Bronchial Thermoplasty: Radiofrequency Energy in the Airway for Treatment of Severe Asthma

By Atul Mehta, M.D., and Serpil Erzurum, M.D.

Cleveland Clinic is participating in a clinical trial of bronchial thermoplasty, a new technique that applies radiofrequency energy to airway walls to treat moderate to severe persistent bronchial asthma in adults.

Bronchial thermoplasty is an electrocautery treatment designed to reduce the contractability of airway smooth muscle. In patients with chronic airway inflammation, an increased mass of airway smooth muscle has been shown to correlate to airway hyper-responsiveness and asthma severity. Contraction of airway smooth muscle and consequent airflow obstruction can be triggered by an allergen, irritant or psychological stress.

In this trial, bronchial thermoplasty is performed using the Alair System (Asthmatx, Inc.), which has a flexible catheter with an expanding loop at the end designed to make contact with bronchial airway walls.
Dear Colleagues,

Caring for patients with complex respiratory diseases or conditions demands the expertise of an interdisciplinary team of specialists. Cleveland Clinic’s structure, a group practice with all specialties under one roof, is particularly well suited for the practice of pulmonary medicine. This issue of Respiratory Exchange, our publication for physicians with an interest in management of pulmonary and allergic conditions, illustrates these points.

The publication highlights activities of four Cleveland Clinic areas that regularly collaborate to care for patients with respiratory disorders: Pulmonary, Allergy & Critical Care Medicine; Thoracic & Cardiovascular Surgery; Thoracic Imaging; and Pulmonary Pathology.

In this issue of Respiratory Exchange, you will find articles indicative of the diversity of our work – including diagnostic and therapeutic innovations and advances in asthma, transplant and cancer.

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

We hope you find a few minutes in your busy day to review Respiratory Exchange, and that you find it valuable and informative.

Sincerely,

Herbert P. Wiedemann, M.D.
Chairman, Department of Pulmonary, Allergy & Critical Care Medicine

Thomas W. Rice, M.D.
Head, Section of General Thoracic Surgery; Department of Thoracic & Cardiovascular Surgery

Carol F. Farver, M.D.
Director, Pulmonary Pathology; Division of Pathology & Laboratory Medicine

Moulay Meziane, M.D.
Head, Section of Thoracic Imaging; Division of Radiology

Online Access to Your Patient’s Treatment Progress

Whether you are referring from near or far, our new eCleveland Clinic service, Dr.Connect, can streamline communication from Cleveland Clinic physicians to your office. This new online tool offers you secure access to your patient’s treatment progress at Cleveland Clinic. With one-click convenience, you can track your patient’s care using the secure Dr.Connect Web site. To establish a Dr.Connect account, visit eeclevelandclinic.org or e-mail drconnect@ccf.org.

Outcomes Data Available

The latest outcomes data from Cleveland Clinic departments involved in the treatment of respiratory diseases are available. Our outcomes booklet offers summary reviews of medical and surgical trends and approaches. Charts, graphs and data illustrate the scope and volume of procedures performed in our departments each year. To view outcomes booklets for respiratory diseases as well as many other Cleveland Clinic medical and surgical disciplines, visit clevelandclinic.org/quality.

CME Calendar

Physicians are welcome to attend the following upcoming symposia:

**Chest Malignancies** | Sept. 16
InterContinental Hotel & MBNA Conference Center
Cleveland, OH

**Second Cardiothoracic CT Summit** | Oct. 27
Naples Grand Resort & Club
Naples, FL

**Pulmonary Hypertension Summit** | Nov. 17-18
Intercontinental Hotel & MBNA Conference Center
Cleveland, OH

For more information about these events, call Cleveland Clinic Department of Continuing Education at 216.444.5696 or 800.762.8173 or visit clevelandclinicmeded.com.
After reaching the targeted airway, the loop is expanded and 10 seconds of radiofrequency energy is delivered. The loop is then collapsed and moved slightly to treat the adjacent section of the airway wall. The process is repeated a total of 60 to 70 times to treat the targeted segment of airway. Treatments take 30 minutes and can be performed under local anesthesia. Generally, a total of three treatments are performed, each three weeks apart.

Canadian trials have shown significant improvements in airflow and symptom-free days in participants. The only reported direct side effects are mucus formation and occasional blanching of the airway causing visible white streaks. Treatments have improved quality of life for patients, and three years post-treatment, there has been no evidence of loss of effectiveness.

To discuss enrolling a patient, please contact Rhonda Bognar, RRT, Research Coordinator for the AIR study, at 16.445.1756.

Dr. Atul Mehta is Medical Director of Lung Transplantation, Head of the Bronchology Section, and Vice Chairman of the Pulmonary, Allergy and Critical Care Medicine Department. He can be reached at 216.444.2911 or at mehtaa1@ccf.org.

Dr. Serpil Erzurum is Chairman of Pathobiology and on staff in Pulmonary, Allergy and Critical Care Medicine. She can be reached at 216.445.5764 or erzurus@ccf.org.
New Cleveland Clinic Asthma Center Focuses on Patient Care and Research

By Serpil Erzurum, M.D., and David Lang, M.D.

