New HHT Center Opens
Multidisciplinary Care, Groundbreaking Therapies

By Joseph Parambil, MD

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is an inherited autosomal dominant disorder that results from mutations in genes whose protein products influence TGF-β superfamily signaling in vascular endothelial cells.

The disease, therefore, clusters in predisposed families with episodic recurrent nasal and gastrointestinal bleeding, visible telangiectasias on the lips and fingers, and larger arteriovenous malformations (AVMs) in the pulmonary, hepatic, cerebral and other circulatory beds. These features, presented as follows, are incorporated in the Curaçao criteria and used to define HHT:

1. **Epistaxis** – spontaneous, recurrent nosebleeds
2. **Mucocutaneous telangiectasias** – multiple at characteristic sites, including the lips, oral cavity, fingers, nose
3. **Visceral lesions** – gastrointestinal telangiectasias with or without bleeding, pulmonary AVMs, hepatic AVMs, cerebral and spinal AVMs
4. **Family history** – first-degree relative with HHT

---

Also in this Issue

- Treating Patients with Sarcoidosis and Small Fiber Neuropathy
- Close Link Between Pulmonary Hypertension and Blood Cell Abnormalities
- Chronic Thromboembolic Pulmonary Hypertension
Dear Colleagues:

Welcome to the Winter 2012 issue of Respiratory Exchange, which highlights the latest work of our pulmonary, critical care medicine, allergy and clinical immunology staff in Cleveland Clinic’s Respiratory Institute – and our collaboration with thoracic surgery, thoracic radiology and pulmonary pathology.

In this issue, you will find articles that demonstrate our recent continued growth in our clinical programs, research and innovative treatment modalities in areas such as hereditary hemorrhagic telangiectasia, pulmonary arterial hypertension, sarcoidosis and bronchial thermoplasty, among others.

For additional information about our ongoing clinical and research activities in respiratory disorders, please visit clevelandclinic.org/pulmonary (current and archived issues of Respiratory Exchange are available here) and clevelandclinic.org/thoracic.

I hope that you enjoy this issue of Respiratory Exchange and find it useful in your practice. As always, please feel free to contact us at our toll-free number for physicians, 866.CCF.LUNG (866.223.5864), if you have any questions or would like to refer a patient. We welcome the opportunity to work with you.

Sincerely,

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

New HHT Center Opens continued

The diagnosis is classified as definite if three criteria are present, possible or suspected if two criteria are present and unlikely if there are fewer than two criteria. Although inherited as an autosomal dominant condition, HHT is not apparent at birth. Rather, it evolves with age (not infrequently into adulthood) as a distinct phenotypic pattern, since the mutations display late-onset penetrance. Despite this age-related penetrance, there is profound variation in disease expression between different members of the same family, suggesting epigenetic influences that modify the clinical phenotype.

Genetic testing of patients and their family members can confirm the presence of mutations within implicated genes and three of the genes mutated in HHT have been identified: endoglin, ACVRL1/ALK1, and more rarely, SMAD4.

Since the clinical manifestations of HHT are pleiotropic and protean, families with this disorder are best served at an HHT Center of Excellence that facilitates the comprehensive coordination of care from multiple specialists necessary for appropriately treating and screening these patients. The model of care at Cleveland Clinic has always been an integrated approach between the various disciplines of medicine and we have recently created a new center for managing this complex disease. Here are two examples to illustrate our capacities in managing this multisystem disorder:

**CASE 1 – INNOVATIVE THERAPY WITH BEVACIZUMAB**

A 76-year-old female was assessed for progressive exertional dyspnea over the past four months. She has a known history of HHT, with mutation identified in the ACVRL1 gene. She has had chronic epistaxis for the past 54 years for which periodic evaluations by ENT have resulted in various treatment modalities including KTP laser therapy, fibrin sealant nasal packing, septodermatoplasty and intranasal injections of bevacizumab. She began having episodes of lower gastrointestinal bleeding 17 years prior, with her last episode occurring 16 months prior from a jejunal AV M that was endoscopically cauterized.

She had adjusted to her chronic medical condition and was stable until four months prior when there was an increase in frequency and severity of nosebleeds, further drop in hemoglobin to 6 to 7 gm/dL despite continuing intravenous iron sucrose and, despite these above measures, her hemoglobin averaged 8 to 9 gm/dL. Screening for AVMs in other vascular beds identified two stable small pulmonary AVMs (feeding vessels of 1.2 mm and 0.9 mm) in the left lower lobe and multiple hepatic AVMs with evidence of hepatic artery to hepatic vein shunting (Figure 1).

She had had to adjust to her chronic medical condition and was stable until four months prior when there was an increase in frequency and severity of nosebleeds, further drop in hemoglobin to 6 to 7 gm/dL despite continuing iron infusions requiring hospital admissions for packed red-blood-cells transfusions, and the development of progressively worsening dyspnea. On examination, she had bounding peripheral pulses, lower extremity edema, lung crackles, and was hypoxic on room air with a SpO2 of 85 percent, requiring 2 L/min of supplemental O2 to maintain saturations.

Chest radiographs showed cardiomegaly with pulmonary vascular congestion and diffuse interstitial pulmonary edema. Surface echocardiogram showed normal LV size and systolic function with Stage I diastolic dysfunction, mildly dilated RV with mildly reduced systolic function with an estimated RVSP of 67 mmHg and severe bialtrial enlargement. Right heart catheterization established high-output heart failure causing pulmonary hypertension with the following hemodynamics:

| RA: 15 mmHg | RV: 58/12 mmHg | PA: 58/22 mmHg |
| mPA: 34 mmHg | PCWP: 20 mmHg | PVR: 0.9 W units |
Despite diuretic therapy and increasing the frequency of iron infusions, she remained refractory in high-output heart failure. Due to her advanced age and chronic anemia, she was not considered a candidate for liver transplantation. Given anecdotal reports on the possibility that anti-angiogenic therapy with anti-vascular endothelial growth factor antibodies (bevacizumab) might be effective in reducing the size of liver AVMs and thereby useful in the treatment of the high-output heart failure, she was administered six cycles of intravenous bevacizumab.

By the second cycle, she noticed resolution of leg edema, improvement in exercise capacity, and requested a prescription to return oxygen tanks back to the supplier. At her fifth cycle, she developed an episode of epistaxis that was controlled with intranasal injection of bevacizumab. On follow-up in four weeks after her sixth cycle, she felt the best she had been in years and was able to go to her local gym, exercising three days a week by walking on a treadmill for 20 minutes. Testing now showed her hemoglobin had improved to 12.5 gm/dL (Figure 2) and repeat echocardiogram eight weeks after her last infusion showed normal LV size and systolic function with Stage I diastolic dysfunction, normal RV size and systolic function with an estimated RVSP of 36 mmHg and moderate biatrial enlargement.

---

**Figure 1:** Early enhancement of the hepatic veins and IVC from innumerable vascular shunts between branches of the hepatic artery and hepatic veins consistent with AVMs (1A). MRI abdomen performed three months after bevacizumab treatment shows persistence, but reduction in size and number of hepatic AVMs (1B).

**Figure 2:** Serial measurements of blood hemoglobin levels show resistance to treatments with intravenous iron therapy, but a progressive rise in values with the administration of bevacizumab.
A 24-year-old man was assessed after a deletion mutation was identified in the MH2 domain of the SMAD4 gene. He was diagnosed with juvenile polyposis syndrome eight months prior for which, due to significant colonic disease burden, he underwent total colectomy with ileo-rectal anastomosis. He was subsequently referred for further evaluations. On history taking, besides the episode of hematochezia that identified his colonic polyposis, he reported recurrent spontaneous mild episodes of epistaxis for the past 14 years, and had not required blood transfusions, or local interventions by ENT or shown evidence of iron deficiency anemia. On physical examination, there were telangiectasias on the lips and nasal cavity, with no other significant findings.

