A Unique Lung Transplant Program

By Marie Budev, DO, MPH; Gosta Petterson, MD, PhD; Kenneth McCurry, MD

Cleveland Clinic performed 157 lung transplants in 2009, setting an international record for lungs transplanted in a single year. The survival outcomes at one year for the patients transplanted in 2009 remains at or above the national average and our long-term survival also is above the national average.

One out of every 10 lung transplants in the US was performed at Cleveland Clinic in 2009. These included three heart/double-lung and three double-lung/liver transplants. We attribute these high numbers and good outcomes to more aggressive donor utilization, teamwork and strong institutional support. We expect to have performed more than 120 transplants in 2010, based on our volume estimates through mid-December.

We welcome complex cases, and care for many patients who have been turned down by other centers for being too old or having multiple co-morbidities. We evaluate many hundreds of end-stage lung disease patients every year, from the United States and elsewhere. The new lung allocation scores (LAS) have not affected our average wait times, in which almost one-third of those listed get new lungs in 30 days, and 90 percent are transplanted within a year. Nationally, only 40 percent get a transplant in that time. Although we transplant more high-acuity cases, our hospital and 30-day mortality remain low. Our survival rates are generally at or above the national average.

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With five lung transplant surgeons and a team of transplant pulmonologists, supported by specialists in Infectious Disease, Immunology and other specialties, our program is well-prepared for what may be an annual 200 or more lung transplants in the near future. Over the years, we have built a professional environment where physicians can thrive and practice medicine to the best of their abilities. As a result, everyone works as a team and the patient gets the very best care before, during and well beyond surgery. We have the support of the full institution, from nurses to administrators. Our transplant coordinators are experienced, competent and sensitive to our patients.

Kenneth McCurry, MD, was designated as the UNOS primary surgeon and surgical director of Heart and Heart-Lung Transplant in 2010. Marie Budev, DO, MPH, was designated as the UNOS primary physician and medical director in 2009. Gosta Pettersson, MD, PhD, primary surgeon and surgical director until 2009, continues to study all aspects of lung transplantation and to refine its techniques.

Cleveland Clinic is a leader in research and innovation in lung transplantation. Team members lead and participate in multicenter trials, including studies of primary graft dysfunction, acute rejection therapy, and induction therapy and ex vivo perfusion. Dr. McCurry has a research appointment in the Department of Pathobiology, where he is investigating means to increase utilization and developing therapies to improve post-transplant outcomes. His research interests include reperfusion ischemia injury – a persistent cause of morbidity and mortality in the early post-transplant period. One advantage of high patient volumes is the opportunity to perform more randomized studies.

Cleveland Clinic recently received two R34 planning grants from the NIH. The first is examining antibody mediated rejection in lung transplant and its treatment and the second is looking at lung transplant and chronic rejection.
A greater use of lungs from donation after cardiac death (DCD) could help increase the number of transplants. Today, most transplanted organs come from donation after brain death, reflecting a long-standing bias in favor of brain death organs. A 2008 study at Cleveland Clinic evaluated all DCD lung transplants performed in the United States from 1987 to 2007 and determined that survival after lung transplant using DCD donors was excellent and, in fact, better than survival after brain-death donation.¹

In 2007, Dr. Pettersson performed the world’s first bronchial artery revascularization (BAR) in lung transplantation. In lung transplant, these arteries are routinely ignored, leaving bronchi dependent on venous blood supply. As a result, serious and sometimes fatal bronchial healing problems occur in 15 percent of lung transplant patients. Dr. Pettersson revascularized the bronchi by attaching the patient’s left mammary artery to a major bronchial artery in the donor lungs. Since then, 26 patients have been transplanted with BAR at Cleveland Clinic, with 25 patients having excellent airway healing. Assessment of long-term results (e.g., incidence of BOS) is underway.

