

# Research Awards Nationwide 2010-2011

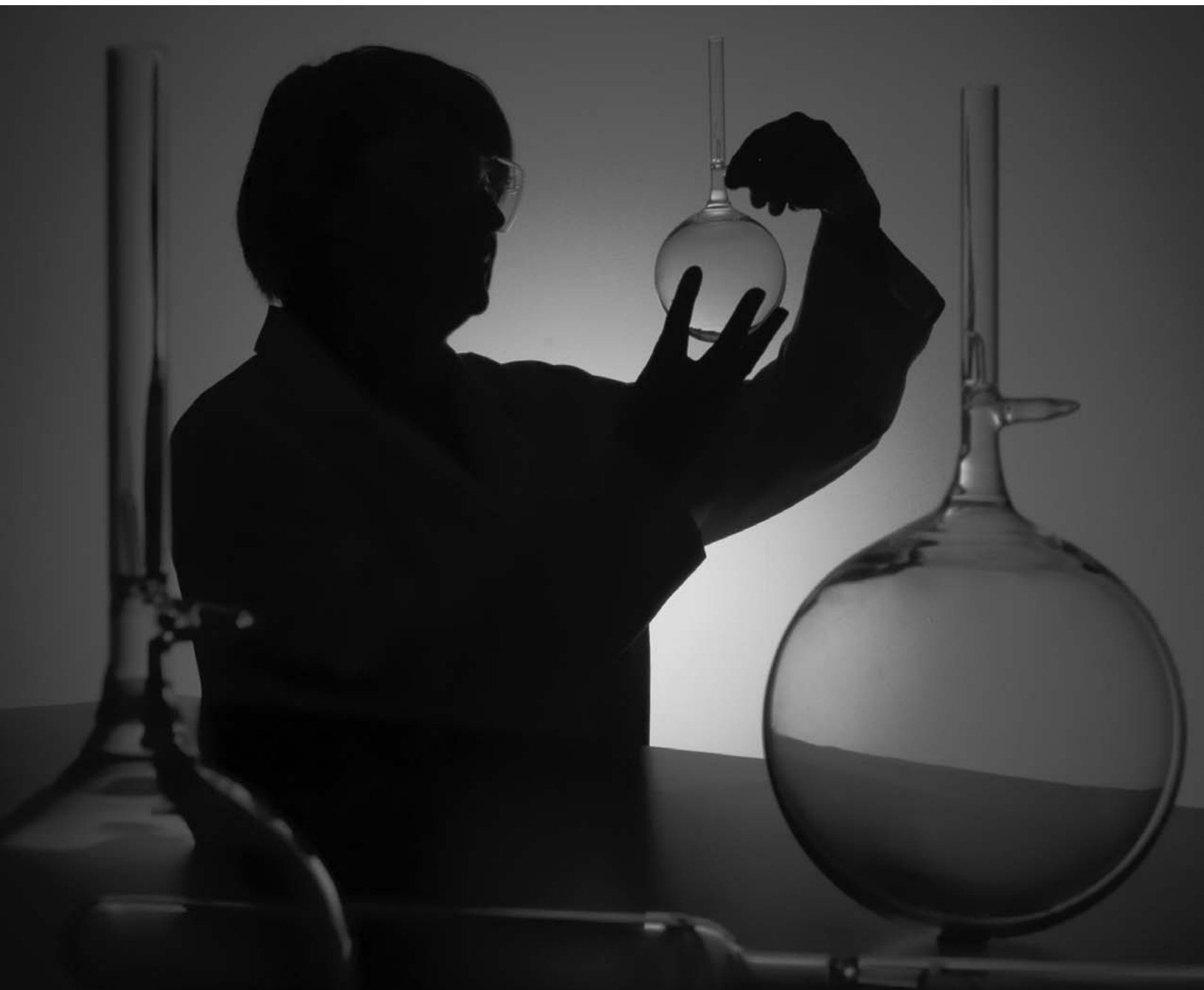
† AMERICAN LUNG ASSOCIATION® [lungusa.org](http://lungusa.org) / 1-800-LUNGUSA





# Research Awards Nationwide 2010-2011

‡ AMERICAN LUNG ASSOCIATION® [lungusa.org](http://lungusa.org) / 1-800-LUNGUSA



## **Research Awards Nationwide 2010–11**

American Lung Association  
National Headquarters  
1301 Pennsylvania Avenue, NW  
Suite 800  
Washington, DC 20004-1725  
Phone: (202) 785-3355  
Fax: (202) 452-1805

New York City Office  
14 Wall Street, Suite 8C  
New York, NY 10005-2113  
Phone: (212) 315-8700  
Fax: (212) 608-3219

<http://www.LungUSA.org>  
Copyright © 2010 by the American Lung Association  
American Lung Association is a registered trademark

*Fighting for Air*

Designed by Our Designs, Inc., Nashville, TN  
Printed and bound by Hard Copy Printing, New York, NY

---

# CONTENTS

---

Introduction	5
Asthma	7
Disorders of the Lung's Blood Vessels and Acute Lung Injury	17
COPD, Smoking, and Air Pollution	21
Tuberculosis	27
Other Lung Infections	33
Lung Cancer	39
The Immune System, Inflammation and Lung Scarring	45
Diseases of Infants and Children	51
Glossary	57
Topic Index	63
Reviewers	64

---

*The mission of the  
American Lung Association  
is to save lives by  
improving lung health and  
preventing lung disease.*

---

---

## INTRODUCTION

---

**T**he lungs are the doorway to life, providing oxygen and eliminating carbon dioxide. Since they are in constant contact with both the outside air and the body's internal environment, the lungs are uniquely vulnerable to disease. Every year, over 390,000 Americans die of lung disease, making it the third most frequent cause of death in this country. An additional 38 million of us are living with chronic lung diseases such as asthma and emphysema.

The mission of the American Lung Association is to save lives by improving lung health and preventing lung disease through research, advocacy, and education. The American Lung Association Nationwide Research Program supports both the basic and applied sciences related to lung health. Our Asthma Clinical Research Centers Network consists of 18 Centers and a Data Coordinating Center that conduct clinical studies around the country on solutions to real life problems in managing asthma.

The American Lung Association supports basic and clinical research through training and "seed" grants for beginning investigators, which play a critical role in attracting and retaining talented scientists focused on lung research. Research is the key that will unlock the door to a better tomorrow for all people with lung disease.



---

## ASTHMA

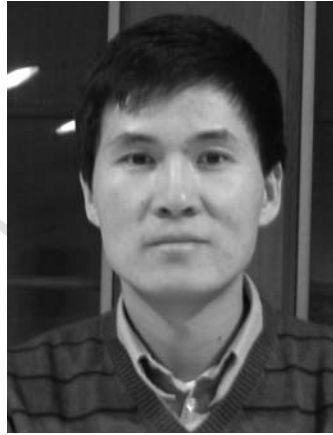
---

**C**lose to 24.6 million Americans have asthma, and 12.8 million of them have had an asthma attack in the past year. Asthma is a leading serious chronic illness in children. Although rates have stabilized, medical professionals continue to be concerned with the dramatic increase in the number of asthma sufferers over the past two decades, during which asthma prevalence almost doubled. The enormous impact on the health and well-being of those who are afflicted and the great cost of health care related to asthma are increasingly serious concerns, as is the fact that asthma kills almost 3,500 Americans each year.

There is reason for optimism despite these bleak facts. Research on asthma offers a real chance for dramatic success, as it is to a great extent, a reversible disease. The American Lung Association supports extensive research in asthma in a number of critical areas. Because asthma often runs in families and affects the various races differently, investigators are studying the genes associated with the disease. Cellular and molecular mechanisms of the allergic and inflammatory responses involved in asthma are being studied. The important role of obesity in increasing the severity of asthma is being studied, as are the basic hypotheses for the asthma epidemic of the last generation. New asthma treatments are being examined, some quite novel such as the potential for using stem cells, and promising new methods for managing the disease, especially in emergency rooms and inner city populations, are being sought.

The American Lung Association's Asthma Clinical Research Centers Network is also conducting a number of studies, ranging from investigations into the genetic basis of asthma to examinations of the role of heartburn in precipitating asthma to novel treatments based upon soy proteins. Other Network projects are evaluating the effectiveness of educational programs in controlling asthma.

## American Lung Association Scholar: Asthma



---

**QUAN LU, PhD**  
**Harvard University**

---

Beta-agonists, the mainstay of asthma drugs, bind to the beta2-adrenergic receptor (b2AR) in the lung to relax smooth muscles and to reduce constriction in the airways. The medicine allows a person with asthma to breathe easier as the airway relaxes and gets bigger. But over time, beta-agonists become less effective. Many people with asthma find they have to take more and more of the drug in order to get relief from their asthma. This is because the receptors on the cells targeted by the drugs become degraded as they are bombarded by beta-agonists repeatedly. This means that fewer and fewer receptors are available to lock onto the asthma drug. Eventually, the drug may stop working completely.

Quan Lu, Ph.D., is searching for genes that are involved in the degradation of these receptors. With a Biomedical Research Grant from the American Lung Association, Dr. Lu is using a powerful tool developed in his lab that inactivates genes one at a time in order to study which genes are involved in this degradation process. With the tool, they will screen all 28,000 human genes in a “gene inactivation library” in the lab. They will use cells that produce beta2 receptors in order to look for genes that are involved in degrading the receptors when flooded with beta-agonists.

“We know that some people respond better to beta-agonists than others, and we want to find those genetic differences that account for this,” Dr. Lu says. “What’s exciting is that we could find genes that provide a target to improve beta-agonist therapy.” He notes that this is the first step in a long process. “In later stages of the research we plan to study why certain genes are critical for beta-agonists’ response, and then eventually we would hope to develop a therapy based on this research that would increase beta2-receptors on cells so they would have a better response.”

To see a complete description of Dr. Lu’s research project, please go to page 11.

**SCOTT ALPER, PhD**

National Jewish Health, Denver, CO

*Biomedical Research Grant* • Funded by the American Lung Association

---

**Seeking Genes That Affect Asthma and COPD**

---

***Genes that Affect Inflammatory Lung Disease.***

One feature that asthma and COPD share is that inflammation can either cause or worsen both diseases. The researchers are investigating the possibility of modifying inflammation during the progression of disease as an approach to developing novel diagnostic and treatment options. They will use immune cells to identify novel genes that regulate inflammation. They will compare the data generated by these cells to known lung disease-specific information from human patients in order to identify novel genes that regulate inflammatory lung diseases. These candidate disease genes will be further studied in mouse models of lung disease. The novel genes found could be used for better diagnosis and management of at-risk patients, and could lead to alternate monitoring strategies and prevention strategies. The novel genes could also be potential targets for the development of new treatments.

**TRACEY BONFIELD, PhD**

Case Western Reserve University, Cleveland, OH

*Biomedical Research Grant* • Funded by the American Lung Association

---

**Stem Cells May Reduce Lung Inflammation in Asthma**

---

***Mesenchymal Stem Cells Suppress Lung Inflammation.***

Inhaled corticosteroids are the standard anti-inflammatory medication for people with asthma and are effective in many cases. However, there are still a substantial number of people with asthma who have symptoms even when adding long-acting beta2-agonists to their treatment. Long-term treatment with oral steroids, a treatment for severe asthma, can have serious side effects. Therefore new treatment options are still needed. The researchers will study a type of stem cell called mesenchymal stem cells as a potential asthma treatment. These stem cells, made in the bone marrow, may be able to reduce inflammation in the airways, the immune system's response to

asthma. These stem cells are already used to suppress inflammatory response after bone marrow transplants in humans. The researchers will use a mouse model of asthma to test the effectiveness of the stem cells on reducing lung inflammation.

**REBECCA GAIL BRESLOW, MD**

Brigham and Women's Hospital, Boston, MA

*Senior Research Training Fellowship* • Funded by the American Lung Association

---

**Immune System Receptors May Provide Insight Into Asthma**

---

***The Role of Leukocyte Immunoglobulin-like Receptors on Mononuclear Phagocytes in Antigen-Induced Pulmonary Inflammation.***

Asthma is a disease that affects millions of people in the United States. The search for new medicines to help people with this disease is an important public health issue. The researchers will study a family of receptors called leukocyte immunoglobulin-like receptors that are on the surface of cells in the immune system that are involved in allergic lung disease. Some of these receptors may help prevent or cure disease, but others may make disease worse, so more investigation is needed about how these receptors affect allergic lung disease. The researchers' long-term goal is to understand more about how these receptors work so that they can identify those that are the most likely to be good candidates as therapeutic targets to treat asthma. The researchers will use a model in which mice inhale dust mite allergen, which contributes to asthma in humans. In other studies, they will use human blood cells and lung tissue to more directly investigate the contributions of the receptors in humans. They expect that the studies will bring them closer to identifying new therapeutic targets that could be used to reduce the incidence and severity of asthma.