Given the presence of the mutation within the MH2 domain that increases risks of identifying concomitant HHT, he underwent screening for the presence of silent disease. CT chest identified two AVMs, one in the right middle lobe with a 3.6 mm feeding vessel (Figure 3) and another in the right lower lobe with a 1.3 mm feeding vessel. MRI of the brain showed a supratentorial dural arteriovenous fistula that was confirmed by cerebral angiography (Figure 4) while doppler ultrasonography of the liver was unremarkable for telangiectasias or vascular masses. With this constellation of findings, he met the Curaçao criteria for an additional diagnosis of definite HHT. Due to the risks of serious neurological events with pulmonary AVMs supplied by a feeding artery at least 3 mm in diameter or larger, he underwent prophylactic coil embolotherapy of the right middle lobe AVM.

As a consequence of these findings, his parents and six siblings underwent genetic testing and the mutation was identified in his mother, three brothers and one sister. Clinical evaluations identified subclinical HHT in three members.

As described above, today the spectrum of associated manifestations within HHT has extended beyond the typical pathology of telangiectasias and AVMs. More recently pulmonary hypertension in the context of pulmonary arteriopathy or high output cardiac failure, immune dysfunction, hypercoaguability associated with elevated plasma levels of factor VIII, and juvenile gastrointestinal polyposis are increasingly being recognized as features, usually with distinct genetic profiles. Patients with HHT require comprehensive coordination of care from multiple specialists necessary for appropriate treatments. As illustrated above, the multi-faceted integrated approach between the various disciplines of medicine at Cleveland Clinic would easily fit to allow us to manage HHT patients and their families.

Dr. Joseph Parambil is the Director of our new HHT Center and an associate staff member in the Department of Pulmonary, Allergy and Critical Care Medicine. His special interests include interstitial lung disease, pulmonary hypertension and general pulmonary medicine. He can be reached at 216.444.7567 or parambj@ccf.org.

Figure 3: Contrast-enhanced CT of the chest shows a 2.1 x 1.3 cm well-defined nodular lesion in the right middle lobe anteriorly (arrow), with a 3.6 mm feeding artery (arrowhead), suggestive of an arteriovenous malformation.

Figure 4: Cerebral angiography demonstrates a right supratentorial dural arteriovenous fistula (arrow) with arterial supply from branches of the right meningohypophyseal trunk and distal branches of the right internal maxillary artery, draining into the sigmoid sinus.
Using Short-cycle Business Intelligence Methods to Guide and Improve Process and Outcomes in Respiratory Therapy

By Madhu Sasidhar, MD

The adoption of electronic health records has resulted in the creation of clinical data warehouses with rich clinical information. Cleveland Clinic’s Section of Respiratory Therapy has been a leader in protocol guided management of patients. Recently, we have started to use short-cycle business intelligence (BI) methods to improve process, enhance efficiency and optimize outcome during weaning and liberation from mechanical ventilation.

We modified our existing mechanical ventilation weaning protocols to capture key performance indicators (KPI) from the therapists’ documentation (figure below). These KPIs were analyzed using BI dashboards to characterize spontaneous breathing trials (SBT), sedation level and extubation in the medical intensive care unit (MICU). Reasons for failure were examined and iterative improvements were made in the weaning and extubation process. Using short-cycle BI, persistent sedation was identified as the leading reason for failure of spontaneous breathing trials, resulting in modification of sedation protocols. Continuous process improvement resulted in higher rate of extubation and reduced duration of mechanical ventilation from 6.3 to 4.4 days. We are extending the use of this methodology to other aspects of respiratory care.

Dr. Madhu Sasidhar is Head of the Section of Respiratory Therapy. He can be reached at 216.445.1838 or sasidhm@ccf.org.

Recommended Reading
Treating Patients with Sarcoidosis and Small Fiber Neuropathy

By Daniel A. Culver, DO, Joseph G. Parambil, MD, Jinny Tavee, MD, and Lanzhou, MD

Mrs. B, a 44-year-old patient with chronic pulmonary sarcoidosis, was dissatisfied after her last office visit with her local physician. While her physician was pleased that she had excellent functional capacity and stability of her chest radiograph and spirometry, she was frustrated that the problems most bothersome to her were not addressed. Her symptoms were mainly attributable to small fiber neuropathy (SFN), but until recently the medical community neither recognized it nor had therapies to offer for it.

Chronic pain is one of the most frequent and salient patient-reported symptoms in sarcoidosis populations. Common complaints include arthralgias, classic neuropathic pain, headache and chest pain. The relationship of this pain to measurable sarcoidosis activity is typically nebulous, leading to frustration for both physicians and patients alike. Moreover, when augmented immunosuppression is attempted, the pain is often the only feature of sarcoidosis not to show a demonstrable response. In the end, these patients are commonly diagnosed with fibromyalgia. However, in sarcoidosis patients with SFN symptoms, pain scores are markedly higher than in those without SFN symptoms.

Immune-mediated loss of thinly myelinated (Aδ fibers) and unmyelinated (C fibers) small nerves is common in sarcoidosis, although the pathophysiologic mechanisms involved are unknown. These fibers mediate cutaneous sensations such as pain and temperature and autonomic responses such as sweating, heart rate and bowel motility. As a result, a wide variety of symptoms may be related to SFN (box below). In the Dutch sarcoidosis population, abnormal small nerve fiber testing has been found in 30 to 69 percent of subjects with neuropathic symptoms and in 14 percent without symptoms. In our experience, the higher estimate of SFN prevalence is more accurate, in part because no single diagnostic test has a high negative predictive value in symptomatic patients.

When it is suspected, small fiber neuropathy can be diagnosed with several modalities. Thermal threshold testing and measurement of intraepidermal nerve fiber density (IENFD) assess sensory nerve involvement. Quantitative sudomotor axonal reflex testing (QSART), cardiovagal testing and tilt table testing may be helpful in cases with predominant autonomic symptoms. In our institution, these tests are generally complementary. These patients are typically evaluated in our combined neurosarcoidosis clinic.

---

**Small Fiber Neuropathy Symptoms**

- Pain (typically burning or tingling, but also including headaches & chest pain)
- Paresthesias
- Sheet intolerance
- Restless legs syndrome
- Poor bowel motility
- Flushing
- Orthostatic symptoms
- Sicca symptoms
- Urinary incontinence
- Sexual dysfunction

---

Figure 1A: Normal skin biopsy, showing normal small nerve fibers (arrows).
Measurement of IENFD in a set of three cutaneous punch biopsies is thought to be the most sensitive marker of SFN (estimated to be up to 88 percent), but the true accuracies of all of the tests are unknown since there is no diagnostic gold standard. Figures 1A and B depict typical findings in normal and affected skin – the widespread application of skin biopsy for diagnosing SFN is limited by its availability in the U.S. to only a handful of larger medical centers. Granulomas are not found in these biopsies. A key feature of sarcoidosis-associated SFN is that it is not length-dependent, in contrast to many other causes such as diabetic neuropathy.

Even without specific treatment, recognition of SFN as a cause of a patients’ symptoms is important to validate the patient’s experience, assuage concerns about other causes, and to limit unnecessary use of immunosuppressive agents. For mild to moderate disease, usual therapies include GABA analogues, tricyclic antidepressants, selective serotonin reuptake inhibitors and pain medications. We have not found that corticosteroids or cytotoxic agents are typically helpful. A single case report from the Netherlands suggested that infliximab may be helpful, but it has been mainly disappointing for SFN in our experience.

For severe, disabling disease, we recently reported dramatic effects of intravenous immunoglobulin (IVIg) therapy in patients refractory to other approaches. The patients with good responses to IVIg had rapid improvement of their symptoms, with marked improvement in quality of life, functional capacity and ability to work. Most of the patients who respond to IVIg do so within two to three infusions. We have also observed that a subset (approximately 1/3) of our patients experience no apparent benefit from IVIg. The reasons for the differential responses between patients are unclear. Since IVIg is expensive and has important potential toxicities, its efficacy needs to be confirmed in a controlled trial prior to its widespread adoption.

Reach our authors: Dr. Dan Culver (pulmonology) at 216.444.6508 or culverd@ccf.org; Dr. Joseph Parambil (pulmonology) at 216.444.7567 or parambj@ccf.org; Dr. Jinny Tavee (neurology) at 216.445.2653 or taveej2@ccf.org; and Dr. Lan Zhou (neurology) at zhoul2@ccf.org.

