Translating Basic Science Into Human Clinical Trials for Rare Pulmonary Disease  Mani S. Kavuru, M.D.

Pulmonary clinicians and research scientists at The Cleveland Clinic are making striking progress in clarifying the pathogenesis of human pulmonary alveolar proteinosis and in advancing new therapeutics for this rare lung disorder.

Long considered a “medical curiosity” by researchers and clinicians, pulmonary alveolar proteinosis (PAP) produces a chronic pneumonia-like syndrome with accumulation of lipoproteinaceous material within the alveoli of the lungs in otherwise healthy young adults.

A CLUE TO THE MYSTERY

Seven years ago, researchers noted the development of a characteristic PAP-like pathology in mice that have a targeted gene deletion of the granulocyte macrophage-colony stimulating factor (“GM-CSF knock-out mice”). This remarkable observation identified the hematopoietic growth factor GM-CSF as being indispensable to normal surfactant homeostasis or clearance, at least in mice.

Since then, researchers and clinicians within the Clinic’s Department of Pulmonary and Critical Care Medicine have extended the murine-model observations to better understand the role of GM-CSF in normal adults.

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DEAR COLLEAGUES:

Welcome to the first issue of Respiratory Exchange, a publication for physicians from the Cleveland Clinic’s Department of Pulmonary and Critical Care Medicine. Respiratory Exchange focuses on information of interest and value to you, the specialist in pulmonary and critical care medicine, or allergy and clinical immunology.

In this issue, we feature the latest in asthma-related research advances, interventional bronchology using SEMS, and the results of clinical trials related to pulmonary alveolar proteinosis.

We hope you find Respiratory Exchange valuable. Please contact us at our new toll-free number 866/CCF-LUNG (223-5864) if you have any questions or if you would like to refer a patient. We welcome the opportunity to work with you.

Sincerely,

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

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FROM BENCH TO BEDSIDE

Beginning in 1999, Clinic pulmonologists became involved in an investigator-initiated open-label trial with subcutaneous GM-CSF in patients with idiopathic PAP. A cohort of 25 PAP patients from throughout the United States participated, and over half of the patients obtained a dramatic improvement in their lung disease with GM-CSF administration.

Related studies involving more than 40 PAP patients at the Clinic demonstrated that all patients have a circulating and neutralizing antibody against native GM-CSF. These patients are functionally devoid of the effects of GM-CSF in the lungs.

AUTOIMMUNITY AND GENETICS

Additional Clinic research on the murine models has shown that the local effects of GM-CSF on lung cells are crucial to keep the lungs free of the excess surfactant material. Human idiopathic PAP is distinct from the murine models in that specific autoimmunity is the pathway for GM-CSF depletion. Collaboration with the Clinic’s departments of Immunology and Anatomic Pathology is driving the development of an autoimmune murine model of PAP, and, in collaboration with the Department of Medical Genetics, the possible role of genetic polymorphisms is being examined.
Proposed model of human pulmonary alveolar proteinosis (PAP) pathogenesis.

1. In normal lungs, GM-CSF induces maturation of monocytes into alveolar macrophages and promotes surfactant degradation by the mature alveolar macrophage.
2. In PAP, IL-10 inhibits GM-CSF synthesis.
3. IL-10 stimulates B-cell production of anti-GM-CSF antibody, which neutralizes GM-CSF activity.
4. This decreased availability of GM-CSF leads to immature macrophages and undegraded surfactant that accumulates in the lung, resulting in PAP.

ADDITIONAL TRIALS UNDERWAY

Currently, The Cleveland Clinic is recruiting patients with PAP for two separate trials: 1) a three-year, randomized, placebo-controlled trial with GM-CSF over one year, and 2) an open-label trial with mycophenolate (an agent that inhibits antibody production by B-cells).

CONVENTIONAL TREATMENT

For patients too ill to qualify for a clinical trial or who are unresponsive to trial therapies, conventional whole-lung lavage remains a lifesaving modality.