**KA YOUNG CHUNG, PhD**

Stanford University, Stanford, CA  
*Senior Research Training Fellowship* • Funded by the American Lung Association

---

Learning Details of Protein Complex Could Aid in Asthma Drug Development

---

***The Structure of a G Protein Coupled Receptor-G Protein Complex.*** Most asthma drugs target a protein called G protein-coupled receptors (GPCR-G) in certain cells in the airway and blood. These receptors are produced in cell membranes, and transfer signals into the cells by coupling with molecules called G proteins. Once activated by receptors, G-proteins control on or off “switches” within the cell that regulate various cell functions. It is important to understand the precise mechanism of how GPCR activate G proteins in order to develop new drugs that target GPCR signaling pathways while reducing side effects. The researchers will use a technology called mass spectrometry to study GPCR-G protein coupling and devise a molecular model. This structural information of GPCR-G protein complex will open new possibilities for drug development targeting GPCRs.

**OLIVER HAWORTH, PHD**

Brigham and Women’s Hospital, Boston, MA  
*Senior Research Training Fellowship* • Funded by the American Lung Association

---

Anti-Inflammatory Substances May Lead to New Asthma Treatments

---

***Promoting Resolution of Allergic Airway Inflammation.*** During an asthma attack, the bronchial tubes become inflamed. Most inflammatory responses are “acute,” meaning they last only briefly and then go away when the cause of the irritation is removed. The end of the inflammatory response is called the “resolution” phase. Until recently this phase was thought to be a passive event. However new research has shown that this phase is the result of an active process, with new molecules produced to promote resolution. Recently distinct anti-inflammatory substances called “resolvins” derived from polyunsaturated fatty acids commonly found in oily fish (long known to be beneficial to health) have been discovered and shown to have potent

anti-inflammatory actions. When resolvins are administered to mice that have airway inflammation similar to asthma, the inflammation goes away much faster. The researchers found that resolvins sped up resolution of airway inflammation in part by increasing the production of anti-inflammatory substances called lipoxin A4 and interferon gamma. The researchers will explore the mechanism by which resolvins increase production of lipoxin A4 and interferon gamma, which may lead to new asthma treatments.

**SHAMSAH KAZANI, MD**

Brigham and Women’s Hospital, Boston, MA  
*Asthma Clinical Patient Care Research Grant* • Funded in partnership between the American Lung Association and the Chest Foundation

---

Assessing Why Leukotriene-Modifying Drugs Help Only Some With Asthma

---

***Leukotriene Pathway Polymorphisms: Asthma Pharmacogenetics and Exhaled Biomarkers.***

Leukotrienes are chemicals that contribute both to asthmatic inflammation and bronchial muscle contraction. For some people with asthma, leukotriene-modifying drugs lessen symptoms, improve breathing capacity, and reduce the frequency of asthma attacks. They can also be used in combination with other asthma medicines for more severe disease. But up to half of people with asthma do not respond to leukotriene-modifying drugs. They also can affect other types of asthma treatment. The researchers plan to define the genetic variations in the way leukotrienes affect people with asthma, and the ability of these variations to change people’s response to asthma therapy. They will also measure leukotriene levels in exhaled breath samples to determine if these levels can predict the underlying genetic variations. The results of this research will help scientists to predict which patients would benefit from or be resistant to particular asthma therapies, decreasing illness due to use of ineffective medications and/or side effects.

**HYUN-HEE LEE, PhD**

Children's Hospital Boston, Boston, MA

Senior Research Training Fellowship • Funded by the American Lung Association

---

**Exploring Immune Cells' Role in Development of Asthma**


---

***TIM-1 Costimulation and NKT Cells in Asthma.***

In order to develop more effective therapies for asthma, a greater understanding is needed of the immune system's role in the disease. Immune cells called natural killer T (NKT) cells are crucial for the development of asthma in mouse models. NKT cells are also present in the lungs of people with asthma. The researchers will evaluate whether an asthma susceptibility gene called TIM-1 activates NKT cells and enhances their survival. They will study how TIM-1 affects the function of NKT cells and determine the specific way in which this occurs. These studies will demonstrate a novel way in which NKT cells regulate immune responses in the development of asthma. Because NKT cells appear to play such an important role in the development of asthma, these studies could provide new approaches for the prevention, therapy and cure of asthma.

**QUAN LU, PhD**

Harvard University, Boston, MA

Biomedical Research Grant • Funded by the American Lung Association

---

**Genetic Tool May Help Explain Why Beta-Agonists Lose Their Effectiveness**


---

***Novel Regulators of Beta2-Adrenergic Receptor Down-regulation.*** Asthma is a chronic lung disease that affects millions of people, including 7 million children in the United States. Beta-agonists, the most widely used asthma drug, work on the beta2-adrenergic receptor (b2AR) in the lung to relax smooth muscles and reduce constriction in the airways. However, over time, beta-agonists become less effective, mainly because continued stimulation of receptors by beta-agonists reduces the amount of functional receptors in the lung. Improved understanding of this process would benefit asthma therapy. Using a powerful genetic tool developed in their lab, the researchers hope to identify critical genes that play an important role

in this degradation of the beta2-adrenergic receptor and understand their roles in the process. The research may provide new ways to improve beta-agonist-based asthma therapies.

**VERA MOISEENKOVA-BELL, PhD**

Case Western Reserve University, Cleveland, OH

Biomedical Research Grant • Funded by the American Lung Association

---

**Study of "Irritant Receptor" in the Airways Could Lead to Future Asthma Drugs**


---

***Structure-Functional Analysis of TRPA1: Ion Channel Involved in Airway Inflammation and Asthma.***

Asthma is a complex lung disorder caused by inflammation in the airways. Airway irritants can cause a variety of lung problems. The researchers are studying a newly discovered protein called TRPA1, a so-called "irritant receptor" that detects irritation in the airways and is key in the development of airway inflammation. They will develop an extensive understanding of the structure and function of TRPA1. By studying the three-dimensional structure of this protein, they hope to find out how irritants such as smoke, vehicle exhaust, and air pollution trigger asthma. This knowledge could lay the groundwork for future studies that could ultimately help in designing anti-inflammatory medication that could significantly improve the lives of asthma patients.

**KARI CHRISTINE NADEAU, MD, PhD**

Stanford University, Stanford, CA

Allergic Disease Award • Funded in partnership between the American Lung Association and the AAAAI Foundation

---

**Defining the Role of Ambient Air Pollution in Children's Asthma**


---

***The Role of Ambient Air Pollution in the Modulation of the Immune System in Asthma.***

Studies have demonstrated that short-term and long-term exposure to ambient air pollution leads to detrimental changes in the lung and blood. Children have been found to be at the highest risk of the untoward health effects of ambient air pollution. The researchers will study the role of air pollution in asthma. They will study whether children with increased chronic exposure to air pollution have increased asthma and will define specific

molecular mechanisms associated with air pollution and asthma in children. The researchers will compare children, both with and without asthma, in two California communities, Fresno and Stanford. Fresno, the third most polluted city in the United States, has been shown to have an asthma prevalence five times higher than the nationwide average. They will study function of immune cells called T cells from children in both cities. The study will include analysis of individual air pollution exposure data, health questionnaires and lung function tests. The researchers hope to learn whether specific exposures, the health outcomes of individual children, and changes in the immune system are correlated.

#### **MARINA REZNIK, MD**

Montefiore Medical Center, Bronx, NY  
*Clinical Patient Care Research Grant* • Funded by the American Lung Association

---

#### **Can Home-Based Asthma Program Help Inner-City Children?**

---

##### ***Health Worker Home-Based Asthma Intervention.***

Asthma disproportionately affects low-income African-American and Hispanic children living in inner cities. Not taking daily asthma medications as prescribed by the doctor has been implicated as one of the major factors in poor asthma outcomes in these communities. The researchers will evaluate the effectiveness of a home-based asthma education program called Wee Wheezers delivered by Community Health Workers, who share many of the experiences of the people in the community. The program is designed to improve adherence to medication and parental asthma knowledge, in order to reduce asthma symptoms and Emergency Department asthma visits. The study will include 250 children ages 2-7 being treated for persistent asthma, and their parents. They will be randomly assigned to routine care from their doctor, or the Wee Wheezers program. The researchers will determine whether the program is effective in decreasing the number of asthma symptom days, increasing adherence to taking prescribed asthma medication, and decreasing asthma-related Emergency Department visits. The study will also compare parental asthma knowledge and asthma management practices between the two groups.

#### **YUI-HSI WANG, PhD**

Cincinnati Children's Hospital Medical Center, Cincinnati, OH  
*Allergic Disease Award* • Funded in partnership between the American Lung Association and the AAAAI Foundation

---

#### **Unique Type of White Blood Cell May Provide Clues to Allergic Asthma**

---

***The Roles of IL-17-Producing TH2 Memory/Effector Cells in Allergic Asthma.*** Severe allergic asthma often results from an uncontrolled immune response and airway inflammation. A type of long-living white blood cell called memory type-2 T-helper cells (Th2) is believed to be the principal cell type that causes recurrent symptoms in patients with allergic asthma. These memory Th2 cells can produce substances called Th2 cytokines that trigger a potent allergic immune response. Another immune factor, called interleukin-17, has an important role in triggering airway inflammation. The researchers have discovered a unique type of Th2 cell that can produce both Th2 cytokines and interleukin-17, thereby inducing a potent allergic response as well as airway inflammation. They will study the factors that regulate the production of these unique Th2 cells and identify their roles in driving the severity of chronic allergic asthma. The study will provide new insights into the nature of long-lived Th2 cells and may pave the way for improved diagnosis and treatment of allergic disease.

#### **ZHONG-XIN WU, MD**

West Virginia University, Morgantown, WV  
*Biomedical Research Grant* • Funded by the American Lung Association

---

#### **Researching How Secondhand Smoke Leads to Asthma**

---

***Neural Mechanisms of Secondhand Smoke-Induced Airway Hyperresponsiveness in Early Life.*** While many studies link embryonic and early environmental tobacco smoke (ETS) exposure with childhood asthma and other lung diseases, the underlying mechanisms that cause these changes in the womb and early life remain unknown. The researchers will study changes in the airways induced by exposure to ETS during early life that potentially leads to increased susceptibility and occurrence of asthma and other lung diseases later in childhood or as adults. They will focus on nerve

growth factor (NGF), which is essential in promoting and maintaining growth and survival of the nervous system. Disruption of normal production and release of NGF after inhaling smoke results in changes in the airways which leads to disease-related abnormalities in the respiratory system. They will study whether ETS enhances production of NGF during pregnancy and shortly after birth in mice, and examine whether these changes cause increased susceptibility to asthma in early life and beyond, into adulthood.

### **CUNEY YILMAZ, PhD**

UT Southwestern Medical Center, Dallas, TX

*Biomedical Research Grant* • Funded by the American Lung Association

---

#### Investigating the Relationship Between Obesity, Diabetes and Lung Problems

---

***Structure-Function Relationships in the Fatty Diabetic Lung.*** Obesity and type-2 diabetes are major health problems that often coexist and affect multiple organs, including the lung. Both diabetes and obesity can cause low-grade inflammation in the lung, restrict the volume of air the lung can take in, and cause abnormal breathing responses to exercise stress. These lung problems are usually moderate in young patients, but accelerate at a faster than normal rate with aging. The reduced lung function may contribute to serious heart and lung problems in older people and in the presence of other factors that put stress on the lung such as exposure to tobacco or environmental pollutants, lung diseases or heart and kidney diseases. There is a need to understand how and why obesity and diabetes affect lung structure and function, and whether their adverse effects on lung health can be reversed with treatment. The researchers will use a novel technique to measure heart and lung function in a rodent model of genetic obesity-associated diabetes, which will help them better understand the loss of lung function related to this condition. The study will also provide a model to test the effectiveness of potential treatment approaches.

### **NIVES ZIMMERMANN, MD**

Cincinnati Children's Hospital Medical Center, Cincinnati, OH

*Allergic Disease Award* • Funded in partnership between the American Lung Association and the AAAAI Foundation

---

#### Acid May Play Important Role in Asthmatic Airways

---

#### ***Mechanism of Airway Acidification in Asthma.***

Despite intense research and significant advances in clinical care, asthma is still not well controlled in some patients. This results in acute asthma flare-ups and Emergency Department visits. Understanding how asthma develops is likely to provide the rationale for new treatments. Clinical studies have shown that the airways of people with asthma become acidic, and that buffering airway acid improves symptoms. However, more information is needed about acid in the airways of people with asthma. Using a mouse model, the researchers will explore the role and mechanism of airway acidification in asthma. The researchers have already found that mouse airways are acidified when they are inflamed, which occurs in asthma. The study findings could have considerable implications for the development of therapies that target airway acidification in asthma and other diseases that involve inflammation of the airways including COPD and cystic fibrosis.

## **Asthma Clinical Research Centers: A Unique Network to Benefit Patients**

The Asthma Clinical Research Centers (ACRC) Network, sponsored by the American Lung Association, conducts large clinical trials that provide vital information about caring for people who have asthma. The Network comprises 18 clinical Centers and a Data Coordinating Center, making it the largest of its kind. Its unique focus on large numbers of patients differentiates it from current other federally funded and commercial research, and provides practical information about asthma care that has direct benefits for patients.