Asthma, already one of the most common chronic diseases in the world, has in recent years become more prevalent and more severe. Several government agencies are charged with surveillance of asthma, including the National Institute of Health’s National Asthma Education and Prevention Program (NAEPP), Department of Health and Human Services (Healthy People 2010), as well as the Centers for Disease Control.

Their surveys reveal that more than 20 million American adults suffer from asthma (NAEPP 2002), and nearly half of asthma sufferers do not have their asthma under control. School surveys suggest that up to 25 percent of school-aged children have asthma and it is the leading cause of school absenteeism. Asthma is increasing in all age groups but growing fastest among children, with incidence among the very young almost doubling since 1980.

Cleveland Clinic has formed a new Asthma Center to advance our understanding of asthma through laboratory and clinical investigation, and to provide optimal personalized and comprehensive asthma care that is easily accessible to patients.

**Asthma Center Services**

Our multidisciplinary center offers in-depth diagnostic and treatment services for adults and children with asthma. Evaluation at the Asthma Center includes a complete range of allergy, immunology, pulmonary physiology, and interventional evaluations and consultations. Care is integrated with medical and surgical specialists who help manage conditions associated with asthma. Our familiarity with unusual syndromes allows us to identify and address uncommon or unsuspected triggers of asthma. For patients whose asthma is not optimally controlled, we offer participation in unique investigative studies. These studies explore disease pathogenesis and apply new diagnostics, biologic-based medications and treatments.

**Translation of Bench and Bedside Research to Patient Care**

Our center combines basic science, clinical research and clinical practices with the goal of improving quality of life for individuals with asthma.

Researchers are using proteomic technologies to define new noninvasive biomarkers of airway inflammation that will help us design specific treatment regimens. Several noninvasive tests, including exhaled breath analyses and urinary oxidative biomarkers, are being tested. Based on recent evidence that assessment of noninvasive biomarkers leads to superior management of asthma, biomarkers such as exhaled nitric oxide (NO) are also available for use in the care of patients (figure 1).

Our investigator-initiated and multicenter NIH studies are identifying the genetic and environmental factors related to severe asthma. Recent laboratory studies here describe the local lung microenvironment required for the survival and maturation of mast cells, a pivotal cell in the mechanisms of asthmatic inflammation (figure 2). Epidemiologic studies of the patterns of urban asthma morbidity and mortality are defining characteristics of populations at risk for sudden asthma death.

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Figure 1

Collaborative studies here have contributed to the understanding and development of exhaled nitric oxide (NO) in the evaluation of lower airway inflammation in asthma. Oxidative and nitrosative events in the asthmatic lung contribute to injury and inflammation. Persistently increased oxidants and NO in asthma lead to reactive nitrogen species formation, and subsequent oxidation and nitration of proteins, which cause alterations in protein function that are biologically relevant to airway injury/inflammation. Eosinophil peroxidase and myeloperoxidase, which are leukocyte-derived enzymes, amplify oxidative events, and are another enzymatic source of NO-derived oxidants and nitrotyrosine formation in asthma. Concomitant with increased generation of oxidative and nitrosative molecules in asthma, loss of protective antioxidant defense, specifically superoxide dismutase (SOD), contributes to the overall toxic environment of the asthmatic airway.

Proteomic studies at our center reveal that increased NO in asthma leads to NO-derived protein modifications and inflammation as shown on 2-D electrophoretic analyses of asthma samples. Quantitative modifications of proteins in the airway, or in serum and urine, also are being developed as biomarkers of airway inflammation by the Hazen laboratory.

Adapted with permission from the Massachusetts Medical Society. Erzurum, SC. Inhibition of Tumor Necrosis Factor α for Refractory Asthma. N Engl J Med. 2006;354:754-757. Copyright © 2006 Massachusetts Medical Society. All rights reserved.


As a participant in the NIH-sponsored Severe Asthma Research Program (SARP), our center is enrolling patients in studies directed toward uncovering unique biochemical phenotypes of the severe asthma patient. We are also enrolling patients in outcome studies evaluating the clinical effectiveness and long-term safety of anti-IgE therapy, inhibitors of tumor necrosis factor alpha and bronchial thermoplasty [see cover article].

For questions about the Asthma Center or to discuss a referral to a study, please contact Marcelle Baaklini, Program Manager for Lung Biology Research, at 216.445.1756 or baaklim@ccf.org.

**Dr. Serpil Erzurum**, Chairman of Pathobiology and on staff in Pulmonary, Allergy and Critical Care Medicine, leads the Pathobiology of Asthma program project. Program members include: Mark Aronica, M.D., Suzy Comhair, M.D., Raed Dweik, M.D., Fred Hsieh, M.D., and David Lang, M.D., from Pulmonary, Allergy and Critical Care Medicine, as well as Stanley Hazen, M.D., Ph.D., Cell Biology; Vincent Hascall, Ph.D., Biomedical Engineering; and Jaharul Haque, Ph.D., Cancer Biology. Dr. Erzurum can be reached at 216.445.5764 or erzurus@ccf.org.