The Cleveland Clinic is one of only a few centers in the country where simultaneous bilateral lung lavage is offered. Performed by a team that includes anesthesiologists and pulmonologists, the bilateral approach has the advantage of reducing both anesthesia time and hospital stay.

For practicing pulmonologists confronted with a patient with idiopathic PAP, The Cleveland Clinic serves as a national referral center for clinical management, from conventional whole-lung lavage to novel therapeutic approaches. Additionally, patients can participate in a de facto PAP registry, another tool to help us understand this “medical curiosity.”

Mani S. Kavuru, M.D., director of the Pulmonary Function Laboratory, led the Clinic’s investigation of GM-CSF in PAP patients. Pulmonology’s Mary Jane Thomassen, Ph.D., and Cancer Biology’s Taolin Yi, Ph.D., collaborated on research.

For more information on clinical trials, or to have a patient evaluated, contact Dr. Kavuru at 216/445-6972 or 800/553-5056, ext. 56972.

RECENT PUBLICATIONS


Pulmonologists at The Cleveland Clinic are actively involved in improving the quality of life of patients suffering with large airway obstruction. Our experience using self-expandable metallic stents (SEMS), such as Ultraflex or Wall Stent, adds a new facet to palliative management of patients with malignant or benign large airway obstructions.

**PATIENT EXPERIENCE**

Since the late 1990s, we have placed more than 135 SEMS in patients with thoracic malignancies, airway involvement with relapsing polychondritis, tracheal stenosis and malacia, or dehiscence at the site of anastomosis following lung transplantation. Immediate palliation is achieved in more than 95 percent of patients following the brief procedure.

In the mean follow-up after 87 days in patients with malignancies and after 495 days of those with benign condition, the complication rate was 0.06/pt. month. In just five patients, stents were removed due to lack of improvement or to adverse effects.

**PROCEDURE-ROOM PLACEMENT**

SEMS are placed using a flexible bronchoscope under conscious sedation and local anesthesia, with or without fluoroscopic guidance, in a procedure-room setting, eliminating the risk of general anesthesia and rigid bronchoscopy. The procedure also can be successfully carried out in an ICU setting in ventilator-dependent patients. At The Cleveland Clinic, most stents are placed at the time of initial bronchoscopic evaluation.

For recent publications related to this article, see pg. 6.

**INDICATIONS AND ADVANTAGES**

Major indications for the endobronchial stenting include primary or secondary bronchogenic carcinoma, tracheobronchomalacia, tracheoesophageal fistula and selected tracheal stenoses.

Compared to traditional silicon stents, complications of migration or mucus plugging are seldom encountered. The thin-wire structure of the stents provides higher internal-to-external diameter ratio and, thus, larger airway lumen. Perforation of the airway or the major intrathoracic vessel has not been encountered, probably because the radial force is evenly distributed throughout the length of the stent.

Both covered and uncovered versions of the stents are available in various diameters and selected lengths. Thin-cut or three-dimensional CT scans of the chest are required to select the most appropriate size of the stent.

**DRAWBACKS TO THE DEVICE**

Although SEMS are made of inert alloys, formation of obstructive granulomas is frequent and requires treatment, typically cryotherapy or electrosurgery, for example.

In addition, four to six weeks following placement, the stent may epithelialize and become incorporated in the airway wall. Removing the stent is difficult and remains a major drawback to the device. However, this situation can be avoided by not placing the stent in patients with temporary obstructions.

**SATISFACTORY RESULTS**

Based on our experience, we feel that in select patients, appropriately sized and properly placed self-expandable metallic stents provide satisfactory palliative results for patients with an acceptable rate of complications.

Atul C. Mehta, M.D., vice chairman of the Department of Pulmonary and Critical Care Medicine and head of the Section of Bronchology, uses a number of therapies including Nd-YAG laser photoresection, brachytherapy, cryotherapy, electrosurgery, photodynamic therapy and argon plasma coagulation to treat pulmonary disorders.