The ACRC Network is currently conducting the following studies:

### **SARCA: Study of Acid Reflux and Childhood Asthma**

Co-Funded by the National Institutes of Health's National Heart, Lung and Blood Institute

Acid reflux disease, also known as gastroesophageal reflux disease or GERD, is frequent among people with poorly controlled asthma. It often occurs with no symptoms and can induce constriction of the airways. Poorly controlled asthma patients are frequently treated for GERD with drugs that suppress gastric acid, but this approach is expensive and its benefit has not been established. This clinical trial is testing the hypothesis that children with symptomatic asthma have improved asthma control when treated for gastroesophageal reflux disease with a class of drugs called proton pump inhibitors. Three hundred children between the ages of 6 and 17 who have asthma that is not well controlled with inhaled steroids are being studied, and are randomly assigned to treatment with either a proton pump inhibitor or a placebo. The results will point the way to more effective methods to control acid reflux and prevent it from contributing to asthma.

### **Study of Asthma and Nasal Steroids (STAN)**

Co-Funded by the National Institutes of Health's National Heart, Lung and Blood Institute

Rhinitis and sinusitis are significant causes of morbidity, associated with poor asthma control and increased health care utilization. While the co-existence of asthma and sino nasal disease is well recognized, the interaction between the two processes is not well understood. In previously conducted ACRC trials, researchers have found that over 70% of asthmatics report sinusitis, rhinitis or both. This study will determine if the treatment of chronic sinusitis and rhinitis with nasal steroids improves asthma control, lung function and quality of life in patients with poorly controlled asthma and chronic rhinitis/sinusitis. Four hundred participants aged 12+ will be randomly assigned to treatment with a nasal steroid or a placebo. The results of this study could provide significant new data to guide therapy in patients with poorly controlled asthma.

### **Study of Soy Isoflavones in Asthma (SOYA)**

Co-Funded by the National Institutes of Health's National Heart, Lung and Blood Institute

One possible reason for the increase in asthma prevalence and severity seen over the past decades is the change in diet. Epidemiological and interventional studies designed to identify a key nutrient or antioxidant vitamin that may be responsible for the increase in disease severity have produced inconsistent results. In previous ACRC trials, researchers have reported an association between low soy

genistein intake and more severe asthma. This study will test the novel hypothesis that dietary supplementation with soy isoflavones is an effective treatment in patients with poorly controlled asthma. The study will include 360 patients, age 12+, with low dietary soy intake, and taking either inhaled corticosteroids or leukotriene modifiers for poorly controlled asthma. Participants will be randomly assigned to either a soy isoflavone supplement or placebo. Results will not only increase the understanding of the role of diet in asthma but could potentially identify a novel, safe and relatively inexpensive treatment for patients with asthma.

Since its inception in 2000, the ACRC Network has completed the following studies:

#### **Study of Inactivated Influenza Vaccine in Asthmatics (SIIVA)**

**Results:** The flu vaccine is safe for asthmatics and does not induce an asthma attack.

#### **Effectiveness of Low-Dose Theophylline As Add-On Therapy In Treatment of Asthma (LODO)**

**Results:** Neither montelukast nor low-dose theophylline improved clinical asthma control, although they both improved lung function equally. Inexpensive low-dose theophylline was more beneficial in those patients who had not been prescribed inhaled corticosteroids than montelukast.

#### **The Leukotriene Modifier or Corticosteroid or Corticosteroid-Salmeterol (LOCCS)**

**Results:** Once-daily fluticasone plus salmeterol was as effective as twice-daily fluticasone treatment, while oral montelukast taken once a day was not as effective. However, montelukast did provide control for most patients.

#### **Trial of Asthma Patient Education (TAPE)**

**Results:** Optimistic drug presentation augments the placebo effect for patient-reported outcomes (asthma control) but not lung function. However, the effect of montelukast was not enhanced by optimistic messages regarding treatment effectiveness.

#### **Sinusitis and Rhinitis in Asthma (SIRNA)**

**Results:** A simple, five-item questionnaire, based on the frequency of nasal symptoms, to accurately screen for sinonasal disease was identified and proved more sensitive and specific than sinus CT scans and nasal endoscopy.

#### **Study of Acid Reflux in Adults with Asthma (SARA)**

**Results:** The longstanding practice of prescribing heartburn medication is ineffective and unnecessarily expensive for some asthma patients who do not exhibit symptoms associated with acid reflux.

#### **MeCIS: Methacholine Bronchoprovocation: Influence of High Potency Inhaled Corticosteroids**

**Results:** Have not been published.

## Asthma Clinical Research Centers (ACRC) Participants

**Michael Busk, MD**  
Indiana University  
Indianapolis, IN

**Mario Castro, MD, MPH**  
Washington University School of Medicine  
St. Louis, MO

**Rubin Cohen**  
North Shore University Hospital–  
Long Island Jewish Medical Center  
New Hyde Park, NY

**Emily DiMango, MD**  
Columbia University Medical Center  
New York, NY

**Allen Dozor, MD**  
Children’s Hospital at Westchester  
New York Medical College  
Valhalla, NY

**Lynn Gerald, PhD**  
University of Arizona  
Tucson AZ

**Nicola Hanania, MD**  
Baylor College of Medicine  
Houston, TX

**Kyle Happel, MD**  
Louisiana State University School of Medicine  
New Orleans, LA

**Charles Irvin, PhD**  
University of Vermont  
Burlington, VT

**Rohit Katial, MD**  
National Jewish Medical and Research Center  
Denver, CO

**John Lima, PharmD**  
The Nemours Children’s Clinic  
Jacksonville, FL

**Richard Lockey, MD**  
University of South Florida  
Tampa, FL

**John Mastronarde, MD**  
The Ohio State University  
Columbus, OH

**Joan Reibman, MD**  
New York University  
New York, NY

**Gary Salzman, MD**  
University of Missouri/Kansas City  
School of Medicine  
Kansas City, MO

**Lewis Smith, MD**  
Northwestern Center for Clinical Research  
Chicago, IL

**John Sundy, MD**  
Duke University Medical Center  
Durham, NC

**Gerry Teague, MD**  
University of Virginia  
Charlottesville, VA

**Adam Wanner, MD**  
University of Miami School of Medicine  
Miami, FL

**Stephen I. Wasserman, MD**  
University of California, San Diego  
San Diego, CA

**Robert Wise, MD**  
Johns Hopkins University,  
Center for Clinical Trials  
Baltimore, MD

---

## DISORDERS OF THE LUNG'S BLOOD VESSELS AND ACUTE LUNG INJURY

---

**A**cute lung injury, also known as acute respiratory distress syndrome or ARDS, is a syndrome in which the small blood vessels in the lungs become widely impaired, causing them to leak fluid and inflammatory cells into the lungs as a response to infection, shock, or the presence of noxious agents. Approximately 190,000 Americans are affected with ARDS each year, and it is often the major complication of extensive infection, surgery, trauma, chemotherapy, and lung transplantation. No effective treatment yet exists.

Pulmonary arterial hypertension is a condition in which the blood vessels in the lungs constrict abnormally, forcing the heart to work harder to propel blood through the lungs and causing the blood pressure within the lungs to rise. It occurs in response to a variety of associated disorders, ingestion of certain medications, and also in an “idiopathic” form that is without a known cause.

American Lung Association researchers are attacking the problem of ARDS primarily on the cellular and molecular levels using sophisticated models of disease. Many of these studies are directed toward finding new therapies. The mechanisms of pulmonary hypertension are being studied from several perspectives as well. Here, too, the emphasis is upon understanding the basic mechanisms so that new therapeutic approaches can be tried.

## **American Lung Association Scholar: Disorders of the Lung's Blood Vessels**



---

**ANASUYA SARKAR, PhD**  
**Ohio State University**

---

Many patients in the ICU with sepsis, major trauma or shock suffer from acute respiratory distress syndrome (ARDS), a dangerous condition with no effective treatment. Anasuya Sarkar, PhD, is searching for an explanation of how ARDS develops. She hopes that understanding how a particular protein called caspase-1 injures lung cells in ARDS will one day lead to a treatment for this devastating disease.

With an American Lung Association Biomedical Research Grant, Dr. Sarkar is studying how caspase-1 injures a layer of cells lining the lungs called the epithelium. Damage to this layer of cells leads to infection and a downhill slide for ARDS patients. “We want to understand how injury to these cells happens and what we can do to prevent it,” Dr. Sarkar says.

Caspases are found inside immune system cells called macrophages, which fight infection. “We think the macrophages are packaging caspases in tiny particles and using them like a gun to kill damaged epithelial cells in the lung, which leads to lung damage,” she says. “This process of fighting infection is good at the beginning, but when this cell death continues it can cause life-threatening lung damage.”

Dr. Sarkar is examining the way in which caspase-1 sends signals to epithelial cells. “If we can find the exact mechanism of these cell signaling pathways, it may be possible to develop drugs that block these killing pathways to stop the lung cell injury,” she says.

“The American Lung Association grant is extremely beneficial in supporting me as I start my research,” Dr. Sarkar says. “The data I gather from this project will allow me to expand it, and seek bigger funding.”

To see a complete description of Dr. Sarkar’s research project, please go to page 19.

**KAISER MOHAMMAD BIJLI, PhD**

University of Rochester, Rochester, NY

*Biomedical Research Grant* • Funded by the American Lung Association

---

**Blocking Excess Protein Production May Lead to New Lung Injury Treatments**

---

***Regulation of Endothelial NF-kappaB Activity and ICAM-1 Expression by c-Src.***

Thrombin is an enzyme that promotes blood clotting. It is released during sepsis and tissue injury. Upon its release, it interacts with blood vessel wall cells called endothelial cells and activates these cells. This activation process increases the production of a protein called ICAM-1 on the surface of endothelial cells, which promotes the binding of circulating white blood cells to the endothelium, the layer of cells that line the blood vessels. This binding promotes the migration of white blood cells across the endothelium to the site of inflammation, a process which is implicated in the development of acute lung injury. Although scientists have come to realize that ICAM-1 plays a crucial role in acute lung injury, the precise way this protein is produced remains unclear. The researchers will study the regulation and the role of ICAM-1 in lung injury. This research may reveal ways to block excess production of ICAM-1, leading to new treatment targets for inflammatory diseases involving acute lung injury.

**JEAN-FRANCOIS JASMIN, PhD**

Thomas Jefferson University, Philadelphia, PA

*Biomedical Research Grant* • Funded by the American Lung Association

---

**Can Membrane Protein Prevent Development of Pulmonary Hypertension?**

---

***Role of Cav-1 in the Pathogenesis of Pulmonary Arterial Hypertension: Therapeutic Implications.***

Pulmonary arterial hypertension is a common disease characterized by high blood pressure in the arteries of the lungs which eventually leads to heart failure and death. None of the current drugs cure or halt the progression of this disease. Caveolin-1 is a membrane protein that has recently been shown to be involved in the regulation of pulmonary arterial hypertension. Decreases in Ca-

veolin-1 have been reported in patients with severe pulmonary arterial hypertension. The researchers will study whether a Caveolin-1-mimetic peptide can reverse the development of pulmonary arterial hypertension in an animal model. This research will provide important information on the role of Caveolin-1 in the development of pulmonary arterial hypertension, and may lead to the development of alternative treatments.

**ANASUYA SARKAR, PhD**

Ohio State University, Columbus, OH

*Biomedical Research Grant* • Funded by the American Lung Association

---

**Targeting Protein that Causes Death in Lung Lining May Lead to ARDS Treatment**

---

***ARDS: Injury from Microvascular Caspase-1.***

Acute respiratory distress syndrome (ARDS) is a potentially fatal lung condition that usually occurs in people who are very ill with another disease or who have major injuries. ARDS is characterized by damage to the layers of cells lining the lungs called the epithelium. The researchers are studying a protein called caspase-1 that is normally involved in activating other proteins to fight infection. They have found that caspase-1 is also uniquely capable of killing cells in the epithelium, leading to severe illness in patients with ARDS. They hope that by understanding the complex system of cell communication that caspase-1 uses to kill cells, they will be able to come up with new therapies that target these pathways, thereby preventing the proteins from causing lung cell injury.

**UMAPATHY NAGAVEDI SIDDARAMAPPA, PhD**

Medical College of Georgia, Augusta, GA

*Biomedical Research Grant* • Funded by the American Lung Association of the Southeast

---

**Enzyme Could Help Protect Lungs Against Damage from Injury**

---

***Beta-Nicotinamide Adenine Dinucleotide (b-NAD) Mediated Signaling Cascades Protects and Repairs Endothelial Cell Barrier.*** The severe form of acute lung injury (ALI), called acute respiratory distress syndrome (ARDS) is associated with high death rate (30-50%) affecting all or most of both lungs that occur as a result of illness, injury

or trauma. The injured lung becomes significantly inflamed, resulting in damage to the endothelium, the layer of cells lining the inner surface of blood vessels which provides a selective barrier between blood and the surrounding tissue. These changes in the endothelium make it more permeable, allowing a dangerous buildup of fluid in the air sacs of the lungs. The researchers are studying the dysfunction of the endothelial barrier caused by injury that makes it more porous. They are looking at a molecule called b-NAD that protects and repairs the endothelium. A better understanding of the way in which b-NAD works could lead to treatments for this devastating disease where there is no treatment presently available except putting the patient on a ventilator.

---

## COPD, SMOKING, AND AIR POLLUTION

---

**S**moking is the major cause of chronic obstructive pulmonary disease (COPD), while air pollution can both cause the condition and make it worse. The work of the American Lung Association has been critical in achieving a significant decline in cigarette smoking in the past 30 years, from 37.4 percent in 1970 to 20.6 percent of the adult population in 2008, and in accomplishing important reductions in air pollution during the same time frame. Nevertheless, over 46 million adults still smoke; until recently, teenage smoking has been on the rise; and the American Lung Association estimates that over 175 million Americans live in counties with unhealthy levels of either ozone or particle pollution.