**Asthma Program Project**

Our program project grant, Pathobiology of Asthma, sponsored by the NIH, includes basic and clinical science research projects and fundamental cores to support the study of the causes of asthmatic inflammation. The program aims to identify what initiates and intensifies asthmatic inflammation. We are working on post-translational modifications as mechanisms of injury to lung proteins, and investigating functional consequences of protein modifications in amplification of inflammation and how these protein modifications, as assessed by proteomic technologies, may be used as biosignatures of asthma (figure 1).

Other researchers are identifying the non-cellular structural components of the airway tissues that play an active and instructive role in calling inflammatory cells into the airway (figure 2). The Biological Repository and Database core banks samples from asthmatic patients for the program’s proteomic and genetic analyses, while the Clinical Studies core performs aeroallergen and bronchoprovocation challenge to assess asthma triggers and tests biomarkers for asthma management including exhaled nitric oxide and breath condensates. The ultimate goal of the program is to develop ways to better care for asthmatic patients.

**Figure 2**

**Left panel:** Studies performed in Dr. Hsieh’s laboratory (Proc Natl Acad Sci USA. 2005;102(40):14380-5) suggest that airway epithelium provides a critical microenvironment to direct mucosal mast cell development, and participates in modulating inflammatory cell function in airway inflammatory disorders such as asthma. This image shows mast cells that have been differentiated in the presence of human airway epithelium (scanning electron micrograph, 1500X).

**Right panel:** Pioneering work on how abnormal extracellular matrix accumulates in the airway and its participation in the chronic inflammation of asthma is ongoing in Dr. Aronica’s and Dr. Hascall’s laboratories. Sections from the lung of an asthmatic patient stained for extracellular matrix component hyaluronan (green) reveal that there is abnormal hyaluronan matrix around the airway and the adjacent arteriole and that the hyaluronan is closely associated with inflammatory cells.

**PUBLICATIONS**


FACTT Results: Conservative Fluid Management is Superior
Herbert P. Wiedemann, M.D.

The Acute Respiratory Distress Syndrome (ARDS) clinical trials network (ARDSNet) of the National Heart, Lung, and Blood Institute recently published the results of FACTT (fluids and catheter treatment trial).

STUDY DESIGN
FACTT utilized a factorial trial design in which patients with acute lung injury/acute respiratory distress syndrome underwent two randomizations: 1) a conservative vs. liberal strategy of fluid management, and 2) management with a pulmonary artery catheter vs. central venous catheter. Enrollment of 1,000 patients was completed in October 2005. The primary endpoint was death at 60 days. Secondary endpoints included the number of ventilator-free days and organ failure-free days and measures of lung physiology.

CONSERVATIVE FLUID MANAGEMENT SUPPORTED
The results support the use of a conservative strategy of fluid management in patients with acute lung injury. Although there was no significant difference in the primary outcome of 60-day mortality (5.5 percent in the conservative strategy group and 8.4 percent in the liberal strategy group; P=0.30), the conservative strategy of fluid management improved lung function (including better lung injury scores and oxygenation indices) and increased the number of days free of mechanical ventilation (14.6 vs. 12.1; P<0.001) and intensive care (13.4 vs. 11.2; P<0.001) from day one to day 28. There was no difference in the incidence or prevalence of shock, the number of renal failure-free days or the need for dialysis.

PULMONARY ARtery CATHERET Not Superior
In the other half of this study, pulmonary artery catheter-directed therapy did not improve survival, ventilator-free days or organ function, but was associated with more complications than central venous catheter-guided therapy.

These results suggest that the pulmonary artery catheter should not be used routinely for the management of acute lung injury, but do not preclude the possibility that pulmonary artery catheterization would be beneficial when used in selected subgroups of patients or in conjunction with a hemodynamic management strategy different from the one tested in this trial.


WHAT NEXT?
The ARDSNet will soon embark on new studies of therapeutic approaches in ARDS. Although the protocols are still under development, potential investigations include the use of inhaled beta agonists (for enhanced clearance of pulmonary edema fluid, etc.) and various approaches to enteral nutrition (early vs. late feeding, use of antioxidant components, etc.). Enrollment is expected to begin in late 2006 at the ARDSNet centers, including Cleveland Clinic.

For further information, please visit the NIH’s ARDSNet Web site (ardsnet.org) or contact one of Cleveland Clinic’s ARDSNet coordinators (John Komara, Tony Isabella or Michelle Ferrari) at 216.445.1939.

Herbert P. Wiedemann, M.D., Chairman of the Department of Pulmonary, Allergy and Critical Care Medicine at Cleveland Clinic, served as FACTT Co-Chair.
New Horizons in Thoracic Imaging

Moulay Meziane, M.D.

In the realm of lung cancer detection and treatment, innovative thoracic imaging is the key. Advances in thoracic imaging are enhancing our ability to diagnose lung cancer, as well as to watch its behavior to determine prognosis.

New generation CT scanners and their software allow three- and four-dimensional rendering and evaluation of pulmonary lesions. With the help of tools such as computer-aided diagnosis (CAD) software, very small, easily missed potentially cancerous lesions can be detected. Other systems can sensitively and accurately measure their volume and growth over time. Additional programs will use CT scan images to create a virtual bronchoscopy to guide pulmonologists, making biopsies quicker, safer and more accurate, and leading to more prompt diagnosis and treatment of peripheral parenchymal and mediastinal lesions.