For more information, or to have a patient evaluated, contact Dr. Mehta at 216/444-2911 or 800/553-5056, ext. 42911.
Advances in **Asthma Care and Research**

Serpil C. Erzurum, M.D.

Clinicians and scientists in the Cleveland Clinic's Department of Pulmonary and Critical Care Medicine have played a leading role in a number of important developments in asthma research and treatment.

Asthma patients referred to The Cleveland Clinic have benefited from early access to investigational agents, such as anti-leukotrienes and long-acting, inhaled beta-agonists, and anti-IgE therapy, through clinical trials. For example, Clinic pulmonologist Mani S. Kavuru, M.D., served as principal investigator of the multicenter clinical trial that established the efficacy of salmeterol and fluticasone combined in a new powder inhalation device.

**IDENTIFYING AND INVESTIGATING BIOMARKERS**

Although anti-inflammatory therapy is the cornerstone for preventive asthma management, some patients do not respond to inhaled corticosteroids, and questions remain as to long-term toxicity. Studies to define asthma-related inflammation and to identify noninvasive biomarkers to characterize and study this inflammation are under way.

We have made significant contributions to the study of exhaled airway gases and breath condensate. For example, in the context of an experimental segmental allergen challenge model, we have studied the impact on airway biomarkers by allergen stimulation.

Concomitant with increased reactive species, our research has shown that protective antioxidants are decreased in asthma. One application of our findings is that asthma may be identifiable by specific biomarkers in expired air or in blood studies that reflect the reactive and oxidative chemistry. Researchers at the Clinic are studying the utility of aerocrine markers in the diagnosis and management of asthma over time.

**VIEWING ASTHMA FROM A MOLECULAR PERSPECTIVE**

Clinic asthma researchers use a wide spectrum of innovative technology to investigate the molecular mechanisms of lung disease, including genetic approaches to disease, DNA microarray and proteomics. Susceptibility to allergy and asthma are influenced by responses of immune white blood cells to activation. One immune system response to allergen exposure is to maintain a population of memory T-cells, which are subsequently capable of responding much more rapidly than cells that have never seen the allergen, leading to a brisk allergic response.

Clinic allergist Mark A. Aronica, M.D., has developed a model to investigate the mechanisms by which memory T-cells lead to allergic inflammation in asthma. Under the direction of Jaharul Haque, Ph.D., (Cancer Biology) and allergist Fred Hsieh, M.D., researchers are defining the mechanisms by which mast cells are activated in the allergic processes that trigger asthma. Better understanding of the immune responses ultimately will lay the groundwork for the development of novel strategies to block them.

Another focus of our research is on homeostatic control of Interleukin-4/Interleukin-13-mediated signal transduction and gene expression in allergic inflammation. Studies related to the role and regulation of intracellular signaling in the proliferation and survival of human mast cells also are under way.

**UNDERSTANDING SEVERE ASThma**

Between 5 and 10 percent of patients experience severe, debilitating and sometimes life-threatening asthma. As many as 20 percent of asthmatics have persistent symptoms requiring regular daily treatment. The cause of the variable severity of asthma is being addressed in an NIH multicenter study. The Cleveland Clinic is one of 10 centers in the United States and United Kingdom participating in this collaborative effort.

Clinic pulmonologist and director of the Lung Biology Program Serpil C. Erzurum, M.D., collaborates on asthma research with Clinic allergist David Lang, M.D., and colleagues including Mani Kavuru, M.D., Mark Aronica, M.D., Fred Hsieh, M.D., Raed Dweik, M.D., Stan Hazen, M.D., Ph.D., (Cell Biology) and Jaharul Haque, Ph.D., (Cancer Biology).

For more information, or to have a patient evaluated, call the Department of Pulmonary and Critical Care Medicine toll-free at 866/CCF-LUNG (223-5864).
ENDOBRONCHIAL STENTING
RECENT PUBLICATIONS

Mehta AC, ed.

Mehta AC, ed.

Mehta AC, Dasgupta A.