The American Lung Association supports a broad-based program of research into many aspects of COPD. Laboratory studies and patient-oriented investigations continue to look for answers to the fundamental questions of how the lungs and airways are damaged in COPD and what can be done to treat and prevent this destruction. The role of cadmium, an important pollutant in causing COPD and lung cancer is under investigation. Other investigations are exploring genetic susceptibility to lung damage by cigarette smoke at the molecular level. A treatment for emphysema using a novel approach is being tested in laboratory studies.

The American Lung Association continues to support research on smoking prevention and smoking cessation with an emphasis on motivation and education that is culturally specific across several target, “hard to reach” cultures.

## **American Lung Association Scholar: COPD**



**ESTELLE CORMET-BOYAKA, PhD**  
**Ohio State University**

Cadmium, a toxic heavy metal, is an air pollutant found in coal, diesel exhaust and cigarette smoke. Inhaling cadmium has been linked to lung cancer and chronic obstructive pulmonary disease (COPD). Cadmium's half-life, or the amount of time it takes to decrease by half, is 20 to 30 years, meaning that it accumulates in the body.

Estelle Cormet-Boyaka, PhD, is using an American Lung Association Biomedical Research Grant to study how cadmium affects the lung. She is focusing on a protein in the lung called CFTR, which is involved in the development of cystic fibrosis (CF). Cystic fibrosis is caused by mutations in the CF gene, which makes the CFTR protein. In healthy people, CFTR secretes chloride ions onto the inner surface of the lungs, which helps the lungs to prevent microbial infection. In cystic fibrosis, many mutated CF genes degrade and disappear before they can function. The lack of sufficient chloride secretion can lead to an accumulation of mucus and bacteria in the lungs. This in turn leads to chronic inflammation in the lungs.

Dr. Cormet-Boyaka will be studying the mechanism by which cadmium affects the production and function of CFTR, and causes inflammation. People with CF have two defective CF genes. She says it is possible that people with one defective CF gene, who produce less CFTR, and are exposed to high levels of cadmium, end up with excess mucus and bacteria in the lungs. This could lead to too much inflammation and the subsequent development of lung diseases such as chronic bronchitis, a type of COPD. "Once we understand the role of cadmium on CFTR and its ability to induce inflammation, we want to investigate CFTR's role in other lung diseases linked to cadmium, such as COPD," she says. "If we find that CFTRs are involved, then ultimately drugs being developed for cystic fibrosis that increase CFTR production also might be tested for other lung diseases."

Dr. Cormet-Boyaka is grateful to the American Lung Association for her grant, which she hopes will help her generate enough data to apply for a grant from the National Institutes of Health. "Then we will be able to really investigate the question of whether CFTR is involved in other airway diseases and the contribution of cadmium to that process," she says.

For a complete description of Dr. Cormet-Boyaka's research project, please go to page 23.

**TRACY ADAIR-KIRK, PhD**

Washington University in St. Louis, St. Louis, MO  
*Biomedical Research Grant* • Funded by the American Lung Association

---

**Understanding How Smoking Causes Emphysema**

---

***Effects of Oxidation on the Protease Susceptibility of Elastic Fibers.*** Emphysema is a destructive lung disease that afflicts millions of people worldwide and is the fourth leading cause of death in the United States. Although it is known that smoking is the principal risk factor for developing emphysema, there are still many unknowns about the exact way in which smoking causes emphysema. Cigarette smoke induces inflammatory cells to enter the lung. These cells release enzymes that break down critical proteins of elastic fibers, which are key lung structures that allow the stretch and recoil essential for normal lung function. Inflammatory cells also produce substances called oxidants that promote the development of emphysema by damaging lung cells and inhibiting protective enzymes. The researchers have found that oxidants can also damage elastin, the main component of elastic fibers, making it more susceptible to breakdown by enzymes. Understanding the way in which oxidants cause damage to elastin and promote elastic fiber destruction will provide new insight into development of emphysema and may enhance scientists' ability to develop strategies to prevent the development of emphysema.

**SCOTT ALPER, PhD**

National Jewish Health, Denver, CO  
*Biomedical Research Grant* • Funded by the American Lung Association

---

**Seeking Genes That Affect Asthma and COPD**

---

***Genes that Affect Inflammatory Lung Disease.*** One feature that asthma and COPD share is that inflammation can either cause or worsen both diseases. The researchers are investigating the possibility of modifying inflammation during the progression of disease as an approach to developing novel diagnostic and treatment options. They will use immune cells to identify novel genes that regulate inflammation. They will compare the data generated by these cells to known lung disease-

specific information from human patients in order to identify novel genes that regulate inflammatory lung diseases. These candidate disease genes will be further studied in mouse models of lung disease. The novel genes found could be used for better diagnosis and management of at-risk patients, and could lead to alternate monitoring strategies and prevention strategies. The novel genes could also be potential targets for the development of new treatments.

**ESTELLE CORMET-BOYAKA, PhD**

Ohio State University, Columbus, OH  
*Biomedical Research Grant* • Funded by the American Lung Association

---

**Finding How Cadmium Accumulation in the Lungs Leads to Lung Disease**

---

***Cadmium Alters Lung Function Via Regulation of Ion Transport and Inflammatory Cytokines.*** Cadmium, a toxic heavy metal, is an air pollutant found in diesel exhaust and cigarette smoke. Cadmium inhalation has been linked to lung cancer and COPD. Due to its long half-life of 20 to 30 years (the amount of time it takes for cadmium to decrease by half), cadmium accumulates in the body. The mechanism by which cadmium affects the lung is poorly understood. The researchers will investigate the effect of cadmium on CFTR, a protein which is lacking in people with cystic fibrosis. A reduction of CFTR also may be involved in other lung disease. The researchers will study the mechanism by which cadmium affects the production and function of CFTR and leads to inflammation. Understanding how cadmium inhalation affects lung function will help develop new strategies to prevent and/or protect against cadmium.

**PING-CHING HSU, MS**

Georgetown University, Washington, DC  
*Lung Health Dissertation Grant* • Funded by the American Lung Association

---

**Measuring the Impact of Smoking on Lung Cancer Risk**

---

***Cigarette Smoke-Related Metabolome.*** To better understand the impact of cigarette smoke on lung cancer risk, biomarkers of lung cancer risk are needed. Biomarkers are molecules found in blood,

other body fluids, or tissues that are a sign of a normal or abnormal process, or of a condition or disease. The researchers will identify new biomarkers of lung cancer risk through a powerful method called metabolomics, which measures and analyzes substances in the blood called metabolites. They will investigate whether the number of cigarettes a person smokes per day, how they smoke their cigarettes, and how fast their body metabolizes nicotine will affect how much cancer-causing substances end up in the blood. The information found in the study could be used to evaluate health claims of tobacco products as well as identify former smokers most at risk of developing lung cancer.

#### **SEYED JAVAD MOGHADDAM, MD**

University of Texas M.D. Anderson Cancer Center, Houston, TX  
*Lung Cancer Discovery Award* • Funded in partnership between the American Lung Association and the LUNGevity Foundation

---

#### Seeking to Prevent Lung Cancer in People with COPD

---

***Inflammation-Related Lung Cancer Prevention by Targeting the NF-κB Pathway.*** Many studies have found that smokers with chronic obstructive pulmonary disease (COPD) have an increased risk of lung cancer compared with smokers with comparable cigarette exposure but without COPD. Although smoking causes most cases of COPD, only 25% of smokers develop COPD. A person's susceptibility to developing COPD and lung cancer is thought to reflect genetic variation in the body's inflammatory response to inhaled smoke and to microorganisms colonizing the injured airways of smokers. These facts suggest a link between chronic airway inflammation and lung cancer, but the precise way in which the link works is unknown. The researchers will use a mouse model to study the mechanism responsible for promotion of lung cancer by airway inflammation. They will concentrate on a genetic alteration found in COPD and lung cancer, involving a gene called NF-κB. They will use a genetic strategy and anti-inflammatory agents that inhibit this gene to test whether it may prevent lung cancer. This research could lead to development of anti-inflammatory therapy in patients with COPD at high risk for lung cancer, and patients with early stage lung cancer.

#### **KARI CHRISTINE NADEAU, MD, PhD**

Stanford University, Stanford, CA  
*Allergic Disease Award* • Funded in partnership between the American Lung Association and the AAAAI Foundation

---

#### Defining the Role of Ambient Air Pollution in Children's Asthma

---

***The Role of Ambient Air Pollution in the Modulation of the Immune System in Asthma.*** Studies have demonstrated that short-term and long-term exposure to ambient air pollution leads to detrimental changes in the lung and blood. Children have been found to be at the highest risk of the untoward health effects of ambient air pollution. The researchers will study the role of air pollution in asthma. They will study whether children with increased chronic exposure to air pollution have increased asthma and will define specific molecular mechanisms associated with air pollution and asthma in children. The researchers will compare children, both with and without asthma, in two California communities, Fresno and Stanford. Fresno, the third most polluted city in the United States, has been shown to have an asthma prevalence five times higher than the nationwide average. They will study function of immune cells called T cells from children in both cities. The study will include analysis of individual air pollution exposure data, health questionnaires and lung function tests. The researchers hope to learn whether specific exposures, the health outcomes of individual children, and changes in the immune system are correlated.

#### **ANNE-KARINA PERL, PhD**

Childrens Hospital Medical Center-Cincinnati, Cincinnati, OH  
*Biomedical Research Grant* • Funded in partnership between the American Lung Association and the Alpha-1 Foundation

---

#### Stopping Airway Wall Thickening to Improve COPD Survival

---

***Role of EGF Receptor in Regenerating Airway Epithelium and Airway Wall Thickening.*** Injury of the cells lining the airways can lead to airway wall thickening. Airway wall thickening has been identified as a major predictor of the severity of airway obstruction in COPD patients. It is also implicated in bronchiolitis obliterans syndrome (BOS), which is the main chronic complication after lung transplantation. Using a mouse model,

the researchers will study airway regeneration after acute injury and airway wall thickening after chronic injury. They will focus on the role of epithelial growth factor receptor (EGFR), a substance that is present in the membrane of the lung cells. Previous research has shown that EGFR is increased after cell injury, and that inhibiting EGFR signaling reduces lung scarring. The long-term goal of this study is to get a better understanding of the molecular events that control the steps that lead to airway wall thickening and to use these findings to develop effective therapeutic strategies to improve long-term survival in COPD and after lung transplantation.

#### **MASAHIRO SAKAGAMI, PhD**

Virginia Commonwealth University, Richmond, VA  
*Biomedical Research Grant* • Funded by the American Lung Association

---

#### Triple-Action Potential Treatment for Emphysema

---

***Novel Cinnamic Acid-Based Oligomers for Emphysema.*** Little is known about how smoking causes emphysema, as well as how to effectively control the disease. As a result, its treatment is limited to managing symptoms using bronchodilators and inhaled steroids, with marginal success and no cures. The researchers will test the treatment potential of unique substances called cinnamic acid-based oligomers using a rat model of emphysema. They will study how large a dose is needed to be effective, and how long the treatment lasts. If proven effective, this inhaled treatment could be a brand-new class of drug that aims to simultaneously inhibit three processes in the lung that are thought to be critically involved in the development of emphysema. The researchers will investigate whether by attacking emphysema through three mechanisms, it will have more success than current treatments, which treat one mechanism at a time (such as inflammation or airway constriction).

#### **ZHONG-XIN WU, MD**

West Virginia University, Morgantown, WV  
*Biomedical Research Grant* • Funded by the American Lung Association

---

#### Researching How Secondhand Smoke Leads to Asthma

---

***Neural Mechanisms of Secondhand Smoke-Induced Airway Hyperresponsiveness in Early Life.*** While many studies link embryonic and early environmental tobacco smoke (ETS) exposure with childhood asthma and other lung diseases, the underlying mechanisms that cause these changes in the womb and early life remain unknown. The researchers will study changes in the airways induced by exposure to ETS during early life that potentially leads to increased susceptibility and occurrence of asthma and other lung diseases later in childhood or as adults. They will focus on nerve growth factor (NGF), which is essential in promoting and maintaining growth and survival of the nervous system. Disruption of normal production and release of NGF after inhaling smoke results in changes in the airways which leads to disease-related abnormalities in the respiratory system. They will study whether ETS enhances production of NGF during pregnancy and shortly after birth in mice, and examine whether these changes cause increased susceptibility to asthma in early life and beyond, into adulthood.



---

## TUBERCULOSIS

---

**T**uberculosis (TB) remains an important disease in the United States and a worldwide epidemic that kills approximately 1.8 million people each year. Since it is transmittable and more and more people are migrating or traveling around the world, this international problem is of great concern to Americans. The worldwide AIDS epidemic has reached frightening proportions and is partly responsible for the increase in TB internationally, as the two infections often coexist. More recently, Americans have learned about the potential threat of a deadly form of TB germ that has no effective therapy and kills rapidly.

