure.

- Analysis of data to optimize the beryllium lymphocyte proliferation test (BelPT) criteria for beryllium sensitization suggests that confirmation testing results have higher positive predictive values at any prevalence but confirmation is more important at low prevalences.

- According to the National Supplemental Screening Program (NSSP), beryllium sensitization was detected in 3.6 percent (1,785) of the 49,510 individuals enrolled in the program. The NSSP involves former Department of Energy (DOE) workers not served by (or who do not reside in close proximity to) existing regional programs, as well as former workers from any DOE site who would prefer to see their personal physician.

- New potential tests for detecting beryllium sensitization were presented: carboxyfluorescein diacetate succinimidyl ester detects cell proliferation while the ELISpot assay detects cytokine secretion.

- An overview of recent epidemiologic studies of beryllium sensitization and CBD suggests that workers with lower exposures in nuclear, munitions and aluminum industries show low prevalence of Be sensitization.

- Air, glove and surface exposures give variable data, but taken together they can be helpful in determining and mitigating total exposure.

- Beryllium exposure produces oxidative stress by increasing production of reactive oxygen species and depletion of intracellular glutathione.

- Although CBD clinically resembles sarcoidosis, there are substantial differences in genetic background.

- The Energy Employees Occupational Illness Compensation Program Act enacted in October 2000 has established 11 resource centers nationwide and provided $7.4 billion in total compensation to date.

**Themes:**

- Reassessment of current exposure limits and an overview of OSHA’s rulemaking for beryllium were presented and discussed.

**Projects/Initiatives:**

- The American Thoracic Society statement on CBD is in the final stages of development.

- The Beryllium BioBank sponsored by the DOE has finished specimen collection and data cleanup and is now accepting proposals from researchers.

- The Beryllium-Associated Worker Registry run by the DOE Office of Health, Safety and Security has data on more than 22,000 individuals who received a medical screening examination or were monitored for beryllium exposure. Data can be utilized as a risk management tool.

- NIOSH recently published an alert titled “Preventing Sensitization and Disease from Beryllium Exposure.”
Cleveland Clinic had the honor of hosting the 17th World Congress for Bronchology and Interventional Pulmonology (WCBIP) — and the 17th World Congress for Bronchoesophagology — on June 15-18, 2012. The World Congress takes place every other year, and this is only the fourth time that it has come to the United States.

We were delighted to serve as co-presidents of the Congresses. The WCBIP attracted 865 attendees from 52 countries and six continents.

The major theme of the meeting was the “pursuit of excellence in bronchoscopy.” Featured sessions covered the early diagnosis and staging of lung cancer, transbronchial needle aspiration, management of central airway obstruction, role of bronchoscopy in lung transplant recipients, medical thoracoscopy, pediatric bronchoscopy, percutaneous dilational tracheostomy, education and the role of anesthesiology in interventional pulmonology. Major symposia on bronchial thermoplasty and endobronchial volume reduction were also presented.

A keynote speaker was featured each day. Topics included tracheal transplantation (Martin Birchall, MD), stem cell therapy in major airway disorders (Emmanuel Martinod, MD) and the latest perspectives on lung cancer screening (James Jett, MD). The Congress ended with Jean-François Dumon, MD, of France, the father of interventional pulmonology, reviewing the evolution of therapeutic endoscopy over the last 30 years.

**Scientific Highlights:**

- Preliminary data demonstrated the efficacy of novel endobronchial volume reduction procedures (e.g., coils, biologic glue and steam vapor) for patients with severe emphysema.
- Long-term data (now five years) show the safety and efficacy of bronchial thermoplasty in patients with moderate to severe asthma.
- The combination of endobronchial and esophageal ultrasound in the staging of lung cancer has a diagnostic yield similar to that of mediastinoscopy.
- The diagnostic yield of medical pleuroscopy in properly selected patients is almost 100 percent.
- Complications following percutaneous dilational tracheostomy are less frequent than with surgical tracheostomy.
- Post-transplant surveillance bronchoscopy has value in the early identification of anastomotic complications.

**Themes:**

- Need for establishing proper algorithms and proper patient selection for successful outcomes with endobronchial volume reduction
- Need for additional long-term follow-up of patients undergoing bronchial thermoplasty, especially for those with severe asthma
- Guidelines, consensus statements and educational efforts should reflect various international perspectives (e.g., epidemiology of lung diseases, healthcare delivery systems, economics of healthcare), including those of underdeveloped countries.