In contrast to CT scans that detect the morphology of early cancers, PET scans allow us to detect the metabolic activity of disease for a more accurate diagnosis of malignancies. CT and PET scans can be performed individually or in combination. Resulting PET/CT fusion images show both morphology and metabolic activity of diseases in the same setting.

The PET/CT can determine whether a pulmonary or a lung lesion or lymph node is active or not, which is important for diagnosis, staging and guiding biopsies. It also allows us to gauge response to treatment and detect residual or recurrent disease. This is commonly used for oncology patients. Cleveland Clinic has two PET/CT units.

Looking to the future, Cleveland Clinic is planning a five-year study to assess the impact of CAD technology in thoracic imaging for the diagnosis of lung cancer and its impact on the diseases’ long-term morbidity and mortality.

Dr. Moulay Meziane is Head of the Section of Thoracic Imaging. He can be reached at 216.444.0282 or at mezianm@ccf.org.
Respiratory Exchange

Cleveland Clinic Lung Summit 2007

Save the date for the third annual Lung Summit, April 12-13, 2007, at the InterContinental Hotel & MBNA Conference Center in Cleveland. This year’s topics will include asthma and interventional bronchoscopy.

At the highly successful 2006 summit, “Innovations in Pulmonary and Sleep Medicine,” 26 guest speakers, including two international speakers, plus 11 Cleveland Clinic faculty presented on wide-ranging and relevant topics in the areas of bronchoscopy, lung cancer, sleep apnea and thoracic imaging. Among the innovations and research discussed: VRIXP technology in diseases of the chest, auto fluorescence video bronchoscopy, wireless transmission of polysomnography, and new perspectives in the diagnosis of pulmonary embolism.

Keep abreast of developments in pulmonary, allergy and critical care medicine and general thoracic surgery by attending next year’s conference. For more information about Lung Summit 2007, call 216.444.5696 or 800.762.8173, or visit clevelandclinicmeded.com.

Cleveland Clinic Lung & Heart/Lung Transplantation Fast Facts

Initiation date: 1990
First Pediatric Lung Transplant: Sept. 8, 1991
UNOS approval: March 3, 1993
Medicare approval: Oct. 22, 1997

As of Dec. 31, 2005, 490 lung transplants have been performed at Cleveland Clinic:

- Pediatric 8 (1.6 percent)
- Adult 482 (98.4 percent)

Phone number: 216.444.8282

Lung, Heart/Lung Transplant Program is National Leader

By Atul C. Mehta, M.D., Marie Budev, D.O., M.P.H., and Gosta Pettersson, M.D., Ph.D.

2005 was a record-breaking year for Cleveland Clinic’s Lung and Heart/Lung Transplantation Program. The program noted an increase in the number of procedures compared to 2004. With 65 adult lung transplants performed in 2005, Cleveland Clinic remains a leading lung transplantation center of excellence in the United States.

The average waiting time for transplantation in our program has fallen during the last year and remains short, with a median waiting time of 52 days during 2005. Initiation of the new national lung allocation system in May 2005 has continued to maintain our short waiting time.

Our program has gained a national reputation for accepting challenging and complex transplantation cases, which has led to a significant increase in our referral rate to more than 550 patients in 2005, a 10 percent increase since 2004.

EXPERTISE

Our experience in managing difficult, high-risk patients gives our team, including our surgeons, some of the most valuable surgical experiences in the world. Despite their high level of acuity, patients who have undergone lung transplantation at Cleveland Clinic have an 86 percent survival rate after one year, compared to 75 percent nationally.

Our long-term outcomes continue to improve as well, with 75 percent and 69 percent for two-year and three-year survival rates, respectively. Our 30-day mortality associated with lung transplantation remains low despite the high complexity cases the center manages.

NATIONAL REFERRAL CENTER

We are one of the nation’s premier referral centers for lung transplantation, with referrals coming from all regions of the United States. While carefully expanding our donor acceptance criteria, we also actively participate in donor management and provide further education to our statewide organ procurement agencies to maximize donor utilization and improve the donor lung quality.

Patients listed for lung transplantation at Cleveland Clinic are likely to receive a transplant quickly. In the last three years, there has not been a death on our waiting list.

We have a short hospital length of stay in the majority of cases. We are able to offer our patients and families affordable on-campus residence-like rooms in the transplant hospitality housing unit located within our Guesthouse. This allows for shorter hospital stays and easy access for outpatient treatment in pulmonary clinics, pre- and postoperatively.

Quality assurance and improvement are central to our program, and we remain committed to a statewide quality assurance program by actively participating in the Ohio Solid Organ Consortium. In addition, we provide educational programs and host visits from other lung transplant programs within the state, as well as educational programs for donor management.

To refer a patient for consideration for lung transplant or heart/lung transplant, please call one of our transplant coordinators at 216.444.8282, option 3.
At Cleveland Clinic, COPD is the primary diagnosis for patients transplanted in 2005.