A recent study appearing in the Journal of the American Medical Association shows a wide variability in five-year survival among lung transplant centers in the U.S. It suggests that the choice of where a patient has lung transplantation may be among the most important determinants of success. Although in this study high volume centers (more than 50 a year) do not always have the best outcomes, at Cleveland Clinic, this is not the case. The Cleveland Clinic Lung Transplant Program is able to combine high volumes with high acuity, to achieve outcomes that are at or surpass the national average.

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References

Antibody-mediated Rejection after Lung Transplant: Is it Clinically Significant?

By Carol Farver, MD

Lung transplantation is now an accepted and increasingly common therapy for patients with pulmonary disorders resistant to other therapies and who are progressing toward end-stage lung disease. Though the long-term outcomes are improving, unfortunately, they remain disappointing compared to those of other solid organs, such as heart and kidney. The reported median survival is approximately five years and rejection and infection remain the leading causes of death.

The major focus of rejection has been acute cellular rejection involving specific T lymphocytes, but the improved detection of circulating antibodies against the donor lung present in the lung recipient has introduced another potential form of graft injury, known as antibody-mediated rejection (AMR). This form of rejection is well-documented as a cause of organ failure in other solid organs, such as the heart and kidney, but its role in lung transplantation is not clear. Currently, a focused effort to study this problem by an interdisciplinary team of physicians from the Cleveland Clinic Transplant Center, including pathologists, pulmonologists, immunologists and surgeons is underway.

Antibody-mediated rejection is a form of graft injury thought to be the result of antibodies to donor HLA antigens in the recipient after transplantation, which cause activation of complement in the alveoli of the new donor lung and alveolar injury. This injury can cause a number of respiratory symptoms that may include diffuse pulmonary infiltrates, severe hypoxemia, blood-tinged sputum and, in the most fulminant cases, respiratory failure. This clinical picture is quite nonspecific in this setting and can be difficult to distinguish from complications of infection or cellular rejection. It may occur within minutes or days of transplantation, but also has been implicated in bouts of unexplained respiratory illness in these patients up to two years after surgery.

Figure 1. A biopsy from a transplanted lung in a patient with antibody-mediated rejection (AMR). This pathology shows evidence of capillaritis with hemorrhage, hemosiderin-leaden macrophages and acute inflammatory cells within the interstitial capillaries. (Hematoxylin and eosin; 200x).
The pathologic pattern of injury is similarly nonspecific. The most commonly seen pathology includes diffuse alveolar damage (DAD)/acute respiratory distress syndrome (ARDS) or a small vessel vasculitis (Figure 1), but other patterns of injury also may be possible. As techniques to measure these anti-donor antibodies in the peripheral blood as well as in the transplanted lung have been developed and improved, it has allowed for more sensitive detection of them and for correlation of their presence with both the clinical symptoms and the lung pathology.

The pulmonary pathology section of the Pathology and Laboratory Medicine Institute, including myself and Valeria Arrossi, MD, are working in conjunction with Marie Budev, DO, MPH, Medical Director of the Cleveland Clinic Lung Transplantation Program and Medhat Askar, MD, PhD, Peter Lalli, PhD, Diane Pidwell, PhD and Lynne Klingman of the Allogen Laboratories to study this important clinical problem more closely.

We are presently conducting a study that will measure these antibodies in the blood before transplantation and at each clinic visit after transplantation and evaluate positive staining for antibodies to C3d and C4d as a measure of complement activation in the surveillance biopsy specimens taken from the transplanted lung (Figure 2). We hope this work will define more clearly the clinical and pathologic picture of AMR as a first step to improving outcomes in these patients.

Reach Dr. Carol Farver at 216.225.7695 or farverc@ccf.org.

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Introducing our Expanded MICU and New Bronchoscopy Suites

Increasing our capacity to better serve you

Cleveland Clinic recently expanded its medical intensive care unit (MICU) and opened new bronchoscopy suites to meet an increasing demand for these services.