Sarodia BP, Dasgupta A, Mehta AC.
Management of airway manifestations of relapsing polychondritis.

Dasgupta A, Dolmatch BL, Abi-Saleh WJ, Mathur P, Mehta AC.

ASTHMA CARE AND RESEARCH
RECENT PUBLICATIONS

Comhair SAA, Bhathena PR, Farver C, Thunnissen FBJM, Erzurum SC.
Extracellular glutathione peroxidase induction in asthmatic lungs: evidence for redox regulation of expression in human airway epithelial cells.

Nitric oxide chemical events in the human airway during the immediate and late antigen induced asthmatic response.

Khatri SB, Özkaz M, McCarthy K, Laskowski D, Hammel J, Dweik RA, Erzurum SC.
Alterations in exhaled gas profile during allergen-induced asthmatic response.

MacPherson JC, Comhair SAA, Erzurum SC, Klein DF, Lipscomb MF, Kavuru MS, Samoszuk M, Hazen SL.
Eosinophils are a major source of NO-derived oxidants in severe asthma: characterization of pathways available to eosinophils for generating reactive nitrogen species.

Comhair SAA, Bhathena PR, Dweik RA, Kavuru MS, Erzurum SC.
Rapid loss of superoxide dismutase activity during antigen-induced asthmatic response.

Guo FH, Comhair SAA, Zheng S, Dweik RA, Essa NT, Thomassen MJ, Calloum W, Erzurum SC.

Salmeterol and fluticasone propionate combined in a new powder inhalation device for the treatment of asthma: a randomized, double-blind, placebo-controlled trial.

Eosinophils generate brominating oxidants in allergen-induced asthma.

Effect of segmental allergen challenge on airway nitric oxide, eosinophils and cytokines in asthmatics.
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Herbert P. Wiedemann, M.D.

**Clinical Immunology**  
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- Lower respiratory infection, disease and sleep, asthma, sleep disorders, pulmonary function tests, pleural disease, bronchiolitis obliterans, chronic cough, diffuse lung disease, hyperreactive airways.

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**Specialty Interests:** intensive care (including adult respiratory distress syndrome and sepsis), general pulmonary medicine, exercise testing (dyspnea evaluation)
Mark A. Aronica, M.D., Fred H. Hsieh, M.D., and David M. Lang, M.D., recently joined the Cleveland Clinic’s Department of Pulmonary and Critical Care Medicine.

“The recruitment of Drs. Aronica, Lang and Hsieh from outside institutions, all within the last year, significantly enhances our research program in asthma and allergy,” says department Chairman Herbert P. Wiedemann, M.D.

Dr. Aronica joined the Clinic after completing fellowships in pulmonary and critical care medicine, and allergy and immunology at Vanderbilt University Hospital in Nashville. He completed his residency in internal medicine at the University of Pittsburgh Medical Center, after earning his medical degree from the State University of New York at Buffalo School of Medicine. Dr. Aronica is investigating the role of T-lymphocytes in asthma, utilizing a mouse model of airway hyper-reactivity.

Following a fellowship in allergy and immunology at Brigham & Women’s Hospital in Boston, Dr. Hsieh joined The Cleveland Clinic. He completed a residency in internal medicine at Johns Hopkins Hospital after earning his medical degree from Brown University School of Medicine in Providence. Dr. Hsieh is investigating the role of human mast cells in asthma, with a particular emphasis on how they interact with human airway epithelial cells in the pathophysiology of asthma.

Dr. Lang, who serves as the head of the Section of Allergy and Clinical Immunology at The Cleveland Clinic, was previously the head of allergy and clinical immunology at Thomas Jefferson University, Philadelphia. He completed an allergy and clinical immunology fellowship at Scripps Clinic and Research Foundation, La Jolla, Calif., and an internal medicine residency at Henry Ford Hospital in Detroit. Dr. Lang earned his medical degree from the University of Michigan Medical School in Ann Arbor. His research interests include the epidemiology of asthma and clinical trials.