Electromagnetic Navigation Diagnostic Bronchoscopy: A Prospective Study

Sixty subjects were enrolled at Cleveland Clinic in the largest trial to date of an innovative GPS (global positioning system) technology used for diagnostic bronchoscopy.

The pilot study was conducted to determine the ability and safety of electromagnetic navigation bronchoscopy to sample both peripheral lung lesions and mediastinal lymph nodes with standard bronchoscopic instruments. Electromagnetic navigation bronchoscopy is a novel method to increase diagnostic yield of peripheral and mediastinal lung lesions.

Results from this single-center prospective study of the superDimension/Bronchus system (Herzliya, Israel) have been accepted for publication in the American Journal of Respiratory and Critical Care Medicine. Authors are Drs. Thomas R. Gildea, Peter J. Mazzone, Demet Karnak, Moulay Meziane and Atul C. Mehta.
Cleveland Clinic currently is testing the use of new Self-Expanding Metal Stents (SEMS) for the treatment of airway dehiscence following lung transplantation. Throughout the greater half of Cleveland Clinic’s 16-year lung transplantation program there was no treatment for airway dehiscence, until about seven years ago when Cleveland Clinic pulmonologists came up with the idea of temporarily using airway stents to promote healing of anastomotic dehiscence.

Airway dehiscence is a disruption of the juncture where the donor lung is connected to the recipient’s bronchial tube. Dehiscence generally occurs within three to six weeks after transplantation. The virtue of using airway stents was not recognized until we began using them temporarily to promote healing. Before then, there was no good treatment for airway dehiscence. It often led to death in patients with single lung transplantation. When airway dehiscence occurs, a stent is inserted in the airway and remains in place for six to eight weeks, offering added support to the airway while it promotes healing. Once sufficient healing has occurred, the stent is removed.

The SEMS being used at Cleveland Clinic are made of the metal alloy Nitinol, named for the Nickel-Titanium Naval Ordinance Laboratory where it was first developed by the U.S. government. Nitinol SEMS are flexible, lightweight and sturdy. They maintain their shape and function well within an internal body temperature. The thin, wire mesh tubes are collapsed inside a sheath for easier deployment. Once the SEMS are in place and deployed, they self-expand to the necessary extent, to snugly fit and support the patient’s airway.

In the current clinical trials, the Nitinol SEMS are usually implanted during an outpatient procedure, under local anesthesia, in a conscious-sedation environment. The stent later is removed during another outpatient procedure. The temporary implantation of SEMS for the treatment of airway dehiscence is the only treatment available for lung transplant patients who develop this severe complication.

Nationwide, 1,500 to 1,600 lung transplants are performed each year. Cleveland Clinic became the nation’s leading lung transplantation center in 2004, after performing 64 lung transplants that year. Of those lung transplant patients, approximately 15 percent develop airway complications, including dehiscence.

While the Nitinol SEMS are manufactured either left uncovered or covered with a layer of impermeable substance, such as silicone or polyurethane, it is the uncovered SEMS that are used for the treatment of airway dehiscence. The uncovered SEMS allow for drainage of secretions and pus, thus promoting safer, better healing, whereas the covered stents can lead to biofilm formation and consequently infection. Covered SEMS do have their place in pulmonary treatment, primarily to prevent airway obstruction caused by tumors or growths that might otherwise obstruct the airway. In those cases, the covering prevents the growth from attaching itself to the stent, thereby avoiding greater, more complicated obstruction.

While there is no ideal stent, SEMS should only be used in benign conditions after exhausting other options. However, when SEMS are the only treatment option, as in the treatment of airway dehiscence, they can be highly successful and save lives.

**Improving Lung-Transplant Survival**

More than 500 lung transplants have been performed at Cleveland Clinic since the beginning of its lung transplantation program. The five-year survival rate during 1990 to 1999 was 41 percent, but that rate increased to 49 percent in the following five years between 2000 and 2005, an 8 percent improvement. Advancing the treatment of post-surgical complications, such as airway dehiscence, improves lung-transplant survival.
Pulmonary Fibrosis and Gough Sections: Using Old Techniques to Answer New Questions

Carol Farver, M.D.

The study of gross pathology is paramount to understanding diffuse parenchymal lung disease. Historically, a variety of techniques have been used to correlate the clinical disease with the gross pathology. One such technique is Gough sectioning. Developed in the early 1950s, it is a method to thin section entire organs, mount them on paper and quantitate the gross findings. Early studies focused on lungs affected by emphysema. We have recently begun to use this technique to study fibrosing lung diseases, specifically examining lungs resected at the time of transplantation from patients with idiopathic pulmonary fibrosis (figure 1).

The pathologic pattern of injury found in lungs from patients with idiopathic pulmonary fibrosis is referred to as usual interstitial pneumonia (UIP), named as such because it is the “usual” cause of idiopathic pulmonary fibrosis. The injury in UIP has a characteristic distribution, occurring first in the subpleural and paraseptal regions in the bases of the lung and gradually progressing to involve the more superior and proximal areas. The sequence of events that results in this fibrosis in UIP lungs occurs throughout the lungs at different foci and at different times, producing a pathologic picture of heterogeneity (figure 2A). This sequence starts with injury to the epithelium, resulting in an inflammatory response that is followed by foci of organizing fibrosis, referred to as fibroblastic foci (figure 2B), and, finally, deposition of collagen, resulting in irreversible fibrosis. These fibroblastic foci are characteristic to UIP and, therefore, have been the focus of much recent research.