MICU

Our MICU, led by Jorge A. Guzman, MD, now has 43 beds to better handle higher volumes due to growth in our lung transplant and critical care transport programs and high-acuity patients. Board-certified intensivists provide in-house coverage 24/7. We project more than 2,000 admissions per year due to this increased capacity. In view of our high transfer population (35 percent of admissions), patient outcomes remain excellent, with mortality rates below the risk-adjusted predicted values and improving infection rates.

Bronchoscopy Suites

In 2010, we opened four new bronchoscopy suites to accommodate increasing diagnostic and therapeutic bronchoscopy volumes. We have some of the world’s most extensive experience with electromagnetic navigation, lung transplant-related airway disease, self-expanding metallic stents, management of airway complications due to histoplasmosis, benign airway diseases and metallic stent removal. In 2009, we performed 2,572 bronchoscopies, a 38 percent increase in five years. Importantly, our complication rates remained low.

No Patient Too Sick…
No Patient Too Far

Cleveland Clinic’s Critical Care Transport is designed to help critical care patients anywhere in the world get the care they need. We transport critically ill and injured patients via ground mobile ICU, rotor wing aircraft (helicopter), and fixed wing aircraft (jet).

- Our transport teams are staffed with Acute Care Nurse practitioners (ACNPs), formally trained as critical care interventionalists
- Treatment can begin during transport, thus providing the highest possible quality of care
- We can transport patients requiring special critical care needs including intra-aortic balloon pumps, ventricular assist devices or extra corporeal membrane oxygenation

To transfer a patient, call 800.533.5066

The new bronchoscopy suites were possible in part thanks to a generous contribution by Patricia Brundige in memory of her husband, Thomas.
Research Advances

Cleveland Clinic’s Asthma Center leverages translational research to support and enhance patient care and outcomes

By Sumita Khatri, MD, MS

Physicians and specialists from a variety of medical and surgical disciplines as well as subspecialties work collaboratively at Cleveland Clinic’s Asthma Center to deliver state-of-the-art clinical services and novel agents or approaches to diagnose and treat primary adult and pediatric asthma patients.

Moreover, under the leadership of co-directors Sumita Khatri, MD, MS, David Lang, MD, and Serpil Erzurum, MD, the Asthma Center remains at the forefront of developing innovative treatments through clinical trials and leveraging translational research that supports and enhances patient care.

For example, we are involved in a unique research partnership with the U.S. Environmental Protection Agency to evaluate whether hospital presentations for asthma in Northeast Ohio are temporally associated with poor air quality, and whether certain sources of air pollution may partially explain patterns of hospital presentations. Our preliminary work has demonstrated that proximity to major highways and roadways is a risk factor in asthma morbidity.

Another research project is investigating hyaluronan (HA) as a central mediator of inflammation and remodeling in the asthmatic airway. Our research will determine the utility of HA as a biomarker for asthma and disease activity. We also are investigating low molecular weight HA as a therapeutic for asthmatic inflammation. Additionally, clinical investigators are examining the pathways between HA and lymphocytes that occur within the lung during asthmatic inflammation, which may lead to the development of new, novel therapeutics.

Cleveland Clinic researchers also are investigating how angiogenic remodeling is involved in the genesis of asthma. Circulating CD34+CD133+ pro-angiogenic stem cells are essential in new blood vessel formation. During their post-natal life, these cells reside in the bone marrow. Although rarely found in the peripheral blood circulation, these stem cells can be rapidly mobilized by angiogenic factors. These stem cells have opened new perspectives of angiogenesis and how it may play a role in the origins of asthma. Our clinical investigators have shown circulating bone marrow-derived CD34+CD133+ progenitor cells in asthma are higher than in healthy controls, and are key players in the initiation of vascular remodeling in the airways. More recently, we reported that these progenitors regulate eosinophil trafficking to asthmatic lungs via increased expression of eotaxin-1, a main chemoattractant for eosinophils. These progenitor cells release their pre-synthesized eotaxin content after contact with vascular cells of allergen-exposed lungs. Circulating progenitors also have the potential to differentiate into several lineages relevant to asthma including mast cells and eosinophils. These findings provide emerging evidence that circulating pro-angiogenic stem cells are pro-inflammatory. Our ongoing research is investigating whether pro-angiogenic stem cell-derived eotaxin can serve as a biomarker for disease outcome, and if inhibition of these stem cells can benefit clinical outcomes in asthmatics.