Recommended Reading


Close Link Uncovered Between Pulmonary Hypertension and Blood Cell Abnormalities

By Samar Farha, MD, and Serpil Erzurum, MD

Interestingly, PAH patients are known to be prone to develop overt myeloid diseases, such as myelofibrosis or thrombocytopenia. Likewise, patients with myeloproliferative diseases, such as primary myelofibrosis and myeloid leukemia, often develop associated pulmonary hypertension, and the treatment of the underlying myeloproliferative process causes regression of pulmonary hypertension. All of this has caused speculation regarding a role for myeloid disease in PAH pathogenesis.

We recently uncovered a molecular link between PAH and bone marrow diseases. As reported in our Blood paper, we found that myeloid progenitor cells were increased in PAH patients – in the bone marrow, blood, and lungs. In addition, hypoxia-inducible factors (HIF), the protein complexes that govern the body's response to low oxygen concentrations including myeloid responses and the proteins whose production they regulate, such as erythropoietin (EPO) and hepatocyte growth factor (HGF), were all increased in PAH patients. The blood vessel endothelial cells in the PAH lung obtained from patients undergoing transplantation produced higher-than-normal levels of HGF, progenitor cell recruitment factor, and stromal-derived factor alpha, which serve an important role in the formation of new blood vessels by recruiting myeloid progenitor cells to localized sites for angiogenesis. Because HIF, EPO, and HGF regulate bone marrow progenitor cell numbers, mobilization and recruitment, this indicates that there may be an abnormal feedback loop connecting blood and lung vascular cell behavior.

Strikingly, some degree of occult myelofibrosis was present in all patients with PAH who were studied. Furthermore, among patients with the familial form of PAH, many of their nonaffected family members also had fibrosis of the bone marrow. This suggests that the bone marrow abnormalities might be a concurrent event and govern the development of pulmonary vascular disease. These studies provide more evidence for the interdependence of hematopoiesis and pulmonary vascular angiogenesis. The findings have significance for the development of new treatment strategies, which might aim to target the bone marrow myeloproliferative process in PAH to block the angioproliferative course of the disease.

Dr. Samar Farha is a Cleveland Clinic pulmonologist specializing in critical care and pulmonary hypertension. She can be reached at 216.444.3229 or farhas@ccf.org. Dr. Serpil Erzurum is the Chair of the Department of Pathology and Co-Director of the Asthma Center. She can be reached at 216.445.7191 or erzurus@ccf.org.

Recommended Reading:
**Update: What’s New With Bronchial Thermoplasty?**

By Sumita Khatri, MD, MS

Bronchial thermoplasty (BT) is a new therapeutic modality recently FDA-approved for the treatment of severe refractory asthma not well controlled on high-dose inhaled corticosteroids and long-acting bronchodilator therapy. This treatment is designed to target airways’ smooth muscle, which contributes to bronchoconstriction in asthma.

During BT, radiofrequency energy is applied to provide thermal treatment of visible airways > 3 mm in diameter. A specialized catheter, introduced via a bronchoscope, is used to apply the treatments. Treatments occur in three sessions spaced three weeks apart. Each session targets a different area of the lungs; the right lower lobe is treated first, then the left lower lobe, and finally bilateral upper lobes (right middle lobe is excluded to avoid the potential complication of right middle lobe syndrome). Most treatments occur in the outpatient setting, with an observation period to ensure proper recovery. The most common side effect of the treatments is a temporary exacerbation of asthma, which occurs most commonly within a day of the procedure but resolves in most cases a week afterwards. To minimize the chances of experiencing this side effect, patients are treated for three days prior, the day of, and the day after the procedure with oral steroids. Similar to the criteria in the multi-center AIR2 clinical trial, patients who are 18 to 65 years old, current non-smokers for the past three days prior, the day of, and the day after the procedure with oral steroids. Similar to the criteria in the multi-center AIR2 clinical trial, patients who are 18 to 65 years old, current non-smokers for the past year, and have refractory symptomatic asthma on appropriate controller therapy are considered for this treatment at Cleveland Clinic.

Results from the double-blinded placebo controlled AIR2 study demonstrated significant improvement in asthma quality of life in the BT group: a significant decrease in severe exacerbations, and an 84 percent reduction in emergency department visits in those receiving BT. Data from ongoing followup of these patients demonstrated a sustained reduction in proportion of individuals having severe exacerbations.

Since FDA approval, there has been significant interest among severe asthma patients to consider this therapy. Physician or self-referred patients are evaluated by members of our Asthma Center, including pulmonary and allergy physicians, and our asthma educator. In certain cases, consultation with other affiliated specialists (such as otolaryngologists, gastroenterologists and sleep physicians) is requested to address co-morbid conditions.

To date, several patients have completed therapy at Cleveland Clinic, with improvement in their asthma symptoms and reduction in daily steroid use. Several others are awaiting treatment. Outcomes of eligible patients are being followed in a multicenter registry study to help determine which patients are most likely to benefit from the procedure. In addition, Cleveland Clinic has recently become a site for the post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma, a five-year followup trial sponsored by AsthmaRx, Inc./ Boston Scientific, the producers of the Alair® system, which is used in BT.

Dr. Sumita Khatri is Co-Director of the Asthma Center and Medical Director of the Bronchial Thermoplasty Program. She can be contacted at 216.445.1701 or khatris@ccf.org. To make a referral, call 216.445.6266.

**Recommended Reading**


Meeting the Management Challenges of Neuromuscular Diseases

By Loutfi Aboussouan, MD

The neuromuscular diseases seen in Cleveland Clinic’s Respiratory Institute include amyotrophic lateral sclerosis (ALS), multiple sclerosis, various dystrophies and myopathies, motor sensory neuropathies (Charcot-Marie-Tooth disease), post-polio syndrome, myasthenia, diaphragm paralysis, Pompe disease and quadriplegia. These disorders pose specific challenges, each with individualized approaches to prognosis, diagnosis and management.

Respiratory manifestations contribute significantly to the morbidity and mortality of neuromuscular diseases. These include support of failing ventilation, control of sleep disruption, and management of secretions. Although a falling vital capacity usually does not result in hypoventilation until late in the course of the disease, the patchy nature of some disorders may result in earlier respiratory manifestations as can be seen in some ALS patients. More importantly, even in the absence of daytime respiratory symptoms, patients with neuromuscular disorders and early diaphragmatic involvement are vulnerable to hypoventilation during sleep, particularly in phasic rapid eye movement (REM) sleep. Therefore, sleep disruption is often the “canary in the coal mine” signal of early involvement of the diaphragm. Moreover, some neuromuscular disorders such as the dystrophies, Charcot-Marie-Tooth and Pompe disease may have associated obstructive sleep apnea.

Noninvasive ventilation is an important modality of treatment in patients with diaphragm impairment, sleep disruption and associated sleep disorders. While initial settings are often established empirically, further refinement of the settings can be obtained from sleep studies. One aspect of the multidisciplinary approach to the care of these patients is the close relationship between the Respiratory Institute and Cleveland Clinic Neurological Institute’s Sleep Center that has resulted in the development of specific titration protocols for the management of neuromuscular disorders.

Another example highlighting the importance of a multidisciplinary approach is the particularly strong collaboration between the Cleveland Clinic Neurological Institute’s Center for ALS and the Respiratory Institute’s neurological clinic. Patients initially seen in the center for ALS undergo close monitoring using a hand-held spirometer and are referred to the Respiratory Institute’s neurological clinic in case of a decline in lung function. This collaboration ensures a continuity of followup and early identification of pulmonary problems. For instance, of the 660 individual patients seen at the ALS Center since 2004, more than 400 have been referred for pulmonary evaluation because of symptoms or abnormalities in spirometric screening. Of those, more than 300 have been started on noninvasive ventilation, providing a large database of experience in management with close followup. Our experience indicates that support of hypoventilation with non-invasive ventilation improves survival and quality of life (Figures 1 and 2).