One area of research focuses on defining the 3-D structure of these fibroblastic foci and determining the physical properties of the peripheral lung that incite their development. Correlating computer-generated images of these foci with the Gough sections will help us understand their 3-D morphology and distribution within the lung. Using immunohistochemistry of these full-mounted sections, we will study inflammatory cytokines and pro-fibrotic mediators in these lungs and correlate these cellular events with the morphology. We hope these studies further elucidate the cellular events of this devastating disease and provide clues to more effective therapies.

Dr. Carol Farver, departments of Anatomic Pathology, and Pulmonary, Allergy and Critical Care Medicine, can be reached at 216.445.7695 or at farverc@ccf.org. The team involved in this project includes biomedical engineer and physician Jeffrey Chapman, M.D., Pulmonary, Allergy and Critical Care Medicine; and Ms. Gwen Goss, Anatomic Pathology.

Figure 1 (above) Gough, whole-mount section of lung with usual interstitial pneumonia (UIP) showing fibrosis and early honeycomb changes, predominantly in the bases (elastic stain).

Figure 2 (left) Microscopic section of usual interstitial pneumonia revealing the heterogeneity of lung injury (A), and fibroblastic foci [see arrow] (B), characteristic of this pathology (hematoxylin and eosin stain).
Advancements in Targeted Therapy for Lung Cancer

Cleveland Clinic physicians are exploring innovative targeted therapies for lung cancer including smart drugs, stereotaxis and new surgical techniques. Their efforts are crucial to battling lung cancer, since no effective screening tool exists, and 76 percent of non-squamous cell lung cancer is not diagnosed until stage III or IV.

Lung cancer is a formidable foe because the disease distorts the lung’s normal grid-like vascular pattern and low cell permeability into disorganized, highly kinked, and thus, highly permeable tumor vasculature. In addition, the lung’s continuous motion makes it difficult to target and narrow the treatment field.

SMART DRUGS UNDER INVESTIGATION

By Tarek Mekhail, M.D., M.Sc.

Clinical trials of the smart drug, bevacizumab (Avastin), originally approved by the FDA for advanced colon cancer, are under way at Cleveland Clinic. Bevacizumab is an antibody that binds to the vascular endothelial growth factor, leading to interruption of blood vessel growth in tumors.

Preliminary results from clinical trials of bevacizumab in combination with chemotherapy have shown improvement and increased survival in some lung cancer patients. We also are exploring adding bevacizumab earlier, combining it with different targeted agents, or targeting different receptors in cancer cells, and other drugs with similar inhibiting effects are being investigated.

These new oral agents do not have side effects typical of chemotherapy, allowing the patient to live a more normal or near-normal life.

Dr. Tarek Mekhail is Director of the Lung Cancer Oncology Program at the Cleveland Clinic Taussig Cancer Center. He can be reached at 216.445.1785 or at mekhait@ccf.org.

Smart Drugs

Smart drugs are targeted drugs that have the ability to seek out specific receptors that have been identified in cancer cells, bind to them and interfere with their function in some specific manner. Although smart drugs have been around since the 1970s – notably, tamoxifen, which binds to the estrogen receptor protein, blocking estrogen to stop breast cancer growth – bevacizumab is the first anti-angiogenic smart drug.
STEREOTAXIS FOR LUNG CANCER HOLDS PROMISE
By Gregory Videtic, M.D., CM, FRCPC

Stereotaxis is currently being used for medically inoperable patients with early stage lung cancer with no lymph node involvement. This is a fragile population including patients with compromised respiratory systems due to emphysema, heart disease or lung transplantation.

Movement of the lung and tumor during respiration makes it difficult for radiation oncologists to restrict the size of the treatment field and ensure minimal treatment of normal lung tissue during conventional radiation therapy. Also, the total dose deliverable to the cancer can be limited by the risk of damage to surrounding healthy tissue.

Stereotaxis is based on the same principle used in Gamma Knife brain surgery. Multiple rays at differing angles, each weak on its own, are directed at a single pinpoint target where their combined energy is exceptionally powerful.

The Cancer Center’s Novalis system produces stereotactic radiation strong enough to accomplish in only three to five treatments over the course of about one week what would take standard radiation about seven to ten weeks of treatments. Novalis provides superior accuracy in establishing the target frame by matching CT scan coordinates with infrared markers placed on the patient’s skin for reference, creating a virtual tumor image similar to time-lapse photography. At the same time, techniques are used to limit breathing motion during treatment, enhancing accuracy. In that regard, Novalis is designed to give real-time confirmation of the patient’s tumor position. It gives a highly reliable and reproducible “aim,” confirming the target was accurately hit and radiation was delivered.

In the 45 lung cancer patients treated with stereotaxis at Cleveland Clinic over the last two years, mortality is zero.