Finally, Cleveland Clinic is collaborating with the National Institutes of Health in the Severe Asthma Research Program (SARP), an observational study to better characterize asthma’s pathology. Through such NIH-sponsored research programs and investigator-initiated studies, Asthma Center investigators are making advances in the understanding of the pathophysiology of asthma, therapeutic targets for asthma, and epidemiology of asthma. Moreover, profiling of asthma enables physicians to better determine which patients will benefit from various therapeutic modalities, such as biologic therapies or interventions, such as bronchial thermoplasty.

Recommended Reading


Bronchial Thermoplasty: A New Asthma Therapy Available at Cleveland Clinic.

By Thomas Gildea, MD and Sumita B. 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. BT involves the application of radiofrequency energy in a controlled manner to provide thermal treatment to airways. This new procedure, which occurs in three separate sessions, is now offered as part of the comprehensive management of patients with asthma in the Respiratory Institute. Clinical trials demonstrate the feasibility, relative safety and improved clinical outcomes in patients with severe asthma who undergo BT when medical therapies do not control their symptoms. 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.

Asthma is a chronic inflammatory condition of the airways characterized by episodic symptoms of breathlessness, cough, and wheezing. The chronic airway inflammation can lead to persistent airflow obstruction that can be difficult to manage and control, even with the best available medical therapies. Bronchoconstriction in asthma is characterized by increased airway smooth muscle (ASM), airway closure and hyperresponsiveness temporarily reversed with acute bronchodilators, but medical therapy targeting ASM is not available. This potential gap in the management of asthmatics is what is targeted by this new therapeutic modality, BT.

Background on Bronchial Thermoplasty:
The use of this technology to treat airway smooth muscle began with animal studies which showed feasibility of using radiofrequency energy to decrease ASM. Subsequent clinical studies and trials in patients that were non-asthmatics or had mild to moderate persistent asthma, and finally moderate to severe refractory asthma were performed and helped identify appropriate candidates, anticipated adverse events, and expected outcomes.

Observational studies in mild to moderate persistent asthmatics demonstrated a steady improvement in airway hyperresponsiveness and symptom-free days up to two years after BT. In the Research in Severe Asthma (RISA) trial, patients with severe asthma undergoing BT were studied for safety, changes in asthma symptoms and ability to reduce daily inhaled or oral corticosteroids. After treatment, there were reductions in rescue inhaler use and improved asthma quality of life scores. The Asthma Intervention Research (AIR) trial was a prospective randomized non-blinded study performed to determine whether asthma control could be improved after BT. Morning peak flow, rescue medication use, Asthma Quality of Life Questionnaire (AQLQ) and Asthma Control Questionnaire (ACQ) scores were all significantly improved.

With BT treatment, there was an encouraging reduction in the number of mild exacerbations with 10 fewer mild exacerbations per subject per year. Cleveland Clinic participated in the latest randomized clinical trial, the AIR2 trial. This study included a control ‘sham’ group that received bronchoscopy; however, radiofrequency energy was not delivered across the BT catheter. Results showed a 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 (ED) visits in those receiving BT.

Clinical trials demonstrate that adverse events can occur with bronchial thermoplasty, making appropriate patient selection key to the success of this procedure. The most frequent side effects are symptoms of airway irritation such as cough, dyspnea, wheeze and bronchospasm. Therefore, close post-procedure monitoring for early and aggressive management of short-term exacerbations (up to six weeks after the last session) is warranted. Patients should be aware that less frequent but severe adverse events can include infections, pleurisy and bleeding.