Dr. Atul Mehta is a member of the medical staff in the Advanced Lung Disease Section of the Department of Pulmonary, Allergy and Critical Care Medicine and Transplant Center. He can be reached at 216.444.6503 or mehtaa1@ccf.org.
Respiratory Institute Selected Clinical Trials

Consider offering your patients 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.

ARDS

Randomized Trial of Rosuvastatin for Acutely Injured Lungs from Sepsis (SAILS study)

This NIH-sponsored multicenter study will assess the efficacy and safety of oral rosuvastatin (Crestor®) in patients with sepsis-induced acute lung injury (ALI). It is designed to examine whether rosuvastatin therapy will improve mortality in patients with sepsis-induced ALI.

ELIGIBILITY: Intubated patients with evidence of SIRS-related ALI/ARDS within 48 hours of meeting criteria. Exclusion criteria include current statin use and the inability to absorb enteral drugs.

PRINCIPAL INVESTIGATOR: Herbert P. Wiedemann, MD, MBA
STUDY COORDINATOR: Michelle Ferrari, RN | 216.445.1939

ASTHMA

Severe Asthma Research Program (SARP)

Sponsored by the National Heart, Lung, and Blood Institute, this is a multicenter observational study designed to evaluate the pathology of asthma.

ELIGIBILITY: Individuals (18-55 years old) will be phenotyped by collecting demographic, clinical and biomarker information to determine how severe asthmatics may differ from nonsevere asthmatics and healthy controls.

PRINCIPAL INVESTIGATOR: Serpil Erzurum, MD
STUDY COORDINATOR: Emmea Mattox | 216.445.1756

Imaging Inflammation in Asthma

Sponsored by the Strategic Program for Asthma Research/American Asthma Foundation, the purpose of this research is to assess lung inflammation in individuals with asthma compared with healthy controls.

ELIGIBILITY: Measurements will be obtained by injecting patients (18-55 years old) with an FDA-approved radioactive material and performing imaging scans of their lungs.

PRINCIPAL INVESTIGATOR: Serpil Erzurum, MD
STUDY COORDINATOR: Emmea Mattox | 216.445.1756

Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma (PAS2)

Supported by Boston Scientific, the objective of this study is to evaluate durability of treatment effect and to continue to evaluate the short- and long-term safety profile of the Alair® System in patients with severe persistent asthma.

ELIGIBILITY: Patients age 18-65 years, currently taking maintenance medication (inhaled corticosteroid at a dose < 1000 µg beclomethasone per day or equivalent and a long-acting β2-agonist at a dosage of ≥ 100 µg per day salmeterol or equivalent), pre-bronchodilator FEV1 of ≥ 60% of predicted, nonsmoker for ≥ 1 year, smoking history of < 10 pack years.

PRINCIPAL INVESTIGATOR: Sumita Khatri, MD, MS
STUDY COORDINATOR: JoAnne Baran, RN, BSN | 216.444.5023

Mometasone Furoate/Formoterol Fumarate MDI Fixed Dose Combination vs. Mometasone Furoate MDI Monotherapy in Adolescents and Adults with Persistent Asthma

Supported by Merck/Schering-Plough Research Institute, this 26-week randomized, double-blind, active-controlled study has been designed to compare the incidence of serious asthma outcomes in subjects treated with MF/F MDI BID vs. those treated with MF MDI BID. To demonstrate the risk/benefit of MF/F compared with MF in the same study population, this study will also evaluate whether the addition of F to MF reduces asthma exacerbations.

ELIGIBILITY: Patients 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 12 months 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, and (c) daily albuterol/salbutamol (used on most days) without any other asthma controller in the 4 weeks prior to randomization. Patients must be able to discontinue their 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. Exclusion criteria include patients with unstable asthma; COPD, cystic fibrosis or other significant, non-asthmatic lung disease; a clinically significant abnormality, illness or disorder of any body or organ system; a cumulative history of smoking greater than 10 pack years; an asthma exacerbation within 4 weeks of randomization; or more than 4 separate asthma exacerbations within the last 52 weeks.