Patients with unilateral or bilateral diaphragm weakness often present with dyspnea on exertion and with difficulty breathing in the supine position. Although the condition is often labeled as idiopathic, a close collaboration with neurologists can ensure that a diagnosis is made when possible. A specific diagnosis may be of prognostic significance. For instance, patients with neuralgic amyotrophy and other causes for diaphragm impairment may often at least partially recover lung function over several years (Figure 3).
There are surgical approaches to the management of neuromuscular disorders. For patients with diaphragm paralysis and no expected recovery, diaphragm plication is a surgical option that can result in lifelong improvements in lung function and dyspnea. Diaphragm pacing, which can be implanted using a laparoscopic approach, is currently used in patients with spinal cord injury. Preliminary results indicate that diaphragm pacing may be useful in select patients with ALS.

Dr. Loutfi Aboussouan is a member of the Department of Pulmonary, Allergy and Critical Care Medicine, with special interests in general pulmonary medicine, chronic obstructive pulmonary disease, neuromuscular diseases, sleep medicine, long-term ventilator care, pulmonary rehabilitation and teaching. He can be reached at 216.444.0420 or aboussl@ccf.org

Recommended Reading


Identifying Novel Markers to Predict Prognosis and Outcomes in Mastocytosis
By Fred H. Hsieh, MD

Systemic mastocytosis is a heterogeneous disorder characterized by the abnormal growth and accumulation of mast cells in the body. It has protean manifestations and often eludes diagnosis for a long period of time. Systemic mastocytosis is associated with an activating mutation in the c-KIT gene (KIT D816V) in more than 85 percent of cases, but the presence of this mutation does not predict whether the disease will behave in an indolent or aggressive fashion; other genetic determinants that may influence disease activity or survival remain incompletely characterized. Along with my colleagues in the Respiratory Institute, I follow many patients with mastocytosis and am involved in studies attempting to identify novel genetic or other clinical markers that may predict prognosis and outcomes in mastocytosis. For example, we have recently completed a study identifying novel mutations in TET2, a member of the tet oncogene family of proteins, in subjects with mastocytosis. Mutations in TET2 have been described in a variety of myeloid-lineage neoplasms. We identified previously unknown mutations in TET2 exon 3 in subjects with indolent and aggressive systemic mastocytosis and in TET2 exons 3 and 11 in subjects with mastocytosis and concomitant myeloproliferative disease. Various TET2 single-nucleotide polymorphisms (SNPs) were found both in mastocytosis subjects and in normal controls, but only mutations leading to non-conserved amino acid changes were identified in mastocytosis subjects. Studies are ongoing to characterize these specific mutations in the entire registry database of subjects with cutaneous and systemic mastocytosis followed by Respiratory Institute physicians (currently more than 85 cases) and to understand the mechanism by which these specific TET2 mutations alter TET2 function and influence mast cell biology.

Imatinib Mesylate for Aggressive Systemic Mastocytosis

From 2003-2006, investigators in the Respiratory Institute, in collaboration with colleagues in the Taussig Cancer Center, initiated a clinical trial of imatinib mesylate (Gleevec, Novartis) for the treatment of systemic mastocytosis. Imatinib mesylate is a potent inhibitor of various receptor tyrosine kinases, including c-KIT. Somatic cell mutations in the c-KIT gene are associated with > 80 percent of mastocytosis cases, with the most common mutation identified in mastocytosis being c-KIT D816V. However, this particular c-KIT D816V mutation had been shown to be resistant to imatinib. In this study, we sought to determine the safety and efficacy of imatinib in patients with systemic mastocytosis who had no identified mutation that conferred imatinib resistance (such as c-KIT D816V). Patients with systemic mastocytosis with an associated hematologic non-mast cell disorder and aggressive systemic mastocytosis without detectable known c-KIT mutations were identified and subjects consented to a six-month, dose-escalation protocol of imatinib starting at 400 mg per day. At the end of the six-month treatment period, serum tryptase had fallen up to 44 percent with improvement in mastocytosis skin lesions and subjective symptom improvement with regards to pruritis, flushing and other vasomotor manifestations. However, bone marrow examination after therapy demonstrated persistent mast cell infiltration and complete remission was not achieved in any subject. Imatinib was generally well-tolerated although dose-dependent toxicity was noted, especially in patients > 65 years of age. In 2009, imatinib mesylate was approved by the FDA for use in patients with aggressive systemic mastocytosis without c-KIT D816V mutations or in cases where the c-KIT mutation status is unknown.

Dr. Fred Hsieh is a staff physician in the Respiratory Institute and board-certified in Allergy and Immunology. He has a joint appointment with Pathobiology. His specialty interests include asthma, allergic disorders and mast cell function. Dr. Hsieh can be reached at 216.444.3504 or hsiehf@ccf.org.
In this special feature, we take a behind-the-scenes look into the work being done in the laboratories of three of our staff here in the Respiratory Institute.

**Understanding Hyaluronan Production in the Asthmatic Airway**

By Mark Aronica, MD

Asthma is a chronic inflammatory disease in which the genetic background and the immune system interact with environmental factors to elicit overt manifestations of the disease. Inflammatory cells recruited into the lungs, mainly T lymphocytes, monocytes/macrophages, mast cells and eosinophils, act as the primary mediators in the acute- and late-phase asthmatic response. As a consequence of the chronic inflammation, lung morphology may become altered even in milder forms of the disease. Among the changes that are frequently noted are extracellular matrix (ECM) deposition, subepithelial fibrosis, goblet cell hyperplasia, smooth muscle hypertrophy and increased formation of post capillary venules, indicative of angiogenesis. ECM components, such as hyaluronan (HA) and proteoglycans, are deposited in the submucosa, and it is thought that the accumulation of these molecules compromiss the biomechanical properties of the airway tissue. The goal of our lab is to define the mechanisms and pathways associated with HA production, deposition and signaling in the asthmatic airways and to use this understanding to develop innovative and robust strategies to diagnose and treat asthma.

Dr. Mark Aronica is a member of the Section of Allergy and Clinical Immunology, specializing in asthma and allergic disorders. He can be reached at 216.444.6933 or aronicm@ccf.org.

**Fibroblast Migration and Transdifferentiation in Pulmonary Fibrosis**

By Mitch Olman, MD

Our laboratory-based research is focused on the pathogenesis of the fatal and untreatable disorder of idiopathic pulmonary fibrosis. 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 non-kinase (FRNK), can block TGF-beta (TGF-β) induced myofibroblast differentiation, and the development of pulmonary fibrosis in vivo. In ongoing work, we have also 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 have defined the pathway by which such a complex signal travels.

At the bedside, we are privileged to co-chair a nationwide, NIH-sponsored, multicenter clinical trial of the anticoagulant warfarin in idiopathic pulmonary fibrosis. This approach will hopefully lead to improved outcomes. This trial has recently been completed and will soon be published. A NIH trial to evaluate the plasma coagulation system in patients with pulmonary fibrosis, and thereby inform the drug trial, is ongoing in my laboratory. In the event you would like to enroll patients with idiopathic pulmonary fibrosis in national clinical trials, feel free to contact me.

Dr. Mitch Olman is a staff physician in the Respiratory Institute with a primary appointment in the Department of Pathobiology. Contact him at 216.445.6025 or olmanm@ccf.org.

**Recommended Reading**


Chronic Thromboembolic Pulmonary Hypertension

By Gustavo A. Heresi, MD, Nicholas G. Smedira, MD, and Raed A. Dweik, MD

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease characterized by elevated pulmonary pressures and pulmonary vascular resistance (PVR) due to proximal thromboembolic obstruction and distal remodeling of the pulmonary vasculature, which lead to right ventricular (RV) failure and premature death. The correct identification of patients afflicted with CTEPH is of the utmost importance, as it currently represents the only form of pulmonary hypertension that is potentially curable by means of pulmonary thromboendarterectomy (PTE). Cleveland Clinic is one of very few centers in the country that offers this highly complex operation.