What patients can expect:
Once a patient is referred for evaluation for bronchial thermoplasty, our office will contact the patient, gather outside records, and schedule a visit with specialists who perform the procedure. Any further necessary testing will be performed to properly assess candidacy for BT.

A full course of treatment requires three separate bronchoscopic procedures. Each lower lobe is treated in its own procedure and then both upper lobes are treated in the same procedure. The right middle lobe is not treated. Each is separated by approximately two to three weeks. Patients are assessed prior to and on the day of the procedure to ensure relative disease stability before proceeding with the treatment.
Bronchoscopy is performed under conscious sedation, (fentanyl/midazolam/topical lidocaine) via a transnasal approach with a flexible bronchoscope. Glycopyrrolate is used to decrease secretions. Radiofrequency (RF) or thermal energy is directed in the airways by deploying a wire basket in a catheter via the (2 mm) working channel with the intent of treating accessible airways 3 to 10 mm in diameter. Each actuation of the system delivers RF energy to heat the tissue. The technique requires meticulous catheter placement of each 5 mm treatment zone with direct approximation, but no overlap. A treatment map is generated to assure complete, but not duplicate, treatment in all reachable segments. Patients are observed for airway reactivity, asthma exacerbations, or other complications during an extended recovery and monitoring period during which bronchodilators are given and spirometry performed. Patients are discharged when they have clinically recovered and spirometry is within 20 percent of baseline.

To summarize, recent clinical trials demonstrate the feasibility, relative safety, and improved clinical outcomes in patients with severe asthma who undergo BT when medical therapies do not control their symptoms. Long-term studies are ongoing to evaluate the duration of effect and safety of BT.

Dr. Thomas Gildea is the Head of the Section of Bronchoscopy in the Respiratory Institute. He can be contacted at 216.444.6490 or gildeat@ccf.org. Dr. Sumita B. Khatri is Co-Director of the Asthma Center and Medical Director, Bronchial Thermoplasty Program. She can be contacted at 216.445.1701 or khatris@ccf.org.

Requirements for Bronchial Thermoplasty at Cleveland Clinic:

- Age 18 – 65 years
- Ongoing severe persistent asthma symptoms despite treatment with inhaled corticosteroid and LABA therapy: Corticosteroid dose (beclomethasone equiv.) (μg/day) ≥ 1,000, and LABA dose (salmeterol equiv.) (μg/day) ≥ 100
- Oral corticosteroid dose (mg/day) ≤ 30
- Pre-Bronchodilator FEV1 (% Predicted) ≥ 50%
- Non-smoker for past year with < 10-pack year history
- Absence of other conditions: interstitial lung disease, Churg-Strauss syndrome, pulmonary hypertension, allergic bronchopulmonary aspergillosis, arrhythmias, immunosuppressant therapy, or need for pacemaker/defibrillator.

For more information or to refer a patient for evaluation, please contact the thermoplasty coordinator Joan Scharf (scharfj@ccf.org), Dr. Sumita Khatri (khatris@ccf.org) or call the referral line at 216.445.6266.

References

A major limiting factor to discovering the mechanisms involved in the pathogenesis of sarcoidosis is the lack of an animal model that approximates the human disease. The models typically used in the past 15 years have been helpful for studying the acute events in Th1- or Th2-polarized responses to complex protein mixes, such as purified protein derivative. Progress toward developing an acceptable sarcoidosis animal model had been hindered by the lack of sarcoid-specific antigens. While the antigen(s) causing sarcoidosis are not known, increasing molecular and immunologic evidence point to mycobacterial virulence factors as strong potential candidates. We recently reported the development of an antigen-specific sarcoidosis murine model using a microbial peptide associated with human sarcoidosis granulomas. (Figure 1)

Using a peptide corresponding to a fragment of mycobacterial superoxide dismutase A (sodA) isolated from sarcoidosis patients, we developed a pulmonary model of sarcoidosis granulomatous inflammation. This work was done in collaboration with investigators from Vanderbilt University, who had previously isolated the sodA peptide and had shown specific immune responses to it in sarcoidosis patients but not control subjects. Features of this model strongly resemble the human disease, including:

- Hilar lymphadenopathy and parenchymal infiltrates were present in the sodA-treated mice, with no gross abnormalities of the heart, liver or spleen and no beads or granulomas found in these tissues.