The basic cellular and immune processes that initiate and control TB infection are being studied, as are the molecules and genes in the TB germ that enable it to infect humans and become resistant to drugs. A greater understanding of how the body's immune system protects against TB and why this defense system sometimes fails is being sought. Studies such as these will provide a solid foundation for developing a better vaccine and newer treatments.

American Lung Association investigators are interested in discovering new drugs to treat troublesome "non-tuberculosis" mycobacterial infection. This infection which may be found in otherwise well middle-aged women resembles TB somewhat but is different. It appears to be rapidly increasing in prevalence.

In addition, a study is being done to determine how best to communicate complex facts about TB infection, TB disease and TB vaccination among Hispanic people residing in the U.S.

## American Lung Association Scholar: Tuberculosis



**EVELINA GUIRADO**  
**Ohio State University**

Tuberculosis (TB) is a disease that affects one-third of the world’s population, resulting in the death of nearly 2 million people each year. With resistance to current TB drugs on the rise, there is an urgent need for new TB therapy. With an American Lung Association Senior Research Training Fellowship, Evelina Guirado, PhD, is starting research on a key component of the bacterium that causes TB—the cell wall—which may yield clues that could be used in the development of new treatments.

Dr. Guirado is studying what happens in the initial stages of TB infection. She is focusing on the relationship between the *Mycobacterium tuberculosis* (Mtb) cell wall and an immune cell called the macrophage, which usually engulfs and destroys bacteria and foreign particles in the lungs but not Mtb. The Mtb cell wall includes molecules called lipoglycans which are decorated with a sugar, mannose, resulting in a sugar coat over the surface of the bacteria. Previous research provides evidence that this sugar coating plays an important role in the immune system’s recognition of TB and its response to it. In fact, sugar coating may help the TB bacteria to survive in the lung and cause infection.

Dr. Guirado hopes to identify key enzymes that make GDP-mannose, an essential building block for the mannose coating of lipoglycans. She will alter the levels of genes involved in the production of GDP-mannose, looking at what happens both when more enzyme is produced and when none is produced, to determine their impact on mannose production in the Mtb cell wall and on the interaction between the TB bacteria and macrophages. “We want to manipulate those genes to see how it affects the macrophage’s response to Mtb,” she says.

“The cell wall of Mtb is an attractive drug target, since mannose has been shown to be essential for the survival of mycobacteria and a number of current antibiotics target molecules in the cell wall,” Dr. Guirado says. “If we find out that having too much of these enzymes that build up the TB cell wall helps the bacteria survive, then scientists could design a drug to block these enzymes.”

For a complete description of Dr. Guirado’s research project, please go to page 30.

**ANDREA COOPER, PhD**

Trudeau Institute, Saranac Lake, NY

*DeSouza Research Award* • Funded by the American Lung Association of the Southwest

---

**Examining Inflammatory Response In Lung Disease Caused By Environmental Bacterium**

---

***The Impact Of Antigen-Specific T Cells On The Immunopathologic Consequences In Mycobacterium Avium-Induced Lung Disease.*** Disease caused by *Mycobacterium avium* (*M. avium*) can occur in smokers, those with impaired lung function, aging women and people repeatedly exposed to aerosol clouds of this environmental bacterium. The disease consists of an inflammatory response in the lung and can progress and cause significant illness. To better understand this inflammatory response, the researchers will use a mouse model of the disease. They will use state-of-the-art techniques to examine the immune cell functions that occur following infection with *M. avium* and determine whether changing these functions alters disease development. The findings will highlight potential mechanisms that can be examined in targeted human studies and may suggest potential treatments.

**MARY ANN DE GROOTE, MD**

Colorado State University, Fort Collins, CO

*American Lung Association/NTM Info & Research Career Investigator Award* • Funded in partnership between the American Lung Association and NTM Info & Research, Inc.

---

**Discovering New Drugs To Fight Mycobacteria**

---

***In vitro and in vivo testing of agents for activity against Mycobacterium abscessus.*** A family of bacteria called the non-tuberculous *Mycobacteria* can infect both healthy people and people with compromised body defenses when they are exposed through aerosols, inoculations or medical/surgical procedures. These bacteria are particularly problematic when a person has certain lung conditions. Non-tuberculous *mycobacteria* infections are felt to be an emerging public health problem in the United States. One in particular, *Mycobacterium abscessus*, can cause destructive lung disease and skin infections that can be very hard to treat because the bacteria tend to be resistant to many antibiotics. Little is known about the most effec-

tive antibiotic therapies to treat *M. abscessus*. The researchers will work with Dr. Scott Franzblau at the University of Illinois, Chicago, an expert at discovering drugs against the *mycobacteria* family. His group will screen libraries of compounds to see which ones are active against *M. abscessus*. The next step will be to test the most active compounds in an animal model validated by Dr. Diane Ordway at Colorado State University. This research may be useful in discovering new drugs against *M. abscessus*.

**BOUKE CATHERINE DE JONG, MD, PhD**

New York University, New York, NY

*Biomedical Research Grant* • Funded by the American Lung Association

---

**Studying Variant of TB Bacterium May Provide Insights to Fight the Disease**

---

***Defective ESAT-6 Secretion as a Mechanism of Attenuation of M. africanum.*** Only a small number of people who become infected with the bacterium that causes tuberculosis will get sick themselves. It is not understood why some people get sick while the majority stays healthy after infection. One way to increase the understanding of immunity to TB is to study differences in “behavior” between different strains of the TB bacterium and to search for bacterial genes that cause those differences. The researchers will study a variant of *M. tuberculosis*, called *M. africanum*, which is abundant in West Africa. *M. africanum* patients and their household members are less likely to mount an immune response to a protein called ESAT-6, which is produced by the TB bacteria and is essential to their causing disease. Preliminary findings suggest that *M. africanum* secretes less ESAT-6 than *M. tuberculosis*. The researchers will study the mechanism of defective ESAT-6 secretion in *M. africanum* by manipulating a bacterial gene that is thought to explain the difference. A better understanding of how the ESAT-6 protein works could form the basis for new drugs that would interrupt its secretion. ESAT-6 is part of a candidate TB vaccine, and this study will inform TB vaccine development, which aims to prevent lung disease caused by TB.

**EVELINA GUIRADO, PhD**

Ohio State University, Columbus, OH

*Senior Research Training Fellowship* • Funded by the American Lung Association

---

 Enzymes that Make Sugar Coating in TB Bacteria  
 May be Target for Drug Therapy
 

---

***Emerging Drug Targets in Tuberculosis: Biosynthetic Enzymes for Cell Envelope Mannose-Containing Lipoglycans.*** Tuberculosis (TB) affects one-third of the world's population and kills nearly 2 million people each year. But with resistance to current treatments on the rise and no reliable vaccine, new treatments are urgently needed. The researchers will study the interaction between the cell wall of the bacterium that causes TB, *Mycobacterium tuberculosis* (Mtb), and an immune cell called the macrophage. Normally the macrophage engulfs and destroys bacteria, but Mtb can evade immune defenses and survive to cause infection. The Mtb cell wall contains molecules named lipoglycans decorated with a terminal sugar called mannose. This sugar coating appears to play an important role in the immune system's recognition of and response to the TB bacteria. The researchers will identify key enzymes that are essential building blocks for lipoglycans involved in the addition of mannose. They will alter the levels of genes expressed to determine their impact on the Mtb cell wall mannose production and the interaction of the TB bacteria with macrophages. Information gained from this research should enhance knowledge of TB infection and may help identify new TB therapy targets.

**PUSHPA JAYARAMAN, PhD**

Brigham &amp; Women's Hospital, Boston, MA

*Senior Research Training Fellowship* • Funded by the American Lung Association

---

 Learning How Immune System Defends Itself Against TB Bacteria
 

---

***Tim3/Tim3L Interaction Induces a Novel Macrophage Activation State and Kills Mycobacterium Tuberculosis.*** *Mycobacterium tuberculosis*, which causes pulmonary tuberculosis, is able to establish chronic infection in humans and evade the body's immune system defenses. Cells of the immune system play an important role in defense

against invading microorganisms. Immune system cells called macrophages engulf microbes and bring them to, and activate, white blood cells called T-cells. Activated T-cells in turn secrete protein chemical messengers called cytokines such as IFN-gamma and TNF-alpha, and kill infected cells. Despite being the first line of defense, macrophages in the lung are the primary target and serve as the reservoir of *M. tuberculosis* infection. The researchers will study how macrophages and T-cells interact with one another to control TB infection and disease. Tim3 is a molecule on the surface of T-cells that has been shown to regulate T-cell responses. Tim3 levels on T-cells are increased following TB infection. The researchers are studying a novel way in which Tim3 on T-cells can activate TB infected macrophages and leads to an efficient killing of *M. tuberculosis*. The results of this research should contribute to knowledge needed to develop novel treatments and vaccines for TB.

**JOAN MANGAN, PhD, MST**

University of Florida, Gainesville, FL

*Social Behavioral Research Grant* • Funded in partnership with the American Lung Association and the American Lung Association of the Southeast

---

 Developing Myth-Busting Messages About a Tuberculosis Vaccine
 

---

***Developing Salient Messages to Facilitate Decisions Regarding Tuberculosis Testing and Treatment Among Hispanics.*** Tuberculosis (TB) is highly stigmatized and poorly understood in many regions of the world. Stigma and misperceptions surrounding TB have been associated with patients delaying seeking care; failing to undergo or complete diagnostic testing; rejecting physicians' diagnoses, and failing to complete treatment. The problem is compounded by the fact that in low- to middle-income countries, the Bacille Calmette-Guérin (BCG) vaccine is given to reduce the risk of developing more severe forms of TB among infants and children who become infected with TB germs. The BCG vaccine does not provide lifetime protection against TB; yet community members tend to believe the vaccine protects a person from becoming sick with TB throughout their life and a positive TB test is due to the vaccine. Studies

indicate that decreasing stigma and clarifying misperceptions has a positive impact on patients' knowledge, attitudes and behaviors. The researchers will develop culturally competent educational messages that lessen the confusion individuals experience about the vaccination and their need for testing and treatment of TB; and test the impact of these messages on foreign-born Hispanic persons' understanding of this risk and intended decisions if testing and treatment is recommended to them in the future.

### **CHARLOTTE MITCHELL, PhD**

Yale University, New Haven, CT

Senior Research Training Fellowship • Funded by the American Lung Association

---

Studying Effects of Protein Chemical Messenger on Cells Lining Airways

---

***Interferon-gamma Effects on the Airway Epithelium Modulate Lung Disease.*** Cells called epithelial cells line the airway, creating a surface called the epithelium. The epithelium is important for protecting and regulating immune responses in the lung. Interferon-gamma (IFN-g) is a protein chemical messenger that is important for defense during disease, but its effect on the epithelium is not known. The researchers have developed a mouse in which the receptor for IFN-g is absent from all cells except airway epithelial cells, which allows only the epithelium to respond to IFN-g. Using this mouse, the researchers can identify how the airway epithelium responds to IFN-g to affect disease. Infection with *Mycobacterium tuberculosis* and pulmonary fibrosis are serious diseases of the lung, and IFN-g is an important factor in both these diseases. The researchers hope to clarify the role of the IFN-g responses by the airway epithelium in mouse models of mycobacterial infection and pulmonary fibrosis. These studies may identify novel pathways that can be used for future treatment of these diseases.



---

## OTHER LUNG INFECTIONS

---

**L**ung infections are common and often deadly. Influenza and pneumonia continue to be responsible for approximately 60,000 deaths annually. Other viruses, most notably the respiratory syncytial (RSV) cause widespread serious disease, including death in the very young and very old. Fungi (molds) are “opportunistic” in that they cause serious disease in lungs already damaged or in people with deficient immune systems such as those receiving chemotherapy or who have AIDS.

American Lung Association investigators are searching for new ways to treat the 30% of the most common form of pneumonia which is resistant to standard antibiotics. Studies are being done to understand why some viral infections may devastate the lungs. Research is continuing to develop methods to control RSV infection and several studies are being done to understand how fungi infect weakened lungs. Finally, an old enemy which never seems to go away, Legionnaires Disease, is receiving new attention.

## **American Lung Association Scholar: Lung Infections**




---

**ALBERT SENFT, PhD**

**Lovelace Respiratory Research Institute**

---

Respiratory syncytial virus (RSV) is a common illness of childhood, which sometimes turns serious and causes an inflammation of the airways called bronchiolitis. But RSV can also cause serious illness in the elderly, particularly adults with chronic obstructive pulmonary disease (COPD) or other underlying illnesses. “People with COPD get many infections that worsen patients’ breathing, and RSV is one of those infections,” says Albert Senft, PhD. “But how RSV persists in exacerbating COPD is not well understood.”

With a Biomedical Research Grant from the American Lung Association, Dr. Senft is studying what RSV does to change the function of cells in the immune system called macrophages, which are specialized white blood cells that are critical for clearing inhaled particles and dying cells from the lung.

He is focusing on a protein called gamma interferon, which makes a chemical signal that activates macrophages and gives them instructions. “After RSV infection, macrophages don’t respond to interferon gamma properly,” Dr. Senft says. “We are trying to see why that is.” He notes that influenza is another virus that also can lead to dangerous bacterial infections. But his lab has found that the influenza virus and the RSV virus work in different ways to cause secondary infections.