While considered a rare disease, the true incidence of CTEPH is not known. CTEPH is triggered by a failure to resorb one or more episodes of pulmonary embolism (PE). However, up to half of patients do not report a history of PE, and prior PE is not required to make the diagnosis. For unclear reasons, chronic thromboembolic obstruction also leads to distal small-vessel vasculopathy, similar to the one seen in idiopathic pulmonary hypertension (PH). This phenomenon explains why CTEPH is characterized by much higher PVR than acute PE with similar levels of macroscopic vascular obstruction.

Evidence suggests that about 3.8 percent of patients will develop CTEPH after one or more episodes of PE. It has been estimated that more than 5,000 cases of CTEPH occur annually in the United States.

Pulmonary vascular disease is suspected in cases of unexplained dyspnea or those with the overt signs and symptoms of PH and RV failure. While Doppler echocardiography is a good screening test, right heart catheterization is mandatory to establish the presence of PH. The measurement of the pulmonary capillary wedge pressure (PCWP) and cardiac output allows for the diagnosis of PH due to left heart disease (PCWP > 15 mmHg) and for the calculation of pulmonary vascular resistance (PVR) to characterize pulmonary arterial hypertension (PCWP < 15 mmHg and PVR > 240 dynes/sec/cm-5). The latter hemodynamic profile is seen in CTEPH, but also in cases of PH due to pulmonary disease (emphysema, interstitial lung disease) and other causes of WHO group 1 PH (idiopathic, connective tissue disease, congenital heart defects, portal hypertension, etc). For this reason, a VQ scan is needed to screen for CTEPH. (Figure 1) A completely normal VQ scan essentially excludes the diagnosis of CTEPH.
Computed tomography (CT) pulmonary angiography is a complementary test that allows for more anatomic definition, especially with the currently used 64-detector row CT and 3-D reconstruction (Figure 2). CT chest also allows for assessment of the pulmonary parenchyma. Full pulmonary function tests are also necessary to exclude significant parenchymal lung disease. Invasive pulmonary angiography is still considered the “gold standard” and is typically performed for operative planning (Figure 3). We recommend coronary angiography in patients older than 50 years old to allow for bypass grafting during the same operation, if needed.

The therapy of choice for CTEPH is pulmonary thromboendarterectomy (PTE). The identification of appropriate surgical candidates (i.e., those patients who will derive the greatest benefit from PTE) is extremely challenging. The decision is informed by a variety of factors, including co-morbidities, local expertise, and, most importantly, an assessment of how much of the increase in PVR is secondary to macroscopic thromboembolic obstruction vs. microvascular disease. Surgery requires the use of cardiopulmonary bypass to deeply cool the patient’s body, followed by circulatory arrest. The access to the disease is through an arteriotomy in each main pulmonary artery (Figure 4), during which the thickened intima containing the fibrosed embolus is identified and an endarterectomy plane started and continued out into subsegmental branches. This is an entirely different operation than embolectomy for acute PE. Surgical specimens obtained are classified into 4 groups: type 1 (thrombus in the main and lobar arteries) (Figures 4 and 5), type 2 (disease proximal to segmental arteries) (Figure 5), type 3 (disease within segmental and subsegmental arteries only), and type 4 (not CTEPH, microvascular disease). Best outcomes are seen with types 1 and 2, while mortality is higher in type 4 disease.

At Cleveland Clinic, Drs. Gustavo A. Heresi (Pulmonary Vascular Program) and Nicholas G. Smedira (Cardiac Surgery) evaluate all CTEPH patients in a comprehensive and coordinated fashion with the help of other specialties such as cardiology and vascular medicine to identify proper candidates for PTE. For patients not deemed to be surgical candidates or those who develop residual PH after PTE, we offer enrollment into a clinical trial of a novel drug for CTEPH called riociguat, with promising early results. As no medical therapy is of proven efficacy in this disease, PH-targeted therapies should never be used to delay the evaluation of CTEPH patients for PTE.

Dr. Gustavo Heresi is associate staff in the Pulmonary Vascular Program and can be reached at 216.636.5327 or heresig@ccf.org. Dr. Nicholas Smedira is staff in Thoracic and Cardiovascular Surgery and can be reached at 216.445.7052 or smedirn@ccf.org. Dr. Dweik is the Director of the Pulmonary Vascular Program. Contact him at 216.445.5763 or dweikr@ccf.org.
Ex Vivo Research Holds Promise for Expanding the Pool of Transplantable Lungs

By Kenneth McCurry, MD

In the United States today, about 1,500 lung transplants are conducted annually and more than 1,800 people are awaiting donors. The need remains great, with current data showing that about one patient dies on the waiting list for every patient who receives a transplant.

In my lab, I am contributing to the emerging field of looking at ways to perfuse currently rejected donor lungs ex vivo to make them viable. This reconditioning system uses a portable device in which donor lungs are put in warm perfusion with continuous monitoring of function for transport to the transplant hospital, eliminating cold ischemia.

Early data from our work has been encouraging. We have been able to establish the ex vivo circuit, perfuse both human and pig lungs and have seen improvement in lung function in many of these organs over six to eight hours of storage in the device to the point that they may be viable for transplantation. This organ care system also could be beneficial if it can improve currently viable lungs, particular since there is a 20 percent to 57 percent rate of primary dysfunction after transplantation.

Our center and others doing similar work across the nation are anticipating the FDA approval of the solutions used to perfuse these lungs in 2012 so that we may be able to offer these lungs to patients.

In addition to work with our own circuits, we will soon be participating in a clinical trial of the Swedish Vivo Line device, an ex vivo system used to recover, evaluate and preserve lungs outside the body for up to 24 hours. The device has recently received the European CE Mark, but is not yet approved in the United States.

My lab also is focusing on pharmacologic strategies, including carbon monoxide and nitrate, to diminish ischemia reperfusion injury. We are interested in whether these pharmacological therapies can enhance lung function and even modify the immunogenicity of the organ to make it less susceptible to rejection.

Dr. Kenneth McCurry is Surgical Director of the Heart-Lung Transplant Program at Cleveland Clinic. He can be contacted at mccurrk@ccf.org or 216.445.9303.
Respiratory Institute Selected Clinical Trials

**SELECTED CLINICAL TRAILS**

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.

**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, as well as biomarker information to determine how severe asthmatics may differ from non-severe 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 to 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)**

Sponsored by Asthmatx, Inc., 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 dosage > 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, non-smoker for ≥ 1 year, smoking history of > 10 pack years.

**PRINCIPAL INVESTIGATOR:** Sumita Khatri, MD, MS  
**STUDY COORDINATOR:** JoAnne Baran, RN, BSN | 216.445.7706

**A Multicenter Longitudinal Study for Disease Profiling Asthma**

Sponsored by Centocor Research and Development Inc., this is a multicenter, longitudinal, exploratory study of biomarkers, clinical and physiological parameters in subjects with mild, moderate and severe asthma and healthy control subjects.

**ELIGIBILITY:** Healthy individuals (18-55 years) and clinically diagnosed asthmatic patients (18-70 years) with a BMI 30 ≤ Kg/m², Nonsmoker for ≥ one year at initial screening, with ≤ 10 pack-year history. Exclusion criteria include pregnancy, diagnosis of COPD, CF or other significant respiratory disorders or clinically significant medical illnesses or disorders, having a bronchodilator response of ≥ 12% and 200 mL from baseline or an FEV1 value < 85% of predicted value at screening, and having a positive Phadiatop test.

**PRINCIPAL INVESTIGATOR:** Sumita Khatri, MD  
**STUDY COORDINATOR:** JoAnne Baran, RN, BSN | 216.445.7706

**KIA**

Sponsored by the NIH and Brigham & 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, prebronchodilator FEV1 ≥ 40% predicted, > 80% compliance with PEF recording and diary recording during the run in period. Exclusion criteria include hospitalization for asthma within the past six 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**

**ELIGIBILITY:** Asthma, ages 18-65 years. Exclusion criteria include diabetes (fasting blood sugar > 100 mg/dL), lactose intolerance, BMI > 30 kg/m², pregnancy, inability to maintain ADD diet.