EARLIER DETECTION IMPROVES PROGNOSIS
By Sudish Murthy, M.D., Ph.D.

In the past, technological limitations and other obstacles made it difficult to detect pulmonary nodules or small masses and to differentiate those that were benign from early stage lung cancer. Most pulmonary nodules are benign, and only 1 to 2 percent are cancerous.

Fortunately, high-resolution guided imagery and bronchoscopy have changed this, allowing us to detect such nodules more successfully in early stages. Early stage lung cancers are far easier to treat surgically; in turn, improving the prognosis.

When early stage cancerous nodules are detected in a patient with no other major health problems, minimally invasive surgery may be possible. Even for patients who are ineligible for surgery, other options exist: radiation surgery, high-frequency radioablation, and conventional radiation.

For patients with locally advanced lung cancer (stage II or stage III), Cleveland Clinic provides a multimodality treatment program that can increase the survival rate by 30 percent to 40 percent. Over three months, patients receive combination chemotherapy and radiation, followed by surgery as treatment.

While such combination therapy is aggressive, it appears to be the best therapy for locally advanced lung cancer. Patient selection is critical; not all patients are able to tolerate this aggressive multimodality therapy program.

Dr. Sudish Murthy is a Cleveland Clinic thoracic surgeon.
He can be reached at 216.444.5640 or murthys1@ccf.org.

Dr. Gregory Videtic is a Taussig Cancer Center radiation oncologist.
He can be reached at 216.444.9797 or at videtig@ccf.org.
Respiratory Diseases | Staff Directory 2006

Department of Pulmonary, Allergy and Critical Care Medicine

Herbert P. Wiedemann, M.D.
Chairman, Department of Pulmonary, Allergy and Critical Care Medicine
216.444.8335
Specialty Interests: intensive care (including adult respiratory distress syndrome and sepsis), general pulmonary medicine, exercise testing (dysnea evaluation)

Raed A. Dweik, M.D.
Director, Pulmonary Vascular Disease Program; Joint Appointment with Pathobiology
216.445.5763
Specialty Interests: asthma, pulmonary hypertension, chronic beryllium disease, critical care, bronchoscopy, nitric oxide in lung physiology and disease, exhaled markers in lung disease

Loutfi Aboussouan, M.D.
216.839.3820
Specialty Interests: general pulmonary medicine, neuromuscular diseases, sleep medicine, long-term ventilator care

Muzaffar Ahmad, M.D.
216.444.6506
Specialty Interests: pulmonary function lab, diagnostic techniques including fiberoptic bronchoscopy, bronchial asthma, lung cancer

Marie Budev, D.O., M.P.H.
Associate Medical Director, Lung Transplantation
216.444.3194
Specialty Interests: lung transplantation, pulmonary hypertension, gender specific pulmonary issues

Jeffrey T. Chapman, M.D.
Director, Interstitial Lung Disease Program
216.444.4222
Specialty Interests: interstitial lung disease, pulmonary hypertension, lung transplantation

Daniel Culver, D.O.
Director, Sarcoidosis Program
216.444.6508
Specialty Interests: sarcoidosis, interstitial lung disease, hypersensitivity pneumonitis

Rand A. Dweik, M.D.
Director, Pulmonary Vascular Disease Program; Joint Appointment with Pathobiology
216.445.5763
Specialty Interests: asthma, pulmonary hypertension, chronic beryllium disease, critical care, bronchoscopy, nitric oxide in lung physiology and disease, exhaled markers in lung disease

Serpil C. Erzurum, M.D.
Chairman, Department of Pathobiology, Lerner Research Institute; Director, Cleveland Clinic General Clinical Research Center; Co-Director Asthma Center
216.445.5764
Specialty Interests: asthma, pulmonary vascular disease, respiratory physiology, lung cancer

Thomas R. Gildea, M.D.
Co-Director, Center for Major Airway Diseases
216.444.6490
Specialty Interests: pulmonary hypertension, interventional bronchology, lung transplantation, critical care

Joseph A. Golish, M.D.
Head, Section of Sleep Medicine
216.839.3820
Specialty Interests: sleep apnea, hypersomnia, sleep disorders, pulmonary disease and sleep, asthma, lower respiratory infection

David Holden, M.D.
216.986.4000
Specialty Interest: general pulmonary medicine

Constance A. Jennings, M.D.
Joint Appointment with Lung Transplantation
216.445.4184
Specialty Interests: pulmonary hypertension, pulmonary thromboembolism, interstitial lung disease, advanced lung disease

Michael Machuzak, M.D.
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

Peter Mazzzone, M.D., M.P.H., FRCP, FCCP
Director, Lung Cancer Program
Director, Pulmonary and Critical Care Fellowship Program
216.445.4812
Specialty Interests: lung cancer, intensive care, physician education

Atul C. Mehta, M.D.
Vice Chairman, Department of Pulmonary, Allergy and Critical Care Medicine; Medical Director, Lung Transplantation; Head, Section of Bronchology
216.444.2911
Specialty Interests: lung transplantation, lung volume reduction surgery, endobronchial and bronchoscopic procedures and interventions, transtracheal oxygen therapy, alpha 1-antitrypsin deficiency