PRINCIPAL INVESTIGATOR: David Lang, MD
STUDY COORDINATOR: Elizabeth Maierson, RRT | 216.444.2901

Mepolizumab Adjunctive Therapy in Subjects with Severe Uncontrolled Refractory Asthma (MENSA)

Supported by GlaxoSmithKline, this randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multicenter study will evaluate two dose regimens of mepolizumab (75 mg intravenous or 100 mg subcutaneous every 4 weeks) compared with placebo over a 32-week treatment period in subjects with severe refractory asthma with elevated blood eosinophils.

ELIGIBILITY: Age 18 years or older with severe, uncontrolled, refractory asthma; with eosinophilic phenotype (blood eosinophil count of ≥ 300/µL within the past 12 months or ≥ 150/µL at screening); on high-dose inhaled corticosteroid (ICS) for at least 12 months; with a pre-bronchodilator FEV1 < 80% of predicted (NHANES III) recorded at screening; and with a previously confirmed history of at least two more exacerbations requiring treatment with systemic CS (intramuscular, intravenous or oral) in the 12 months prior to visit 1, despite the use of high-dose ICS. Exclusion criteria include the presence of a known pre-existing, clinically important lung condition other than asthma; unstable liver disease; current usage of omalizumab or other monoclonal antibodies; or diagnosis of other conditions that could lead to an elevated eosinophil count.

PRINCIPAL INVESTIGATOR: Sumita Khatri, MD
STUDY COORDINATOR: JoAnne Baran RN, BSN | 216.444.5023
cKit Inhibition in Asthma (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 V1 and V3, pre-bronchodilator FEV1 ≥ 40% of predicted, > 80% compliance with PEF recording and diary recording during the run-in period. Exclusion criteria include hospitalization for asthma within the past 6 weeks or > 12 asthma exacerbations within the past year.

PRINCIPAL INVESTIGATOR: Serpil Erzurum, MD
STUDY COORDINATOR: Jackie Sharp, CNP | 216.636.0000

Alternative Diet Day (ADD) for Asthma Control

Sponsored by the National Institutes of Health, this is a randomized, placebo-controlled trial of simvastatin use to reduce 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 V1 and V3, pre-bronchodilator FEV1 ≥ 40% of predicted, > 80% compliance with PEF recording and diary recording during the run-in period. Exclusion criteria include hospitalization for asthma within the past 6 weeks or > 12 asthma exacerbations within the past year.

PRINCIPAL INVESTIGATOR: Serpil Erzurum, MD
STUDY COORDINATOR: Jackie Sharp, CNP | 216.636.0000

Long-Term Oxygen Treatment Trial (LOTT)

Sponsored by the National Institutes of Health, this is a randomized clinical trial of supplemental nasal oxygen therapy vs. no oxygen.

ELIGIBILITY: Patients age ≥ 40 years, FEV1 < 70% of predicted, FEV1/FVC < 0.7, 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 6-minute walk. Exclusion criteria include non-COPD lung disease, Epworth Sleep Scale > 15, SpO2 < 80% for at least 1 minute during 6-minute walk on room air, and chest surgery within 6 months.

PRINCIPAL INVESTIGATOR: James K. Stoller, MD, MS
STUDY COORDINATOR: Richard Rice, MEd, RRT | 216.444.1150

Simvastatin in the Prevention of COPD Exacerbations (STATCOPE)

Sponsored by the National Institutes of Health, this is a multicenter, randomized, placebo-controlled trial of simvastatin use to reduce the frequency and severity of COPD exacerbations in COPD patients who are prone to exacerbations.

ELIGIBILITY: Patients age 40-80 years, post-bronchodilator FEV1/FVC < 70%, post-bronchodilator FEV1 < 80% of predicted, smoking history ≥ 10 pack years, active or nonsmoker, and at least one of the following: 1) current supplemental oxygen use, 2) prescribed systemic corticosteroid and/or antibiotics for respiratory problems within the past year, 3) ER visit for a COPD exacerbation within the past year or 4) hospitalized for a COPD exacerbation within the past year.

PRINCIPAL INVESTIGATOR: James K. Stoller, MD, MS
STUDY COORDINATOR: Richard Rice, MEd, RRT | 216.444.1150

EMPHYSEMA

AeriSeal® System for Hyperinflation Reduction in Emphysema (ASPIRE)

Developed by Aeris Therapeutics, the AeriSeal® System functions as a tissue sealant, physically blocking both small airways and collateral air channels, causing the treated areas to collapse via absorption atelectasis. The resulting reduction in gas trapping and lung hyperinflation restores a more normal physiological relationship between lung and chest wall. The AeriSeal System has been shown in prior open-label investigational studies to reduce lung volume, improve lung function and improve quality of life in patients with advanced emphysema, with a favorable risk:benefit profile.