- Extensive granuloma formation developed throughout the lungs of sodA-treated mice (Figure 2A). Most noncaseating granulomas were concentric to the bead, had several multinucleated giant cells and were localized to the bronchoarterial bundle (Figure 2B). These histological features correlate well with those observed in human sarcoid lungs.

- Macrophages were interspersed throughout the granuloma, albeit most abundantly in the innermost layers closest to the beads (Figure 3A). In addition, CD4+ T cells were abundantly present in the middle layers of mouse granulomas (Figure 3B).

- There was a significant increase in lymphocytes in the BAL of sodA-treated compared to control mice, with a CD4/CD8 skew.

- CD4+ cells from bronchoalveolar lavage responded to the sodA, similar to the immune responses seen in humans.
• Blocking of the Type II major histocomptability complex abolished the immune recognition of sodA by CD4+ T cells. This correlates with the human disease in which mycobacterial antigens presented by these MHC Class II alleles are recognized by sarcoidosis CD4+ T cells.

• As observed in human sarcoid BAL fluid, sodA caused the increase of Th1 cytokines IL-2 and IFN-γ compared to untreated mice. In contrast, the levels of Th2 cytokines IL-4 and IL-5 in the untreated and the sodA-treated mice were the same.

This pulmonary sarcoidosis mouse model shows the immunopathological features seen in active sarcoidosis. These include: a) development of noncaseating granulomas from peptides unique to sarcoidosis; b) cell type and Th1 cytokine patterns similar to those observed in sarcoidosis subjects at presentation; c) dependence on MHC Class II alleles in generating immune responses. This model will facilitate studies aimed at identifying the relevant mechanisms leading to sarcoidosis resolution or progression to fibrosis.

Contact Dr. Carmen Swaisgood at 216.444.4968 or swaisgc@ccf.org and Dr. Daniel Culver at 216.444.6508 or culverd@ccf.org.

Reference
Clinicians for centuries have noted distinct changes in the breath odor of patients with certain diseases such as diabetes and renal failure. However a catalytic point in breath research was Linus Pauling’s identification of over 250 breath compounds during the 1970s. Since this time, pivotal advancements in the field of breath testing have helped revolutionize our understanding of the components of exhaled breath and their etiology in disease. With major improvements in detection technologies (infrared, electrochemical, chemiluminescence, of many) and the application of sensitive mass spectrometers, we are now able to qualitatively and quantitatively measure the thousands of identified compounds in exhaled breath. Providing promise for future technologies, a growing number of FDA approved devices have emerged in the past decade for use in monitoring asthma, diagnosing transplant organ rejection and H. pylori infection, detecting blood alcohol concentration (BAC), and for monitoring breath gases during anesthesia, mechanical ventilation, and respiration among others.

Using highly sensitive equipment such as selected ion flow tube mass spectrometry (SIFT-MS) our team at the Cleveland Clinic has the capability of measuring volatile organic compounds (VOCs) in the parts per trillion (ppt) range in human breath. With our database of hundreds of analyzed samples and access to multiple diseases our group is moving towards identifying relevant VOCs in disease and understanding the origins of VOC from specific metabolic pathways.