Omar A. Minai, M.D.
216.445.2610
Specialty Interests: pulmonary hypertension, interstitial lung diseases, lung cancer, COPD, sleep apnea

Thomas Olbrych, M.D.
216.444.2200
Specialty Interests: general pulmonary medicine, cystic fibrosis

Beverly V. O’Neill, M.D.
216.839.3820
Specialty Interests: general pulmonary medicine, long-term ventilator patients

Joseph G. Parambil, M.D.
216.444.7567
Specialty Interests: interstitial lung disease, pulmonary hypertension, general pulmonary medicine
James K. Stoller, M.D., M.S.
Head, Section of Respiratory Therapy; Joint Appointment with Medical Division Office - Vice Chairman
216.444.1960
Specialty Interests: bronchoscopy, clinical epidemiology, alpha-1-antitrypsin deficiency, respiratory therapy

Moulay Meziane, M.D.
Head, Section of Thoracic Imaging
216.444.0282
Specialty Interests: thoracic radiology, CT, transsternal chest biopsies, occupational lung diseases, lung cancer

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

Jeffrey P. Kanne, M.D.
216.444.3158
Specialty Interests: hematopoietic stem cell transplantation, interstitial lung disease, lung transplantation, occupational lung diseases, congenital disorders of the heart and lungs

Omar Lababede, M.D.
216.444.9014
Specialty Interest: thoracic imaging

Tan-Lucien H. Mohammed, M.D., FCCP
216.444.3867
Specialty Interests: cardiopulmonary imaging – transplantation imaging, interstitial lung disease, upper airway disease

Barbara Risius, M.D.
216.444.6422
Specialty Interest: thoracic radiology

Department of Pulmonary Pathology

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

Department of Thoracic and Cardiovascular Surgery

Gosta Pettersson, M.D., Ph.D.
Surgical Director, Lung Transplantation
216.444.2035
Specialty Interests: lung and heart-lung transplantation

Nicholas G. Smedira, M.D.
Surgical Director, Heart Transplantation and Mechanical Circulatory Support
216.445.7052
Specialty Interests: lung and heart-lung transplantation; pulmonary thromboendarterectomy

Section of General Thoracic Surgery

Thomas W. Rice, M.D.
Head, Section of General Thoracic Surgery
216.444.1921
Specialty Interests: esophageal, pulmonary, mediastinal, chest wall and diaphragm surgery, minimally invasive (laparoscopic and thoracoscopic) and pediatric general thoracic surgery, lung volume reduction surgery

David Mason, M.D.
216.444.4053
Specialty Interests: general thoracic surgery, lung transplantation, minimally invasive thoracoscopic and laparoscopic surgery, lung cancer, esophageal cancer, malignant mesothelioma

Sudish Murthy, M.D., Ph.D.
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 Allergy and Clinical Immunology

David M. Lang, M.D.
Head, Section of Allergy & Clinical Immunology
216.445.5810
Specialty Interests: asthma, allergic disorders, sinusitis, urticaria, anaphylaxis, latex allergy, aspirin sensitivity

Mark A. Aronica, M.D.
Joint Appointment with Pathobiology Assistant Professor, Cleveland Clinic Lerner College of Medicine
216.444.6933
Specialty Interests: asthma, allergic disorders

Sandra Hong, M.D.
440.878.3263
Specialty Interests: allergy, asthma

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

Lily C. Pien, M.D.
216.444.6933
Specialty Interests: allergic rhinitis, asthma, drug allergies, latex allergy, medical education

Cristine Radojicic, M.D.
216.444.6933
Specialty Interests: pediatric and adult allergic rhinitis, asthma
Cleveland Clinic Receives $1.25 Million NIH Grant for Asthma Study

Cleveland Clinic researchers have received a $1.25 million five-year NIH R01 grant to study asthma at the molecular level. Inflammation in asthma leads to the development of abnormal extracellular matrix (ECM), which in turn plays an important role in the development and maintenance of inflammatory cells, leading to chronic inflammation and airway dysfunction. However, the role of specific matrix components, mechanisms by which they function and how these changes relate to asthma, are still poorly understood. Our study, “Extracellular matrix: synthesis and turnover in asthma,” is designed to shed light on these issues.

**Long-term goals of this study are to:**

- Define mechanisms that regulate the synthesis, degradation and organization of the ECM within the lung
- Determine how these matrix components affect inflammation
- Determine their effects on lung structure and function

Mark A. Aronica, M.D., principal investigator, is associate staff in the Pulmonary, Allergy and Critical Care Medicine, and Pathobiology departments. Dr. Aronica’s research team includes Vince Hascall, Ph.D., Csaba Fulop, Ph.D., and Carole de la Motte, Ph.D. Dr. Aronica can be reached at 216.444.6945 or aronicm@ccf.org.

Cleveland Clinic Ranked #3 in Nation

Cleveland Clinic is ranked the third top hospital in the country, according to the latest U.S. News & World Report’s annual survey of “America’s Best Hospitals.” In the Respiratory Disorders category, Cleveland Clinic is ranked #7. For details, visit clevelandclinic.org.