ELIGIBILITY: Age ≥ 40 years; advanced upper lobe-predominant emphysema confirmed by CT scan; MRCD score of ≥ 2 post-pulmonary rehabilitation; 6MWT distance ≥ 150 m post-pulmonary rehabilitation; spirometry 15 minutes after administration of a bronchodilator showing BOTH a) FEV1 < 50% AND b) FEV1/FVC ratio < 70%; plethysmograph-ic lung volumes showing BOTH a) TLC > 100% AND b) RV > 150%, both using the ATS recommended expected values; DLco ≥ 20% and ≤ 60% predicted; blood gases and oxygen saturation showing BOTH a) SpO2 ≥ 90% on ≤ 4 L/min supplemental O2 at rest AND b) PaCO2 < 65 torr; and a smoking history of ≥ 20 pack years with abstinence from 16 weeks prior to the initial screening visit.

PRINCIPAL INVESTIGATOR: Thomas Gildea, MD
STUDY COORDINATOR: Yvonne Meli, RN | 216.445.4215

IDIOPATHIC PULMONARY FIBROSIS

STX-100 in Patients with Idiopathic Pulmonary Fibrosis

Sponsored by Stromedix Inc., this is a randomized, double-blind, placebo-controlled, multiple-dose dose-escalation study of 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% of predicted value, oxygen saturation > 90% on room air at rest, residual volume ≥ 120% of predicted value, FEV1/FVC ratio ≥ 0.65 after use of a 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: Diane Faile, BS, RRT | 216.444.9975

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 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 the breath of those without the disease.

ELIGIBILITY: Age 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 the last 5 years, any history of lung cancer, or immunosuppressive or continuous supplemental oxygen use.

PRINCIPAL INVESTIGATOR: Peter Mazzone, MD
STUDY COORDINATOR: Mary Beukemann | 216.445.8951

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 (LNT) 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: Age ≥ 50 years, ≥ 20 pack year smoking history, undergoing diagnostic evaluation for a new lung nodule with maximal dimensions identified by CT scan ≥ 8 mm and ≤ 20 mm. Exclusion criteria include previous nodule diagnostic procedures; nodule detected by 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, or administration of blood products.

PRINCIPAL INVESTIGATOR: Peter Mazzone, MD
STUDY COORDINATOR: Mary Beukemann | 216.445.8951

LCRT: Validation of a Multi-Gene Test for Lung Cancer Risk
Sponsored by the National Cancer Institute/NIH, this trial is designed to show that the Lung Cancer Risk Test (LCRT) may be useful as a prediction test for determining individuals at risk for developing lung cancer.

ELIGIBILITY: Age 50-90 years, ≥ 20 pack year smoking history, clinical indication for bronchoscopy or healthy volunteer who agrees to undergo diagnostic bronchoscopy.

PRINCIPAL INVESTIGATOR: Peter Mazzone, MD
STUDY COORDINATOR: Meredith Seeley | 216.445.9557

CPORT: Cut-Point Optimization of a Risk Test for Lung Cancer
Sponsored by the National Cancer Institute/National Institutes of Health, this trial is designed to optimize cut-points for each gene included in a 15-gene test for lung cancer risk. The test proposed for optimization in this study involves measuring gene expression activity of the 15 genes indicated on the Lung Cancer Risk Test (LCRT) in normal bronchial epithelial cells (NBEC) obtained at bronchoscopy.

ELIGIBILITY: Age 50 to 90 years, ≥ 20 pack year smoking history, clinical indication for bronchoscopy, and known to have lung cancer or determined to have lung cancer at the time of enrollment.

PRINCIPAL INVESTIGATOR: Peter Mazzone, MD
STUDY COORDINATOR: Meredith Seeley | 216.445.9557

Inherited Genetic Risk Factors Common to COPD and Lung Cancer
Sponsored by the National Cancer Institute/National Institutes of Health, this trial supports the hypothesis that inter-individual variation in gene expression in normal bronchial epithelial cells (NBEC) may be responsible for the variation in risk among smokers. The goal of this study is to determine the association between gene expression values and/or DNA variants in each of multiple high-prior-likelihood genes, alone or in combination, with risk for COPD and/or lung cancer.