He hopes that the research will one day help prevent dangerous bacterial infections that result after RSV infection. “After a viral infection, there is a window of time when you are susceptible to other pathogens. If we can understand what happens to macrophages in RSV infection, and what makes them not do their job well, we might one day be able to diagnose RSV infection and then give therapy to prevent secondary infections,” he says.

The American Lung Association grant has provided Dr. Senft with funding to get his lab started. He says, “The grant is providing preliminary data that I can use to write larger National Institutes of Health grants.”

To see a complete description of Dr. Senft’s research project, please go to page 37.

**AMAL AMER, MD**

Ohio State University, Columbus, OH

*Biomedical Research Grant* • Funded by the American Lung Association

---

**Molecules May Play Role in Restricting Legionella Infection**

---

***The Role of Caspases in Legionella Pneumophila Pulmonary Infection.***

Legionella pneumophila is a bacterium that can cause severe pneumonia and is potentially deadly, especially in the elderly and in individuals with low immunity. Recently, Legionella has been detected in AIDS and cancer patients. It is not known how Legionella persists in a host cell and multiplies to cause disease. The researchers have been studying molecules called caspases and trying to understand their role in Legionella. Caspases have been implicated in the death of cells they invade, called host cells. But the researchers have found that certain caspases can also restrict bacterial infection without affecting the survival of the host cell. They will study how caspases prevent Legionella from establishing infection and causing disease in the mouse cell. Their long-term aim is to use this information to design molecules that can manipulate caspases in the human cell and use them to combat Legionella and other lung microbes.

**SINEM BEYHAN, PhD**

University of California, San Francisco, San Francisco, CA

*Senior Research Training Fellowship* • Funded by the American Lung Association

---

**Studying Potentially Dangerous Fungal Infection Could Lead to Vaccine, Treatment**

---

***Regulatory Networks That Control Cell Morphology and Virulence in the Fungal Respiratory Pathogen Histoplasma Capsulatum.***

Histoplasma capsulatum is thought to be the most common cause of fungal respiratory infections in the world. In the United States, H. capsulatum is endemic in the Mississippi and Ohio River Valleys. It is found in mold form in the soil. Infection occurs through inhaling fragments of fungal filaments and spores that become airborne through disruption of the soil. Once inhaled, the organism converts into a budding-yeast form, which survives and replicates within immune-system cells called mac-

rophages. Outcome of infection depends on the dose of infectious particles as well as the health of the person's immune system. In a person with a damaged immune system, inhaling the mold can result in a life-threatening disease called histoplasmosis. Positive histoplasmin skin tests occur in as many as 80% of the people living in areas where H. capsulatum is common. Infants, young children, and older persons, in particular those with chronic lung disease, are at increased risk for severe disease. The researchers will study how H. capsulatum causes respiratory infections. Findings from this study can be used to develop vaccine and treatment strategies against H. capsulatum infections.

**ALINA BOESTEANU, PhD**

Drexel University, Philadelphia, PA

*Biomedical Research Grant* • Funded by the American Lung Association

---

**Reducing Replication of the Influenza Virus Could Lessen Symptoms**

---

***Phosphoinositide 3 kinase (PI3K) p110delta Isoform and Pathogenicity of Influenza Virus Infection.***

Every year influenza infection causes severe disease in many people around the world. Drugs that reduce virus replication in the lungs can be useful in diminishing the severity and the duration of the disease; however, viruses can change themselves to become resistant to drugs. Therefore there is a need for development of new drugs. Drugs that do not target the virus directly but instead target the host cell machinery that is used by the virus in order to survive and multiply may be less prone to resistance. Extensive research has demonstrated that influenza virus hijacks mechanisms within the cell that control cellular activation. The researchers have found that lack of a specific signaling protein that controls cellular activation also restricts virus replication. They have found that treatment of normal mice with a drug that specifically targets this signaling molecule protected these mice from succumbing when infected with a high dose of the virus. The researchers will explore the virus replication and survival of lung cells infected with the influenza virus. Their research could be used to develop a

drug that targets the signaling molecule to reduce the lung viral load and improve unwanted symptoms associated with influenza virus infection.

#### **ANDERS HAKANSSON, PhD**

State University of New York at Buffalo, Buffalo, NY  
*Biomedical Research Grant* • Funded by the American Lung Association

---

#### Protein Complex in Breast Milk May Fight Pneumonia

---

##### ***The Use of a Human Milk Protein Complex, HAMLET, to Treat Pneumococcal Pneumonia.***

*Streptococcus pneumoniae* (pneumococcus) is the most common cause of bacterial pneumonia and a common complication of influenza and measles virus infections. Pneumococci, like so many other bacterial pathogens, have become resistant to common antibiotics used to treat these infections and currently 30% of strains isolated in the U.S. are not susceptible to penicillin. During the researchers' investigations of the antibacterial activity of breast milk, they discovered a protein complex called HAMLET with potent killing activity against *S. pneumoniae* and other respiratory tract pathogens that cause pneumonia. HAMLET kills pneumococci that are resistant to common antibiotics, and no resistance against HAMLET has been observed. The researchers will investigate the ability of HAMLET to kill bacteria growing in biofilms (the form of growth encountered during infection) and prevent and treat pneumococcal pneumonia in established mouse model systems, which closely resemble human disease. This research has the potential to lead to the development of more effective therapeutic agents against pneumococcal disease, with less risk for resistance development.

#### **MEHMET KESIMER, PhD**

University of North Carolina at Chapel Hill, Chapel Hill, NC  
*Biomedical Research Grant* • Funded by the American Lung Association

---

#### Learning How Tiny Particles Defend the Lung Against Viruses

---

##### ***The Role of Human Airway Epithelium Derived Exosomes in Innate Defense of the Lung.***

Exosomes are tiny particles secreted by different types of cells. They are made from common cell compo-

nents and are wrapped up by molecules found on the surfaces of the cells themselves. The exact role of exosomes is not known. The researchers have found their presence in lung secretions and propose that they play an important role in defending the lung against viruses, including the influenza virus. Some exosomes have special carbohydrate-rich substances coating their surfaces that may control which viruses they might recognize. The researchers will study the structure of exosomes found in lung secretions, and identify which cells they come from and what kinds of viruses they bind to. They will then explore how they interact with viruses. They hope their research will lead to a deeper knowledge of anti-viral defense mechanisms, which could be used to develop new treatments

#### **XUEXIAN LI, PhD**

Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, CA  
*Senior Research Training Fellowship* • Funded by the American Lung Association

---

#### Learning How Inhaled Spores Damage Weakened Lungs

---

##### ***Functional Characterization of BcrA in Invasive and Allergic Bronchopulmonary Aspergillosis.***

Invasive aspergillosis and allergic bronchopulmonary aspergillosis are two lung infections that are caused by the mold *Aspergillus fumigatus*. This fungus normally inhabits organic debris and compost, and produces thousands of spores. In most people, these inhaled spores are not harmful. But in patients with weakened immune systems, these spores cause a potentially deadly type of pneumonia called invasive aspergillosis. In some patients with lung disease such as asthma or cystic fibrosis, *A. fumigatus* can cause an allergic response, called allergic bronchopulmonary aspergillosis, which can worsen asthma and even lead to destruction of the lungs. The researchers have identified a protein called BcrA that turns on genes in *A. fumigatus*. They have made a mutant strain of *A. fumigatus* that lacked BcrA. They have also discovered the genes that are under the control of BcrA, called BcrA target genes. They will make new *A. fumigatus* mutants in which individual BcrA target genes are deleted, and study how they work. The research will provide new information about how

*A. fumigatus* injures the lungs during both invasive and allergic aspergillosis. This information could lead to the development of new approaches to prevent and treat these serious diseases.

### **ALBERT SENFT, PhD**

Lovelace Respiratory Research Institute, Albuquerque, NM  
*Biomedical Research Grant* • Funded by the American Lung Association

---

#### How Does RSV Circumvent the Immune System?

---

##### ***Viral Modulation of Lung Phagocyte Functions.***

Respiratory syncytial virus (RSV) is a common respiratory virus that causes severe illness in the very young and elderly. A large collection of evidence suggests that RSV is adept at circumventing the immune system. This results in an increased risk for developing chronic asthma, as well as severe illness caused by secondary bacterial infection. The mechanisms by which RSV circumvents the immune system are currently unclear. Currently there is no vaccine against RSV and available treatments against the virus are minimally effective. Lung macrophages are specialized white blood cells that are critical for clearing inhaled particles and pathogens from the lung and also regulate the immune system's ability to recognize specific pathogens. The researchers conducted preliminary studies that indicate that RSV impairs macrophage functions that are required for the killing and clearance of pathogens. The researchers will now study how RSV impairs macrophage function. This research may lead to novel therapies to treat and limit RSV-induced disease.

### **JIE SUN, PhD**

University of Virginia, Charlottesville, VA  
*Senior Research Training Fellowship* • Funded by the American Lung Association

---

#### Tamping Down Overactive Immune Responses to Influenza

---

***Regulation of Lung Inflammation by IL-10 Producing Anti-Viral CD8+ Effector T Cells During Acute Pulmonary Virus Infection.*** Influenza virus infection is a leading cause of respiratory illness worldwide and can potentially result in catastrophic illness and widespread death with the emergence of a new pandemic virus strain. The

clearance of influenza virus infection requires an effective immune-system response. But immune responses also contribute significantly to the lung injury initiated by influenza virus infection. This was seen in the 1918 pandemic influenza and the H5N1 avian flu infection, when the immune system over-responded, causing lung inflammation and injury. Therefore, molecules that can counter-regulate these overactive immune responses are needed. The anti-inflammatory cytokine IL-10 is one such molecule with powerful inhibitory effects on the immune system. The production of IL-10 is mainly dependent on a type of white blood cell called the CD8+ cytotoxic T lymphocyte (CTL), which clears the infectious virus from the lungs. The researchers will investigate the way in which these CTLs work in regulating lung inflammation and injury and how they are produced. The results of the study could be used to provide new treatment strategies for curing viral infections in the lung.



---

## LUNG CANCER

---

**L**ung cancer kills more men and women than any other form of cancer. We know that cigarette smoking is responsible for most cases, but our ability to treat this disease is woefully inadequate, resulting in a five-year survival rate of approximately 16 percent of patients. The effectiveness of surgery is limited by our inability to detect cancers early enough to cure them. The effectiveness of chemotherapy is limited by its suppression of the immune system, which is vitally needed to control cancer growth and protect against infection. The effectiveness of radiation is limited by its damage to the lungs.

Studies supported by the American Lung Association address these issues by using the techniques of molecular genetics and cell biology to examine how the body regulates lung cancer cell growth, with the hope of defining how it may control cancer at the cellular level. Basic studies are exploring the genetic abnormalities in lung cancer cells, some with a goal of developing novel methods of prevention. Much work is being done at the cellular and molecular levels as unraveling the complex chemistries involved is key to developing new approaches to treatment.

Studies are being done to understand how lung cancer metastasizes (spreads) as this is the property which makes it lethal. Attention is turning to develop strategies for prevention of lung cancer by vaccine development or inhibition of inflammation. Patient populations are being studied to understand contributing causes to cancer such as heredity or obesity and finally, the human aspect of cancer is taken under consideration in a study to understand the role of depression in the outcome of cancer treatment.

## American Lung Association Scholar: Lung Cancer



**KWOK-KIN WONG, MD, PhD**  
**Dana-Farber Cancer Institute**

This is an exciting time to be studying lung cancer, says Kwok-Kin Wong, MD, PhD. Dr. Wong, the recipient of an American Lung Association Lung Cancer Discovery Award, states that advances in genetics are pushing the field forward. “In the past five or six years, we’ve begun to understand that lung cancer is not a single disease but a complicated set of diseases caused by many genetic mutations,” Dr. Wong says.

As both a laboratory scientist and a physician who treats lung cancer patients, Dr. Wong sees how critically new treatments are needed and what challenges lie ahead to develop those treatments. “To improve the long-term survival of patients with lung cancer, we need a better understanding of the processes involved in lung cancer progression and metastasis, or spread, so we can identify targets for intervention,” he says.

Until recently, there has not been a good model system to study lung cancer metastasis in a living organism. Dr. Wong’s lab has developed a new mouse model with a genetic mutation that spontaneously develops lung cancer that spreads to other organs, so that he can study the pathways that are involved in the cancer’s growth and spread. “We want to figure out which set of genes are activated in people with this genetic mutation that leads to metastasis,” he says. “A better understanding of the genetic events that are involved in metastatic growth will help guide the development of new therapies that can interfere with this deadly process.”

Dr. Wong says the Lung Cancer Discovery Award is critical to helping him conduct his research. “It’s very difficult to get funding from the federal government for research,” he says. “You need a lot of compelling preliminary data. This grant will help me generate data so that I can apply for funding from the NIH (National Institutes of Health).” Lung cancer research has the potential to provide new treatments, but it needs more attention and funding, he says. “We don’t have a lot of advocates compared with breast, prostate and colon cancer,” he says. “We are poised to make important findings, but we need a lot more funding to make discoveries that will directly impact patient care.”

For a complete description of Dr. Wong’s research project, please go to page 43.