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

**ALLERGY**

**Placebo-Controlled, Double-Blind Investigation of the Therapeutic Utility of Xolair for Attenuating Aspirin-Induced Bronchospasm in Patients with Aspirin-Exacerbated Respiratory Disease Undergoing Aspirin Desensitization**

Sponsored by Genentech, Inc., this study is designed to examine the effect of Omalizumab on aspirin-induced bronchospasm occurring during aspirin desensitization in patients with aspirin-exacerbated respiratory disease.

**ELIGIBILITY:** Patients age ≥ 18 years, diagnosis of aspirin-exacerbated respiratory disease (chronic asthma, rhinosinusitis, history of adverse reactions to aspirin and/or aspirin-like drugs), candidate for Xolair (moderate to severe persistent asthma), IgE level of 30-700 IU/ml, IgE mediated (allergic) potential to inhalant allergen(s) by cutaneous or in vitro testing.

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

(continued on next page)
COPD

**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 < .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. Exclusion criteria include non-COPD lung disease, Epworth Sleep Scale > 15, SpO2 < 80% for at least one minute during six-minute walk on room air, and chest surgery within six 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% predicted, smoking history ≥ 10 pack years, active or non-smoker, 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

**IDIOPATHIC PULMONARY FIBROSIS**

**Prednisone, Azathioprine, N-acetylcysteine in IPF (PANTHER)**

This is now a two-arm, randomized clinical trial of N-acetylcysteine vs. placebo. This trial is sponsored by the NIH and being conducted through the "IPF-Net."

**ELIGIBILITY:** IPF diagnosis < 48 months from enrollment, FVC > 50% predicted and DLCO > 30% predicted. Exclusion criteria include clinically significant environmental exposure known to cause IPF and diagnosis of connective tissue disease.

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

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

Sponsored by the 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% 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

**A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of the Efficacy and Safety of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis**

This 52-week placebo-controlled trial, sponsored by Intermune, Inc, of an anti-fibrotic and anti-inflammatory molecule, pirfenidone, vs. placebo (1:1) in patients with mild-moderate IPF. Change in FVC is the primary endpoint.

**ELIGIBILITY:** Age 40-80; FVC between 50% and 90% predicted; DLCO between 30% and 90% predicted; diagnosis of IPF <48 months prior to screening. Exclusion criteria include FEV1/FVC ratio less than 0.8 after a bronchodilator; a positive bronchodilator response; active tobacco use; history of asthma or COPD; comorbid diseases or exposures that may be the cause of pulmonary fibrosis.

**PRINCIPAL INVESTIGATOR:** Joseph Parambil, MD
**STUDY COORDINATOR:** Ron Wehramann, RRT | 216.445.0574

**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:** John Komara, MBA, RRT | 216.445.1939

**PULMONARY HYPERTENSION**

**CHEST-1 (riociguat, stimulator of the soluble guanylate cyclase (sGC))**

Sponsored by Bayer, this is a randomized clinical trial of riociguat (BAY 63-2521) vs. placebo in drug-naïve patients with chronic thromboembolic pulmonary hypertension (CTEPH).

**ELIGIBILITY:** Patients with CTEPH age 18 to 80 years, inoperable or symptomatic six months after pulmonary endarterectomy, mean PAP > 25 mmHg, PVR > 480 dynes.sec.cm-5, PAOP ≤ 15 mmHg, 6MWD 150-450m. Exclusion criteria include TLC < 70%.

**PRINCIPAL INVESTIGATOR:** Gustavo Heresi, MD
**STUDY COORDINATOR:** Diane Fabec, RN | 216.445.7599 and Katie Zak, BS | 216.636.2421

**PATENT-1 (Riociguat, stimulator of the soluble guanylate cyclase (sGC))**

Sponsored by Bayer, this is a randomized clinical trial of riociguat (BAY 63-2521) vs. placebo in patients with idiopathic or heritable PAH or PAH-associated with connective tissue disease, repaired congenital heart defects, portal hypertension or drug use.

**ELIGIBILITY:** Patients age 18 to 80, mean PAP > 25 mmHg, PVR > 300 dynes.sec.cm-5, PAOP ≤ 15 mmHg; 6MWD 150-450m, who are drug naïve or taking an endothelin receptor antagonist (ERA) or an inhaled or subcutaneous prostacyclin analogue. Exclusion criteria include TLC < 70%.

**PRINCIPAL INVESTIGATOR:** Omar Minai, MD
**STUDY COORDINATOR:** Diane Fabec, RN | 216.445.7599 and Katie Zak, BS | 216.636.2421
Save the Date!

June 15 – 18, 2012

17th World Congress for Bronchology and Interventional Pulmonology

17th World Congress for Bronchoesophagology

Renaissance Cleveland Hotel, Cleveland, OH

Atul Mehta, MD | President, 17th WCBIP
Thomas Rice, MD | President, 17th WCBE

During a three-day period, this CME-accredited Congress will feature high-quality educational symposia, which will highlight the cutting-edge issues and new technology that is important to all practitioners in these fields. Sessions will be presented by experts in the field who have the knowledge and skills to review and analyze the data. Poster sessions, hands-on workshops, and exhibits will be incorporated into the Congress to extend learning opportunities. We are certain that participants will find this meeting highly educational as the information presented will be most scientific and evidence based.

Topics
• Early Diagnosis of Lung Cancer
• Endobronchial Staging of Lung Cancer
• Endobronchial Management of Obstructive Airway Diseases
• Lung Transplantation
• Endoscopic Management of Central Airway Obstruction
• Medical Thoracoscopy
• Surgical Management of Airway Lesions
• Bronchoscopy in Pediatric patients
• Bronchoscopy Training
• Nursing Assistance During Bronchoscopy

For more information about the 17th WCBIP and 17th WCBE, visit wcbipwcbe2012.com.

LUNG CANCER

Validation of a Multi-gene Test for Lung Cancer Risk (LCRT)

Sponsored by the National Cancer Institute/NIH, this trial is designed to show that the lung cancer risk test may be useful as a prediction test for determining individuals at risk for developing lung cancer.

ELIGIBILITY: Patients age 50-90 years, ≥ 20 pack year smoking history, and clinical indication for bronchoscopy.

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

SARCOIDOSIS

IV Infusion of Human Placenta-Derived Cells for the Treatment of Sarcoidosis

Sponsored by Celgene Corporation, this trial is studying the safety of intravenous infusion of human placenta-derived cells (PDA001) for the treatment of adults with Stage II or III pulmonary sarcoidosis.

ELIGIBILITY: Patients age 18-75 years, diagnosis of sarcoidosis evidenced by parenchymal disease on chest radiograph, histologic confirmation of granulomatous inflammation and disease duration of ≥ 1 year, FVC of ≥ 45 and ≤ 80% of predicted, and on a stable dose of prednisone, methotrexate, and/or azathioprine for pulmonary sarcoidosis for four weeks prior to infusion of the study drug.

PRINCIPAL INVESTIGATOR: Daniel Culver, DO
STUDY COORDINATOR: Constance Cottrell, PhD, RN | 216.444.3762

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

Sponsored by the University of Cincinnati Physicians Company, 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 to non-US sites.

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

PRINCIPAL INVESTIGATOR: Daniel Culver, DO
STUDY COORDINATOR: Elizabeth Maierson, RRT | 216.444.2901

NOVEL THERAPIES

Oral Iron Supplementation in Pulmonary Hypertension

This is a single-arm, open-label intervention to determine whether iron deficiency in IPAH is correctable with oral iron supplementation.

ELIGIBILITY: Participants > 21 years with the diagnosis of idiopathic pulmonary arterial hypertension, and with iron deficiency (transferrin saturation < 20% and serum ferritin < 100 µg/l). Exclusion criteria include active infection, malignancy, or bleeding, hemochromatosis, chronic inflammatory or autoimmune disease, currently taking experimental/study medications, EPO, iron supplementation, or immunesuppressants, and allergies to iron.

PRINCIPAL INVESTIGATOR: Serpil Erzurum, MD
STUDY COORDINATOR: Erika Lundgrin, MS-IV | 216.445.1756

LUNG CANCER

Validation of a Multi-gene Test for Lung Cancer Risk (LCRT)

Sponsored by the National Cancer Institute/NIH, this trial is designed to show that the lung cancer risk test may be useful as a prediction test for determining individuals at risk for developing lung cancer.