In recent years, one arena we have contributed extensively to is the understanding of the breath biomarker, nitric oxide (NO), in asthma. In the early 1990s NO levels were found to be elevated in the exhaled breath of patients with asthma compared to controls and later linked to eosinophilic airway inflammation. However, initial NO detection devices were large, cumbersome, and nearly impossible to use outside of the research laboratory. In 2003 the first NO asthma monitoring desktop device received FDA clearance representing a hallmark in new breath testing technology. Advantages of exhaled NO monitoring in asthma include its non-invasive nature, ease of repeat measurements, and use in adult and child populations with severe airflow obstruction where other techniques would be difficult or impossible to perform.
Advancements in Breath Testing and Sensor Design

To fully advance the breath analysis field, there had to be a close collaboration between technical experts who typically have a device looking for clinical application, the medical experts who have the clinical problem looking for a test/biomarker that can be helpful in diagnosis or monitoring, and industry/commercial experts who can build and commercialize the final product. This multidisciplinary collaboration is exactly what we have accomplished in our ongoing project: “Breath Analysis: Targeted Sensor Development and Commercialization for Health Care Diagnostics” that was funded with a $3.8 million Third Frontier Award from the Ohio Department of Development (ODOD). Our team brings together a range of world-leading capabilities in academia, industry, and government with extensive experience in sensor development and clinical applications including recognized centers of excellence such as the Electronics Design Center at Case Western Reserve University (CWRU), the Center for Industrial Sensors and Measurement (CISM) at Ohio State University (OSU), NASA Glenn Research Center, Makel Engineering, Inc. (MEI), and the Exhaled Breath Laboratory at the Cleveland Clinic. Our team is currently developing several sensors for potential medical applications including a sensor designed for a home NO monitoring device for asthma.

The Ohio Third Frontier Program support we received has resulted in promising prospects for the future. At OSU a major accomplishment has been successful improvements to the NO sensor based on the electrochemical cell design. Based on the evolving OSU design, NASA Glenn Research Center and CWRU are currently developing advanced methods for miniaturization of the NO sensor technology. This has involved fabrication of thin film sensors within the NASA Microsystems Fabrication Clean Room and testing of the sensor in the Chemical Sensor Testing Laboratory. Further, the ability to fabricate multiple, operational single sensors on the same substrate has been demonstrated which will allow connecting multiple miniaturized sensors on a single compact packaged platform to improve sensitivity and reduce power consumption. Makel Engineering has focused on transitioning the sensors developed by OSU, CWRU, and NASA into portable systems for early clinical evaluation at the Cleveland Clinic and later for home monitoring.

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Recommended Reading


Pulmonary Hypertension Symposium 2010 Recap

The 7th annual Pulmonary Hypertension Symposium was held on November 19, 2010 at Cleveland Clinic. The meeting was a huge success with more than 130 participants who came from 19 states to hear state-of-the-art presentations by 26 distinguished Cleveland Clinic and visiting faculty.

Summit attendees included physicians and other healthcare professionals, researchers and scientists, industry representatives, patients and care givers and patient advocacy groups.

Dr. Raed A. Dweik, Chair of the Symposium and Director of the Pulmonary Vascular Program, presented the inaugural “Award of Merit” to the keynote speaker Dr. Nicholas S. Hill, Professor of Medicine and Chief of Pulmonary, Allergy and Critical Care Medicine at Tufts University School of Medicine. This annual award is presented in recognition of extraordinary contribution to the basic understanding and/or clinical management of pulmonary hypertension.
Developing Breath Biomarkers to Aid Lung Cancer Diagnosis

By Peter Mazzone, MD, MPH

Biomarkers are objectively measured indicators of the state of an individual’s health. They range from commonly measured vital signs to complex molecular signatures. There has been a tremendous amount of interest in the development of novel biomarkers for cancer. A cancer biomarker may help to identify someone at risk of developing cancer, help to diagnose cancer at an early stage, determine the prognosis from the cancer, predict or monitor the response to therapy, or advance our understanding of the pathobiology of the cancer.