**RALPH ARLINGHAUS, PhD**

University of Texas M.D. Anderson Cancer Center, Houston, TX  
*Lung Cancer Discovery Award* • Funded by the American Lung Association

---

**Inhibiting Protein Could Improve Lung Cancer Treatment**

---

***Activated c-Abl in FUS1 Deficient Non-Small Cell Lung Cancer (NSCLC).*** Lung cancer is the leading cause of cancer-related deaths not only in the United States, but globally as well. The high death rate of this devastating disease is related to the fact that most patients are diagnosed at late stages of the disease, mainly due to the lack of symptoms during the early stages. Non-small cell lung cancer (NSCLC) is a major type of lung cancer, accounting for approximately 80% of cases. The researchers have identified a protein called c-Abl kinase that is activated in some non-small cell lung cancer cells and may contribute to the abnormal growth of these cancer cells. Part of the reason that c-Abl is activated is because a gene called FUS1 is defective in about 80% of lung cancer patients. Other factors are also likely to contribute to the protein's activation. The researchers will further investigate why c-Abl is activated in some NSCLC cells. In a mouse model, they will study whether combining drugs that inhibit c-Abl with current therapies for NSCLC increase their effectiveness. The research may lead to a potential target for lung cancer therapy in humans, and might contribute to the development of more advanced methods of early detection to prevent lung cancer.

**JOHN EATON, PhD**

University of Louisville Research Foundation, Inc., Louisville, KY  
*Lung Cancer Discovery Award* • Funded in partnership between the American Lung Association and the LUNGEvity Foundation

---

**Lung Cancer Vaccine Designed to Induce Immune Response**

---

***A Broad Spectrum Lung Cancer Stem Cell Vaccine.*** Both tumors and embryos produce certain genes that are not present in normal adult organisms. Adults mount an immune-system response to some of these gene products. The researchers have designed a prophylactic vaccine composed of mouse embryonic stem cells, which is designed to take advantage of this immune response. The vaccine is meant to prevent cancer. Early stud-

ies found that mice vaccinated with these stem cells are 80-100% protected against the growth of implanted lung tumors. The vaccine also protects against the development of lung cancer induced by a carcinogen. The researchers believe that the vaccinated animals are selectively attacking a small set of cancer stem cells, which give rise to full-blown cancer. Selectively destroying these cells may prevent tumor growth, as well as recurrence of cancer. The researchers will further study this vaccine in mice. If these experiments are successful, they will lay the groundwork for the design of a similar vaccine for humans.

**PING-CHING HSU, MS**

Georgetown University, Washington, DC  
*Lung Health Dissertation Grant* • Funded by the American Lung Association

---

**Measuring the Impact of Smoking on Lung Cancer Risk**

---

***Cigarette Smoke-Related Metabolome.*** To better understand the impact of cigarette smoke on lung cancer risk, biomarkers of lung cancer risk are needed. Biomarkers are molecules found in blood, other body fluids, or tissues that are a sign of a normal or abnormal process, or of a condition or disease. The researchers will identify new biomarkers of lung cancer risk through a powerful method called metabolomics, which measures and analyzes substances in the blood called metabolites. They will investigate whether the number of cigarettes a person smokes per day, how they smoke their cigarettes, and how fast their body metabolizes nicotine will affect how much cancer-causing substances end up in the blood. The information found in the study could be used to evaluate health claims of tobacco products as well as identify former smokers most at risk of developing lung cancer.

**TERESA LIBERATI, DVM, PhD**

Southern Illinois University School of Medicine, Springfield, IL  
*Biomedical Research Grant* • Funded by the American Lung Association of the Upper Midwest

---

**Finding Characteristics That Predispose Smokers To Developing Lung Cancer**


---

***Genetics, Obesity and Inflammation: Exacerbation of Susceptibility to Environmental Carcinogens in the Lung.*** Although many people are exposed to cancer-causing agents like tobacco smoke, few may actually develop lung cancer. Little is known about personal characteristics or pre-existing conditions that change the risk of developing lung cancer across individuals. A better understanding of the impact of genetics, obesity and pre-existing inflammation of the lung as risk factors for lung cancer could support health care providers in the prevention of cancer, allow more accurate prognosis after diagnosis, and perhaps provide new methods of treatment. The researchers will use lung tissue from mice to identify individual characteristics that have the most potential to predispose individuals to the development of lung cancer after exposure to tobacco smoke. They will examine the lung tissue after they have been exposed to the chemical NNK, a component of tobacco known to cause lung cancer. They will also examine inflammation in the mouse lung after NNK exposure in mice who are either obese or have a pre-existing lung inflammation.

**MATTHEW MEYERSON, MD, PhD**

Dana-Farber Cancer Institute, Boston, MA  
*Diane Emdin Sachs Lung Cancer Award* • Funded in partnership between the American Lung Association and the American Lung Association of New York with special thanks to the Emdin Family

---

**Gene Search May Reveal How Healthy Lung Cells Turn Cancerous**


---

***Small Cell Lung Cancer Using Pooled RNAi Library Screens and Single-Template DNA Sequencing.*** Small cell lung cancer (SCLC) is strongly associated with tobacco smoking. The cancer typically grows quickly and tends to spread to lymph nodes and other organs early in the disease, and survival rates are extremely low. DNA alterations in key genes cause cancer. Targeted therapies that block the action of these altered

genes can treat cancer. Currently no targeted therapies exist for the treatment of small cell lung cancer. The researchers will conduct a large-scale search for vulnerable genes that trigger the progression from a normal healthy lung cell to a cancerous one. They will then look at the detailed sequences of these genes to determine if there is a structural explanation as to how these genes promote tumor growth. The long-term goal is to find new drugs that block the effects of SCLC-causing genes and thereby kill the cancer cells, allowing people with lung cancer to live longer with fewer symptoms. The study may also yield information to help diagnose lung disease early in its course.

**SEYED JAVAD MOGHADDAM, MD**

University of Texas M.D. Anderson Cancer Center, Houston, TX  
*Lung Cancer Discovery Award* • Funded in partnership between the American Lung Association and the LUNGeVity Foundation

---

**Seeking to Prevent Lung Cancer in People with COPD**


---

***Inflammation-Related Lung Cancer Prevention by Targeting the NF- $\kappa$ B Pathway.*** Many studies have found that smokers with chronic obstructive pulmonary disease (COPD) have an increased risk of lung cancer compared with smokers with comparable cigarette exposure but without COPD. Although smoking causes most cases of COPD, only 25% of smokers develop COPD. A person's susceptibility to developing COPD and lung cancer is thought to reflect genetic variation in the body's inflammatory response to inhaled smoke and to microorganisms colonizing the injured airways of smokers. These facts suggest a link between chronic airway inflammation and lung cancer, but the precise way in which the link works is unknown. The researchers will use a mouse model to study the mechanism responsible for promotion of lung cancer by airway inflammation. They will concentrate on a genetic alteration found in COPD and lung cancer, involving a gene called NF- $\kappa$ B. They will use a genetic strategy and anti-inflammatory agents that inhibit this gene to test whether it may prevent lung cancer. This research could lead to development of anti-inflammatory therapy in patients with COPD at high risk for lung cancer, and patients with early stage lung cancer.

**EMELYN HELEN SHROFF, PhD**

Stanford University, Stanford, CA

*Senior Research Training Fellowship* • Funded by the American Lung Association

---

**Cells With Self-Renewal Properties May Illuminate Lung Cancer Growth**

---

***Identifying a Cancer Stem Cell Program During MYC-Induced Lung Tumorigenesis.*** In many cases, treatment for lung cancer fails due to cells called cancer stem cells that are resistant to current therapy and are thought to be responsible for tumor maintenance. These cells have the ability to replicate infinitely. The researchers are studying the role of a cancer gene, or oncogene, called MYC, that also regulates stem cell properties. Oncogenes turn normal cells into cancer cells. The researchers are using a mouse model to regulate the production of these oncogenes. By switching off these oncogenes through genetic manipulation, tumors usually regress. But they have identified that in lung cancer caused by MYC, the tumors do not regress when MYC is switched off. Since MYC is also important for regulating self-renewal, the researchers will assess whether lung tumors that do not rely on MYC to grow instead rely on the emergence of a population of stem-cell like cells with self-renewal properties. The researchers hope to identify this population of cells. They will also look for other specific genes that also promote self-renewal and see whether turning off these genes will eliminate their self-renewal properties. Understanding these processes could have a tremendous impact on future development of drugs targeting lung cancer.

**CHRISTOPHER GEORGE SLATORE, MD**

Oregon Health &amp; Science University, Portland, OR

*Social Behavioral Research Grant* • Funded by the American Lung Association

---

**Examining the Role of Depression in Lung Cancer Care**

---

***Depression and Lung Cancer: Association with Mortality and Processes of Care.*** Many people with lung cancer also suffer from depression, an often overlooked disease. Depression may be associated with increased death rates among pa-

tients with lung cancer, and patients with depression may be more likely to suffer from other poor lung cancer care outcomes. Since depression can be treated with well-established therapies, identifying its role in lung cancer care could improve quality of life and decrease illness among the large number of patients who suffer from depression and lung cancer. The researchers will launch a series of four studies to evaluate depression among lung cancer patients enrolled in a study called Cancer Care Outcomes Research and Surveillance Consortium (CanCORS). They will examine the association between depression and outcomes including timeliness of care (the time from first symptoms of lung cancer to treatment), receipt of recommended therapies, and receipt of smoking cessation interventions. This research could help further cement recommendations to screen for depression as well as offer treatment incentives to improve outcomes for the likely large number of lung cancer patients with depression

**KWOK-KIN WONG, MD, PhD**

Dana-Farber Cancer Institute, Boston, MA

*Lung Cancer Discovery Award* • Funded by the American Lung Association and the American Lung Association of New England

---

**Mouse Model of Lung Cancer Will Add to Knowledge of How Cancer Spreads**

---

***Mouse Models of Human Lung Cancer.*** The overwhelming majority of the approximately 180,000 patients diagnosed with lung cancer in the United States each year die from the metastasis, or spread, of their cancer and related complications. To improve the long-term survival of patients with lung cancer, it is critical to develop a better understanding of the processes involved in lung cancer progression and metastasis. Until recently, there has not been a good model system to study lung cancer metastasis in a living organism. The researchers will use a mouse model they have generated that spontaneously develops lung cancer which spreads to distant organs, to genetically dissect the pathways that are involved in lung cancer progression and metastasis. They will also examine the role of the immune system in the

development and progression of lung cancer. This research should yield information that can be used to identify crucial new targets involved in lung cancer progression and metastasis for possible new treatments.

---

## THE IMMUNE SYSTEM, INFLAMMATION AND LUNG SCARRING

---

**T**he body defends itself and resists infection by mounting immune (allergic) and inflammatory responses to foreign invaders such as infecting organisms and particulates. Sometimes these defense systems over-respond and identify the body's own molecules as foreign. When the body turns against itself in this way, disease may be created. One example of this is interstitial lung disease or idiopathic pulmonary fibrosis, in which an excessive inflammatory response to seemingly mild stimuli may lead to permanent scarring of the lungs, disability, and death. There has been an unexplainable rise in the incidence of this fatal disease, primarily in middle aged and older men. Because most lung diseases involve inflammation and the cells of the immune system to some degree, the American Lung Association supports an array of investigations into the basic cellular and molecular processes that underlie these systems.

A wide variety of cells, chemical and immunological mediators, involved in inflammation and scarring are being studied, mainly with advanced techniques of molecular genetics. Researchers are also seeking new ways to prevent the lung scarring that follows certain types of lung inflammation, as well as looking for new treatments for lungs damaged by excess scar tissue formation.

Additional clues are being sought to understand the mystery of Sarcoidosis, a relatively common disease among African Americans in the U.S. which leads to severe disability and even death in a significant minority of victims.

## **American Lung Association Scholar: The Immune System, Inflammation and Lung Scarring**



---

**NATHAN SANDBO, MD**  
**University of Chicago**

---

Nathan Sandbo, M.D., would one day like to be able to tell his patients with idiopathic pulmonary fibrosis (IPF) that there is an effective treatment for them. “Now, when I have to give a patient a diagnosis of pulmonary fibrosis, it is challenging and disconcerting, because there are no effective therapies,” he says.

His patients are his motivation for trying to understand the process by which cells in the lung called fibroblasts become overactive and change shape, leading to fibrosis, or scarring, in the lungs. With an American Lung Association Dalsemer Research Grant, Dr. Sandbo is studying fibroblasts, and hopes that his research could lead to treatments for IPF.

Dr. Sandbo is focusing on how molecular “switches” inside fibroblasts get turned on by signals outside of the cell and lead the fibroblasts to become overactive. One such signal is induced by a substance called Transforming Growth Factor-beta, or TGF-beta. “There is a first wave of TGF-beta signals that goes through the cell, which is well understood,” he says. “But then there is a second signal wave that is less well understood, which may be a new target for therapies for pulmonary fibrosis.” Dr. Sandbo is investigating how this second wave of signaling leads to the production of proteins that change the shape and structure of the fibroblast cells and leads to lung scarring.

There are already some therapies in development that target TGF-beta. But Dr. Sandbo says that because it is a molecule that is involved in normal cell processes as well as disease, using a drug that broadly targets TGF-beta could interfere with normal cell functioning and lead to unintended problems. “If we can identify the molecules and mechanisms involved in this later wave of cell signaling involving TGF-beta, we would have a more specific target for drugs that stop the fibrosis process but don’t interfere with normal tissue functioning,” he says.