ELIGIBILITY: Patients age 50-90 years, ≥ 20 pack year smoking history, and clinical indication for bronchoscopy.

PRINCIPAL INVESTIGATOR: Peter Mazzone, MD
STUDY COORDINATOR: Mary Beukemann | 216.445.8951
## Respiratory Institute Staff Directory

### Department of Respiratory, Allergy and Critical Care Medicine

<table>
<thead>
<tr>
<th>Name</th>
<th>Title/Role</th>
<th>Phone Number</th>
<th>Specialty Interests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbert P. Wiedemann, MD, MBA</td>
<td>Chairman, Respiratory Institute</td>
<td>216.444.8335</td>
<td>Critical care (including adult respiratory distress syndrome and sepsis), general pulmonary medicine, exercise testing (dyspnea evaluation)</td>
</tr>
<tr>
<td>Rendell Ashton, MD</td>
<td>Associate Director, MICU; Director, Pulmonary and Critical Care Fellowship Program</td>
<td>216.636.5321</td>
<td>Critical care, medical education, interstitial lung disease</td>
</tr>
<tr>
<td>Loutfi Aboussouan, MD</td>
<td></td>
<td>216.839.3820</td>
<td>General pulmonary medicine, neuromuscular diseases, sleep medicine, long-term ventilator care</td>
</tr>
<tr>
<td>Jafar Abunasser, MD</td>
<td>Medical Director, ReSCU</td>
<td>216.444.1997</td>
<td>Critical care</td>
</tr>
<tr>
<td>Muzaffar Ahmad, MD</td>
<td></td>
<td>216.444.6506</td>
<td>Pulmonary function lab, asthma, lung cancer</td>
</tr>
<tr>
<td>Marie Budev, DO, MPH</td>
<td>Medical Director, Lung Transplantation</td>
<td>216.444.3194</td>
<td>Lung transplantation, pulmonary hypertension, gender-specific pulmonary issues</td>
</tr>
<tr>
<td>Robert Castele, MD</td>
<td></td>
<td>440.878.2500</td>
<td>General pulmonary medicine</td>
</tr>
<tr>
<td>Chirag Choudhary, MD</td>
<td></td>
<td>216.444.6090</td>
<td>Critical care</td>
</tr>
<tr>
<td>Joseph Cicenia, MD</td>
<td></td>
<td>216.444.8606</td>
<td>Advanced diagnostic bronchoscopy, general pulmonary medicine</td>
</tr>
<tr>
<td>Daniel Culver, DO</td>
<td>Director, Sarcoidosis Program</td>
<td>216.444.6508</td>
<td>Sarcoidosis, interstitial lung disease, hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>James Blackburn, DO</td>
<td></td>
<td>216.444.2318</td>
<td>General pulmonary medicine</td>
</tr>
<tr>
<td>Jean Louis Dupiton, MD</td>
<td></td>
<td>216.444.6500</td>
<td>Critical care</td>
</tr>
<tr>
<td>Raed A. Dweik, MD</td>
<td>Director, Pulmonary Vascular Disease Program; Joint Appointment with Pathobiology</td>
<td>216.445.5763</td>
<td>Asthma, pulmonary hypertension, chronic beryllium disease, critical care, bronchoscopy, nitric oxide in lung physiology and disease, exhaled markers in lung disease</td>
</tr>
<tr>
<td>Fransisco Almeida, MD</td>
<td>Director, Interventional Pulmonary Medicine Fellowship Program</td>
<td>216.444.6503</td>
<td>Advanced diagnostic and interventional bronchoscopy</td>
</tr>
<tr>
<td>Serpil C. Erzurum, MD</td>
<td>Chairman, Department of Pathobiology; Lerner Research Institute; Director, Cleveland Clinic General Clinical Research Center; Co-Director Asthma Center</td>
<td>216.445.5764</td>
<td>Asthma, pulmonary vascular disease, respiratory physiology</td>
</tr>
<tr>
<td>Hany Farag, MD</td>
<td></td>
<td>216.444.2318</td>
<td>Critical care</td>
</tr>
<tr>
<td>Samar Farha, MD</td>
<td></td>
<td>216.444.3229</td>
<td>Interstitial lung disease, pulmonary hypertension</td>
</tr>
</tbody>
</table>
Andrew Garrow, MD  
216.445.9797  
Specialty Interests: critical care, sleep medicine

Manica Isiguzo, MD  
216.839.3820  
Specialty Interests: general pulmonary medicine, interstitial lung disease

Atul C. Mehta, MD  
216.444.2911  
Specialty Interests: lung transplantation, endobronchial and bronchoscopic procedures and interventions, transtracheal oxygen therapy

Thomas R. Gildea, MD, MS  
Head, Section of Bronchoscopy  
216.444.6490  
Specialty Interests: interventional bronchology, lung transplantation

Constance A. Jennings, MD  
216.445.4184  
Specialty Interests: pulmonary hypertension, pulmonary thromboembolism, interstitial lung disease, advanced lung disease

Omar A. Minai, MD  
216.444.6500  
Specialty Interests: pulmonary hypertension, interstitial lung diseases, lung cancer, COPD, sleep apnea

Jorge Guzman, MD  
Head, Section of Critical Care Medicine; Director, MICU  
216.445.5765  
Specialty Interests: critical care, sepsis, shock

Sumita Khatri, MD, MS  
Co-Director, Asthma Center  
Joint Appointment with Pathobiology  
216.445.1891  
Specialty Interest: asthma

Ajit Moghekar, MD  
216.444.6500  
Specialty Interest: critical care

Tarik Hanane, MD  
216.445.5765  
Specialty Interest: critical care

Charles Lane, MD  
216.444.6503  
Specialty Interests: lung transplantation, critical care

Kathrin Nicolacakis, MD  
216.444.6500  
Specialty Interest: general pulmonary medicine

Umar Hatipoglu, MD  
Quality Improvement Officer  
216.636.5344  
Specialty Interests: asthma, acute respiratory distress syndrome, general (diagnostic) pulmonary medicine, critical care

Michael Machuzak, MD  
Medical Director, Center for Major Airway Diseases  
216.444.2718  
Specialty Interests: rigid and flexible bronchoscopy, endobronchial ultrasound, laser, electrocautery, stent placement, bronchoscopic lung volume reduction, transtracheal oxygen catheter placement, lung cancer, pleural diseases, COPD

Mitchell Olman, MD  
Joint Appointment with Pathobiology  
216.445.6025  
Specialty Interest: interstitial lung disease

Gustavo Heresi, MD  
216.636.5327  
Specialty Interests: acute respiratory distress syndrome, pulmonary hypertension, sepsis

Peter Mazzone, MD, MPH  
Director, Lung Cancer Program  
216.445.4812  
Specialty Interests: lung cancer, critical care, physician education

Glenn Meden, MD  
Chief, Division of Pulmonary and Critical Care Medicine at Hillcrest Hospital; Director, ICU at Hillcrest Hospital  
440.312.7140  
Specialty Interests: general pulmonary medicine, critical care

David Holden, MD  
216.986.4000  
Specialty Interest: general pulmonary medicine

Kathrin Nicolacakis, MD  
216.444.6500  
Specialty Interest: general pulmonary medicine

Glenn Meden, MD  
Chief, Division of Pulmonary and Critical Care Medicine at Hillcrest Hospital; Director, ICU at Hillcrest Hospital  
440.312.7140  
Specialty Interests: general pulmonary medicine, critical care

Atul C. Mehta, MD  
216.444.2911  
Specialty Interests: lung transplantation, endobronchial and bronchoscopic procedures and interventions, transtracheal oxygen therapy

Thomas Olbrych, MD  
440.312.7140  
Specialty Interests: general pulmonary medicine, cystic fibrosis, lung transplantation

Beverly V. O’Neill, MD  
Vice President, Medical Operations  
Euclid Hospital  
216.692.7848  
Specialty Interests: general pulmonary medicine, long-term ventilator patients
Aman Pande, MD
440.899.5555
Specialty Interests: critical care, general pulmonary medicine