ELIGIBILITY: Subjects must be enrolled into LCRT or CPORT study.

PRINCIPAL INVESTIGATOR: Peter Mazzone, MD
STUDY COORDINATOR: Meredith Seeley | 216.445.9557

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 that result in chronic rejection following human LTx. Subjects will be recruited who have high PRA percentages prior to their transplant. Serum and BAL samples will be collected prior to lung transplant as well as post-transplant. This study is sponsored by the National Institutes of Health and Washington University in St. Louis, Mo.

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
STUDY COORDINATOR: Chenett Greer | 216.445.9287

LYMPHANGIOLEIOMYOMATOSIS

Letrozole in Pulmonary Lymphangioleiomyomatosis with or Without Measurable Tumors in Lymph Nodes (TRAIL)
In postmenopausal women, estrogens are mainly derived from the action of the aromatase enzyme. Therefore, estrogen suppression might be expected to prevent or delay progression of LAM in this population. Letrozole is an aromatase inhibitor that competitively binds to a subunit of the enzyme, thereby reducing estrogen biosynthesis. The trial is supported by a grant from the Department of Defense, awarded to the University of Cincinnati and the LAM group.

ELIGIBILITY: Post-menopausal women with confirmed LAM and a post-bronchodilator FEV1 ≤ 80% of predicted, or DLCO ≤ 70% of predicted or RV ≥ 120% of predicted. Those with osteopenia or osteoporosis must be receiving appropriate therapy. Exclusion criteria include hormonal therapy within 30 days of screening for the trial.

PRINCIPAL INVESTIGATOR: Joseph Parambil, MD
STUDY COORDINATOR: Diane Faile, BS, RRT | 216.444.9975

PULMONARY HYPERTENSION

Ambrisentan and Tadalafil Combination Therapy in Subjects with Pulmonary Arterial Hypertension (AMBITION)
Sponsored by GSK/Gilead Sciences, this randomized, multicenter clinical trial is designed to compare two treatment strategies: first-line combination therapy (ambrisentan and tadalafil) vs. first-line monotherapy (ambrisentan or tadalafil) in subjects with pulmonary arterial hypertension.

ELIGIBILITY: Idiopathic or heritable PAH or PAH associated with connective tissue disease, drugs or toxins, HIV, or congenital heart defects repaired > 1 year prior to screening; WHO functional class II or III; mPAP of ≥ 25 mmHg; PVR ≥ 300 dynes/sec/cm⁻⁵; PCWP or LVEDP of ≤ 12 mmHg if PVR ≥ 300 to < 500 dynes/sec/cm²; or PCWP/LVEDP ≤ 15 mmHg if PVR ≥ 500 dynes/sec/cm²; 6MWT ≥ 125 m and ≤ 500 m.

PRINCIPAL INVESTIGATOR: Omar Minai, MD
STUDY COORDINATOR: Katie Zak | 216.636.2421

Pulsed, Inhaled Nitric Oxide (iNO) vs. Placebo as Add-On Therapy in Symptomatic Subjects with Pulmonary Arterial Hypertension (PAH)
Sponsored by Ikaria®, this phase 2, placebo-controlled, double-blind, randomized clinical study is designed 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⁻⁵) from baseline to EOS Part 1.

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 years; receiving at least one approved PAH therapy, on stable dose(s) for 12 weeks and clinically symptomatic from PAH; 6MWT of 100-450 m.

PRINCIPAL INVESTIGATOR: Gustavo Heresi, MD
STUDY COORDINATOR: Katie Zak | 216.636.2421
Inhaled Nitric Oxide (Using GeNO Nitrosyl™ System) in Subjects with Pulmonary Arterial Hypertension (PAH, WHO Group 1) and Pulmonary Hypertension Secondary to Idiopathic Pulmonary Fibrosis (PH-IPF WHO Group 3)

Up to 75 subjects undergoing RHC are planned in this phase 2, open-label, dose-escalation study and shall include subjects meeting eligibility criteria classified as WHO Group 1 PAH or WHO Group 3 PH-IPF. Subjects will receive inhaled nitric oxide from the GeNO Nitrosyl™ System to characterize the hemodynamic response and evaluate safety and tolerability.