Lung cancer biomarkers have improved our management of lung cancer patients. Recent examples of commonly used lung cancer biomarkers are PET scanning and EGFR mutation analysis. There is promise that the development of novel lung cancer biomarkers will lead to further improvement in our management of this disease in the near future. Advances in chemoprevention will be most useful if biomarkers are able to identify those at greatest risk of developing lung cancer. Advances in surgical and ablative therapies will be most useful if biomarkers help us to identify lung cancer at the earliest possible stage. Advances in systemic, targeted and individualized therapies may be developed based on the discovery of new biomarkers capable of predicting the nature of one’s lung cancer and the response to specific treatment choices.

A new biomarker can improve on currently used tests by being more accurate, less invasive, less expensive, and/or novel in its intent. To have a clinical impact, the result of the test must affect a decision to the benefit of the patient. In addition to being accurate, an ideal test would be easy to administer, have low risk from its performance and be inexpensive. Our lung cancer program has been involved in the study of an unusual source of biomarkers – the breath.

In prior editions of the Respiratory Exchange, I have outlined our work in discovering breath biomarkers for lung cancer diagnosis. In our most recent work, (unpublished) we recruited approximately 92 patients with untreated lung cancer and 137 control subjects. The control subjects were either at risk for developing lung cancer or presented with indeterminate lung nodules. Study subjects breathed into a crude, portable breath collection instrument that drew tidal mixed expiratory breath over a colorimetric sensor array. The colorimetric sensors were composed of chemically...
reactive dyes printed on a disposable cartridge. The dyes change their color based on the chemical mixture to which they are exposed. The change in colors is analyzed for patterns that can discriminate the breath of lung cancer patients. Our initial analysis suggested an accuracy of around 75 percent for distinguishing lung cancer from controls. The accuracy improved when we considered subtypes of lung cancer. For example, we were able to distinguish adenocarcinoma from controls with an accuracy of 80 to 85 percent, and adenocarcinoma from squamous cell carcinoma with an accuracy approaching 90 percent.

The colorimetric sensor array technology used in our most recent work has made exciting advances since the completion of this project. The latest version of the sensor is composed of pigments printed on a nanoporous medium rather than dyes on a flat surface. This has led to increased stability of the sensor while maximizing the surface area for reaction. These changes, in concert with the use of advanced imaging systems, have improved the sensitivity of the sensor system into at least the low parts per billion level for all relevant chemical classes (>100-fold improvement over the former system). This sensitivity is equivalent to that of the canine olfaction system. We have worked with the sensor developers to design a breath collection interface and delivery system capable of consistently and comfortably collecting and delivering the alveolar portion of the breath to the advanced sensor. We will be leading a multi-institutional trial of this system, beginning in Spring 2011. We also will begin to use this system to look at other disease states.

In concert with the colorimetric sensor system, we are studying a second breath analysis technology. Our single photon ionization mass spectrometer is capable of detecting exhaled volatiles at parts per trillion concentration in real-time. Though this device could become smaller and easier to use over time, its current utility will be to help identify the nature of the discriminatory breath components. This information will allow us to refine the sensor elements of point of care systems, such as the above colorimetric sensor array, optimizing their accuracy.

In addition to breath analysis, imaging advances are certain to impact the management of lung cancer. We are currently collaborating with our chest radiology partners to evaluate one of these advances, computer-aided detection of lung nodules applied to chest X-rays, in a large scale lung cancer screening study supported by the Ohio Department of Development. Subjects at risk for developing lung cancer are randomized to have the advanced chest X-ray or a sham chest X-ray. We have recruited approximately 1,300 subjects to date.

The lung cancer screening trial cohort is an ideal group to assist with our breath test work. In addition, we are hoping to leverage the resources supporting the screening study to grow our blood biorepository of individuals at risk for developing lung cancer and those with proven lung cancer. Many lines of blood test development for lung cancer are being studied. A well-annotated blood biorepository will allow us to participate in blood test development and validation studies capable of leading to clinical advances for our patients.

It is an exciting time for lung cancer researchers. Advances in chemoprevention, early detection, prognostication and prediction of treatment response will all require the development of novel lung cancer biomarkers. We are hopeful that we will see progress in these areas in the very near future.

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