Madhu Sasidhar, MD
Head, Section of Respiratory Therapy
216.445.1838
Specialty Interests: critical care, general pulmonary medicine

Mark A. Aronica, MD
Joint Appointment with Pathobiology
216.444.6933
Specialty Interests: asthma, allergic disorders

Joseph G. Parambil, MD
Director, HHT Center
216.444.7567
Specialty Interests: interstitial lung disease, pulmonary hypertension, general pulmonary medicine

David Skirball, MD
216.444.6503
Specialty Interests: critical care, general pulmonary medicine

Sandra Hong, MD
440.204.7400
Specialty Interests: allergy, asthma

Bohdan Pichurko, MD
Director, Pulmonary Function Lab
216.445.6789
Specialty Interest: general pulmonary medicine

James K. Stoller, MD, MS
Executive Director, Leadership Development; Chairman, Education Institute
216.444.1960
Specialty Interests: clinical epidemiology, alpha 1-antitrypsin deficiency, respiratory therapy

Fred H. Hsieh, MD
Joint Appointment with Pathobiology
216.444.3504
Specialty Interests: asthma, allergic disorders, mast cell function

Jennifer Ramsey, MD, MS
216.445.8407
Specialty Interests: critical care, general pulmonary medicine

Adriano Tonelli, MD
216.444.0812
Specialty Interest: pulmonary hypertension

Rachel Koelsch, MD
216.444.6933
Specialty Interests: pediatric and adult allergic rhinitis, asthma, food allergies, bee and wasp sting allergy, eczema, medication allergies, hives

Deborah Rathz, MD, PhD
Joint Appointment with Emergency Medicine
216.445.8318
Specialty Interest: critical care

Joe Zein, MD
216.444.2318
Specialty Interests: critical care, general pulmonary medicine

Lily C. Pies, MD
216.444.6933
Specialty Interests: allergic rhinitis, asthma, drug allergies, latex allergy, medical education

Anita Reddy, MD
216.444.4506
Specialty Interests: critical care, acute lung injury, interstitial lung disease

Sheila Armogida, MD
330.287.4630
Specialty Interest: allergy

Raymond Salomone, MD
216.444.6503
Specialty Interests: critical care, general pulmonary medicine

Mark A. Aronica, MD
Joint Appointment with Pathobiology
216.444.6933
Specialty Interests: asthma, allergic disorders

Section of Allergy and Clinical Immunology

David M. Lang, MD
Head, Section of Allergy and Clinical Immunology, Director, Fellowship Program
216.445.5810
Specialty Interests: asthma, allergic disorders, sinusitis, urticaria, anaphylaxis, latex allergy, aspirin sensitivity

Cristine Radojicic, MD
216.444.6933
Specialty Interests: pediatric and adult allergic rhinitis, asthma

Sheila Armogida, MD
330.287.4630
Specialty Interest: allergy

Roxana Siles, MD
216.444.6933
Specialty Interest: allergy
PARTNERS IN OTHER DEPARTMENTS
Diagnostic Radiology
Section of Thoracic Imaging

Charles Lau, MD
Head, Section of Thoracic Imaging
216.444.1014
Specialty Interest: thoracic imaging

Ahmed El-Sherief, MD
216.445.7050
Specialty Interest: thoracic imaging

Ruffin J. Graham, MD
216.444.8756
Specialty Interests: pulmonary thromboembolism, lung cancer and thromboembolic disease

Omar Lababede, MD
216.444.9014
Specialty Interest: thoracic imaging

Tan-Lucien H. Mohammed, MD
216.444.3867
Specialty Interests: cardiopulmonary imaging/transplantation imaging, interstitial lung disease, upper airway disease

Rahul Renapurkar, MD
216.445.7050
Specialty Interest: thoracic imaging

Barbara Risius, MD
216.444.6422
Specialty Interest: thoracic radiology

Ruchi Yadav, MD
216.445.7050
Specialty Interest: thoracic imaging

Kenneth McCurry, MD
Surgical Director, Lung Transplantation Joint Appointment with Pathobiology
216.445.9030
Specialty Interests: lung and heart transplantation, ventricular assist devices, heart failure surgery, and lung and heart ischemia-reperfusion injury

Nicholas G. Smedira, MD
Surgical Director, Kaufman Center for Heart Failure
216.445.7052
Specialty Interests: lung and heart-lung transplantation; pulmonary thromboendarterectomy

Pulmonary Pathology

Carol F. Farver, MD
Director, Pulmonary Pathology
216.445.7695
Specialty Interest: pulmonary pathology

Andrea Arrossi, MD
216.444.9120
Specialty Interests: pathology of interstitial lung disease, and pleural and pulmonary tumors

David Mason, MD
216.444.8053
Specialty Interests: general thoracic surgery, lung transplantation, minimally invasive thorascopic and laparoscopic surgery, lung cancer, esophageal cancer, malignant mesothelioma

Sudish Murthy, MD, PhD
Surgical Director, Center for Major Airway Diseases
216.444.5640
Specialty Interests: esophageal, pulmonary, mediastinal, chest wall and diaphragm surgery; minimally invasive lung volume reduction surgery; lung transplant surgery

Section of General Thoracic Surgery

Charles V. Biscotti, MD
216.444.0046
Specialty Interests: cytopathology, gynecologic pathology

Sudish Murthy, MD, PhD
Surgical Director, Center for Major Airway Diseases
216.444.5640
Specialty Interests: esophageal, pulmonary, mediastinal, chest wall and diaphragm surgery; minimally invasive lung volume reduction surgery; lung transplant surgery

Daniel Raymond, MD
216.636.1623
Specialty Interests: general thoracic surgery, lung cancer

Gösta Pettersson, MD, PhD
Vice Chairman, Thoracic and Cardiovascular Surgery
216.444.2035
Specialty Interests: lung and heart-lung transplantation

Douglas Johnston, MD
216.444.5613
Specialty Interests: lung and heart transplantation

Rahul Renapurkar, MD
216.445.7050
Specialty Interest: thoracic imaging

Thomas W. Rice, MD
216.444.1921
Specialty Interests: esophageal, pulmonary, mediastinal, chest wall and diaphragm surgery; minimally invasive (laparoscopic and thorascopic) and pediatric general thoracic surgery, lung volume reduction surgery
RESPIRATORY EXCHANGE  ●  ●  ●  RESEARCH AND NEWS FOR PHYSICIANS FROM THE CLEVELAND CLINIC RESPIRATORY INSTITUTE

CONTACT US

General Patient Referral
24/7 hospital transfers or physician consults
800.553.5056

Pulmonary Appointments/Referrals
216.444.6503 or 800.223.2273, ext. 46503

Allergy Appointments/Referrals
216.444.3386 or 800.223.2273, ext. 43386

On the Web at clevelandclinic.org/pulmonary

SERVICES FOR PATIENTS

Same-day Appointments are available at 216.444.6500.

Medical Concierge
Complimentary assistance for out-of-state patients and families
800.223.2273, ext. 55580, or email medicalconcierge@ccf.org

Global Patient Services
Complimentary assistance for national and international patients and families
001.216.444.8184 or visit clevelandclinic.org/gps

SERVICES FOR PHYSICIANS

Physician Directory
View all Cleveland Clinic staff online at clevelandclinic.org/staff.

Track Your Patient's Care Online
Whether you are referring from near or far, DrConnect offers secure access to your patient's treatment progress at Cleveland Clinic. To establish a DrConnect account, visit clevelandclinic.org/drconnect or email drconnect@ccf.org.

Remote Consults
Request a remote medical second opinion from Cleveland Clinic. MyConsult is particularly valuable for patients who wish to avoid the time and expense of travel. Visit clevelandclinic.org/myconsult, email eclevelandclinic@ccf.org or call 800.223.2273, ext 43223.

Respiratory Exchange
Herbert P. Wiedemann, MD, Medical Editor
Sveta Chudy, Marketing Associate
Ann Bakuniene-Milanowski, Managing Editor
Michael Viars, Art Director/Designer

Respiratory Exchange is written for physicians and should be relied upon for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

© 2011 The Cleveland Clinic Foundation

Stay Connected to Cleveland Clinic