ELIGIBILITY: Age 18-80 years; WHO functional class II-IV; documented diagnosis of WHO Group 1 PAH or documented diagnosis of probable or definite IPF using ATS/ERS criteria.

PRINCIPAL INVESTIGATOR: Adriano Tonelli, MD
STUDY COORDINATOR: Katie Zak | 216.636.2421

Ambrisentan and Tadalafil Combination Therapy in Pulmonary Arterial Hypertension Associated with the Scleroderma Spectrum of Disease (ATPAHSS)

This is a 36-week, open-label study to carefully assess the effects of tadalafil and ambrisentan combination therapy in patients with PAH-SSD. The study is sponsored by the National Institutes of Health and Johns Hopkins University.

ELIGIBILITY: Age > 18 years; mPAP ≥ 25 mmHg, PAWP ≤ 15 mmHg, (PVR) ≥ 3 Woods units; scleroderma defined as systemic sclerosis with diffuse or limited scleroderma meeting the American College of Rheumatology (ACR) criteria.

PRINCIPAL INVESTIGATOR: Omar Minai, MD
STUDY COORDINATOR: Katie Zak | 216.636.2421

Pulmonary Vascular Complications of Liver Disease-2 (PVCLD2)

Sponsored by Perelman School of Medicine at the University of Pennsylvania as a subcontract of the National Heart, Lung, and Blood Institute, 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 active infection, active or recent (< 2 weeks) gastrointestinal bleeding, lung transplant or pregnancy.

PRINCIPAL INVESTIGATOR: Gustavo Heresi, MD
STUDY COORDINATOR: Mario Becerra | 216.445.7599

SARCOIDOSIS

Multicenter Registry of Patients with Sarcoidosis-Associated Pulmonary Hypertension (RESAPH)

Sponsored by the University of Cincinnati Physicians Co., this registry is designed to characterize the demographics, clinical course, hemodynamics, pulmonary physiology and disease management of sarcoidosis-associated pulmonary hypertension in the United States compared with non-U.S. sites.

ELIGIBILITY: Patients with known or newly diagnosed sarcoidosis-associated pulmonary hypertension.

PRINCIPAL INVESTIGATOR: Daniel Culver, DO
STUDY COORDINATOR: JoAnne Baran, RN, BSN | 216.444.5023

VENTILATOR ASSOCIATED PNEUMONIA (VAP)

Intravenous Ceftolozane/Tazobactam vs. Piperacillin/Tazobactam in Ventilator Associated Pneumonia

Cubist Pharmaceuticals Inc. is sponsoring this multicenter, open-label, randomized study, which is designed to compare the clinical cure rates of ceftolozane/tazobactam with piperacillin/tazobactam, a well-characterized β-lactam combination antibiotic commonly used for the treatment of nosocomial pneumonia, in adult patients with VAP.

ELIGIBILITY: Patients age 18 years or older; mechanically ventilated for a minimum of 48 h prior to randomization and on mechanical ventilation at the time of randomization; APACHE II score > 10 and ≤ 35; at least 2 of the following clinical criteria for VAP within the 24-hour screening period: (a) rectal (or other core) temperature at least 38.5°C OR < 35°C, or tympanic temperature at least 38°C OR < 35°C, (b) white blood cell count at least 11000/mm3 OR < 4000/mm3 OR > 10% immature neutrophils, or (c) purulent tracheal secretions; PaO2/FiO2 ratio consistent with acute lung injury (PaO2/FiO2 of 200-299 mm Hg) within the 24-hour screening period; new or progressive infiltrate on chest radiography consistent with VAP; quantitative culture of either a BAL or mini-BAL, a PBS, or an ETA obtained at baseline before administration of any study antibiotic therapy for the current VAP. Exclusion criteria include documented history of any moderate or severe hypersensitivity (or allergic) reaction to any β-lactam antibacterial; ARDS; receipt of more than 36 h of nonstudy antibiotic (in the preceding 72 h) prior to the first dose of study drug for treatment of the current VAP; diagnoses or conditions that interfere with the assessment or interpretation of outcome; history of active immunosuppression, including AIDS; prior receipt of piperacillin/tazobactam, or growth of a piperacillin-resistant Gram-negative pathogen; severe impairment of renal function.

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Winter 2013 | 19
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