Dr. Sandbo says he is grateful for the American Lung Association grant, which has allowed him to hire a technician and purchase supplies to move his research forward. “I’m a young investigator just starting out in my career, and this support is immensely helpful,” he says.

To see a complete description of Dr. Sandbo’s research project, please go to page 49.

**MING-HUI FAN, MD**

University of Pennsylvania, Philadelphia, PA  
*Dalsemer Research Grant* • Funded by the American Lung Association

---

**A Novel Protein May Protect Lungs Against Scarring After Injury**


---

***Elucidating the Mechanism(s) Driving the Anti-fibrotic Effects of Fibroblast Activation Protein (FAP) in the Lung.***

Idiopathic pulmonary fibrosis (IPF) is characterized by progressive lung injury and scarring, with eventual death within two to four years of diagnosis on average unless the patient undergoes a lung transplant. Little is known about the cause of the disease, and no effective medical treatments exist. Fibroblast activation protein (FAP) has the ability to break down scar tissue in the lung. It is produced in the developing embryo and production is turned off shortly after birth. It is not produced in normal healthy adult tissues. Its production is turned on, however, in the setting of injury and wound healing, cancer, and diseases where organs become increasingly scarred and nonfunctional, such as pulmonary fibrosis. The researchers have found mice bred to be deficient in FAP have decreased survival and increased lung scarring. This suggests a protective role for FAP in preventing progression to pulmonary fibrosis after lung injury. The researchers will study the way in which FAP protects against the development of pulmonary fibrosis after lung injury. This research may ultimately lead to new treatment approaches for IPF.

**OLIVER HAWORTH, PhD**

Brigham and Women's Hospital, Boston, MA  
*Senior Research Training Fellowship* • Funded by the American Lung Association

---

**Anti-Inflammatory Substances May Lead to New Asthma Treatments**


---

***Promoting Resolution of Allergic Airway Inflammation.***

During an asthma attack, the bronchial tubes become inflamed. Most inflammatory responses are “acute,” meaning they last only briefly and then go away when the cause of the irritation is removed. The end of the inflammatory response is called the “resolution” phase. Until recently this phase was thought to be a passive event. However new research has shown that this phase is the result

of an active process, with new molecules produced to promote resolution. Recently distinct anti-inflammatory substances called “resolvins” derived from polyunsaturated fatty acids commonly found in oily fish (long known to be beneficial to health) have been discovered and shown to have potent anti-inflammatory actions. When resolvins are administered to mice that have airway inflammation similar to asthma, the inflammation goes away much faster. The researchers found that resolvins sped up resolution of airway inflammation in part by increasing the production of anti-inflammatory substances called lipoxin A4 and interferon gamma. The researchers will explore the mechanism by which resolvins increase production of lipoxin A4 and interferon gamma, which may lead to new asthma treatments.

**LAURA KOTH, MD**

University of California at San Francisco, San Francisco, CA  
*Biomedical Research Grant* • Funded by the American Lung Association

---

**Natural Killer T Cells May Reveal Clues About Sarcoidosis**


---

***Effector Function of Natural Killer T (NKT)***

***Cells in Sarcoidosis.*** Sarcoidosis is an inflammatory disease of unknown cause that has no cure. It can be debilitating and sometimes deadly, and can affect any organ of the body, including the lungs. It is thought to be caused by an abnormal immune-system response. Studies have shown that people with sarcoidosis have an excess of inflammatory cells that produce a pattern of inflammation called a T helper 1-type immune response. Little is known about the regulators of this immune response. The researchers will study whether a recently identified class of immune system cell called natural killer T cells could represent a new target for therapy in sarcoidosis. Several studies have found that the number of natural killer T cells in the blood and lung are significantly lower in people with sarcoidosis compared with healthy subjects. This study will examine why. The researchers will draw blood from people with and without sarcoidosis who are not on immunosuppression, and study the levels of types of natural killer T cells, and study the function of these cells. Knowledge gained from this project may lead to new sarcoidosis treatment strategies.

**CHARLOTTE MITCHELL, PhD**

Yale University, New Haven, CT

*Senior Research Training Fellowship* • Funded by the American Lung Association

---

**Studying Effects of Protein Chemical Messenger on Cells Lining Airways**

---

***Interferon-gamma Effects on the Airway Epithelium Modulate Lung Disease.*** Cells called epithelial cells line the airway, creating a surface called the epithelium. The epithelium is important for protecting and regulating immune responses in the lung. Interferon-gamma (IFN-g) is a protein chemical messenger that is important for defense during disease, but its effect on the epithelium is not known. The researchers have developed a mouse in which the receptor for IFN-g is absent from all cells except airway epithelial cells, which allows only the epithelium to respond to IFN-g. Using this mouse, the researchers can identify how the airway epithelium responds to IFN-g to affect disease. Infection with *Mycobacterium tuberculosis* and pulmonary fibrosis are serious diseases of the lung, and IFN-g is an important factor in both these diseases. The researchers hope to clarify the role of the IFN-g responses by the airway epithelium in mouse models of mycobacterial infection and pulmonary fibrosis. These studies may identify novel pathways that can be used for future treatment of these diseases.

**KATSUhide OKUNISHI, MD, PhD**

University of Michigan, Ann Arbor, MI

*Senior Research Training Fellowship* • Funded by the American Lung Association

---

**Getting Fibroblasts to Work Against Idiopathic Pulmonary Fibrosis**

---

***Protein Kinase A Signaling is Impaired in Fibrotic Lung Fibroblasts and Rescued by Plasminogen Activation.*** Idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP) is a devastating scarring disease of the lung of unknown cause. Fewer than 50% of affected patients survive five years, and its incidence, prevalence and death rate are all on the rise in the United States. Unfortunately, there is no effective treatment for this disorder. Cells called fibroblasts are now recognized as important in the development of lung fibrosis.

A substance produced in the lung called prostaglandin E2 (PGE2) suppresses virtually all the functions of fibroblasts in normal lungs and could be an attractive candidate for an anti-fibrotic drug. But the researchers have found that fibroblasts from the lungs of some IPF patients are resistant to the suppressive action of PGE2. They will study how PGE2 works inside normal fibroblasts, and why it does not work in fibroblasts of patients with IPF. In particular, they will test the possibility that a process called plasminogen activation may be able to restore PGE2 effectiveness in IPF fibroblasts. The research may lay a foundation for the development of a new possible treatment: combined administration of PGE2 plus agents such as urokinase that increase plasminogen activation.

**ANNE-KARINA PERL, PhD**

Childrens Hospital Medical Center-Cincinnati, Cincinnati, OH

*Biomedical Research Grant* • Funded in partnership between the American Lung Association and the Alpha-1 Foundation

---

**Stopping Airway Wall Thickening to Improve COPD Survival**

---

***Role of EGF Receptor in Regenerating Airway Epithelium and Airway Wall Thickening.*** Injury of the cells lining the airways can lead to airway wall thickening. Airway wall thickening has been identified as a major predictor of the severity of airway obstruction in COPD patients. It is also implicated in bronchiolitis obliterans syndrome (BOS), which is the main chronic complication after lung transplantation. Using a mouse model, the researchers will study airway regeneration after acute injury and airway wall thickening after chronic injury. They will focus on the role of epithelial growth factor receptor (EGFR), a substance that is present in the membrane of the lung cells. Previous research has shown that EGFR is increased after cell injury, and that inhibiting EGFR signaling reduces lung scarring. The long-term goal of this study is to get a better understanding of the molecular events that control the steps that lead to airway wall thickening and to use these findings to develop effective therapeutic strategies to improve long-term survival in COPD and after lung transplantation.

**NATHAN SANDBO, MD**

University of Chicago, Chicago, IL

*Dalsemer Research Grant* • Funded by the American Lung Association

---

**Targeting Cell Signaling Process May Stop Scarring  
in Pulmonary Fibrosis**

---

***Control of Pulmonary Myofibroblast Differentiation by Actin Dynamics.*** Idiopathic pulmonary fibrosis (IPF) is a progressive, fatal lung disease, characterized by lung scarring. Currently, no proven, effective therapy exists to alter the natural course of the disease, which, on average, leads to death from respiratory failure within three years from the date of diagnosis. Given the dire prognosis of this condition and lack of treatment options, novel targets for drug therapy are needed to stop the scarring process in the lungs. The researchers are studying the process within lung cells called fibroblasts that lead them to cause scarring in the lungs. They are focusing on a substance called Transforming Growth Factor-beta, which starts a cascade of signals within the cells that leads to scarring. They hope to identify new signaling molecules and events that are involved in this process, which may provide important new targets for drugs that might halt the inexorable progression of IPF.



---

## DISEASES OF INFANTS AND CHILDREN

---

**R**esearch supported by the American Lung Association has contributed significantly to scientific progress in understanding and treating respiratory disorders of infants and children. Deaths of premature infants due to the respiratory distress syndrome (RDS) have decreased dramatically over the past 30 years, thanks to more sophisticated care and modern medicine's ability to replace a critical molecule called "surfactant" that is absent in premature lungs. Improved care techniques can now prolong life in children with cystic fibrosis (CF). A clearer understanding of infant breathing has led to practical measures that have reduced deaths from sudden infant death syndrome (SIDS), or crib death.

Despite these advances, lung diseases and breathing disorders remain leading causes of death in infants up to one year of age. There is still no cure for CF, and the problems of treatment have increased as people with this condition live longer. New technologies allow delivery of more and more premature infants at risk for RDS. Many of those who survive develop a chronic illness called bronchopulmonary dysplasia, which is caused by the pressure ventilators and oxygen used to support life in these fragile infants. More than 75,000 to 125,000 children are hospitalized each year due to respiratory syncytial virus (RSV), and an estimated 0.2-7% of them die of complications related to the disease.

Research supported by American Lung Association investigators this year will examine the process of lung development in order to understand the challenges of the lungs of premature infants. In addition, the mechanisms of lung injury produced by vital but potentially toxic oxygen therapy of premature infants will be studied.

CF, the most common heritable disease of Caucasians, continues to take many lives. Basic studies at the level of the abnormal gene and the cell channels that it codes for, seek to discover a rationale for fundamental new treatments. In addition, new approaches are being sought to treat pseudomonas infection, a major cause of deterioration of lung function in CF.

Innovative studies are being done to identify the factor in human breast milk which protects against pneumonia. This could lead to novel therapeutic agents which is important since the bacteria which cause pneumonia are rapidly becoming resistant to currently used antibiotics.

## **American Lung Association Scholar: Diseases of Infants and Children**




---

**DENISE AL ALAM, PhD**  
**Childrens Hospital Los Angeles**

---

Bronchopulmonary dysplasia (BPD) is a lung disease that occurs most often in babies who were born severely premature—more than 10 weeks before their due date. Babies with BPD have inflammation and scarring in the lungs. About 5,000 to 10,000 babies born in the United States each year have BPD. More babies today have BPD than 30 years ago because more very premature babies survive.

Denise Al Alam, PhD, is using her American Lung Association Senior Research Training Fellowship grant to study the molecular pathways of embryonic lung development. She hopes that the information she gains from this research will be useful in developing treatments for the severe breathing problems in premature babies with BPD.

She is focusing on two particular molecules involved in lung development: a growth factor called Fibroblast Growth Factor (FGF) 9, which is needed for the growth and development of several organs including the lung, and a protein called Pitx2 that sends signals that allow cells to grow and divide.

“By identifying the exact role of FGF9 and Pitx2 in lung development, we will have a better understanding of their value in developing new treatments for BPD,” Dr. Al Alam says. In mice genetically engineered to have no FGF9 or Pitx2 specifically in the lung, Dr. Al Alam found that the lack of these molecules leads to abnormal lung development, but their exact role is still unknown. Also, her lab found that the lack of Pitx2 leads to the death of the mice in utero, before birth.

She notes that human adults with lung adenocarcinomas, a type of lung cancer, have increased levels of FGF9, but there have been no studies in human babies to determine the levels of either FGF9 or Pitx2.

Dr. Al Alam’s grant took on a new urgency for her this year, when she had newborn twins who were born prematurely. “They were in the NICU (neonatal intensive care unit) at the beginning and were having a hard time breathing. So I realize more the importance to find cures for babies with breathing problems,” she says.

For a complete description of Dr. Al Alam’s research project, please go to page 53.

**DENISE AL ALAM, PhD**

Childrens Hospital Los Angeles, Los Angeles, CA  
 Senior Research Training Fellowship • Funded by the  
 American Lung Association

---

Studying Embryonic Lung Development May Lead to  
 Treatment for Breathing Problems

---

***Role of Epithelial FGF9 and PITX2 Signaling During Lung Development.*** Premature infants often have breathing problems because their lungs have not had enough time to develop before birth. Understanding the molecular pathways of embryonic lung development will be the key to treating the devastating problem of breathing problems associated with prematurity. Lung development requires growth factors. One of these important growth factors is called Fibroblast Growth Factor 9 (FGF9). Genetically engineered mouse embryos lacking FGF9 exhibit many defects including decreased lung growth. But the precise role of FGF9 beyond the early embryonic phase of lung development remains unknown. In addition a gene called Pitx2 is also known to play an important role in lung development. Proper development of the cells lining the airsacs, called epithelial cells, is crucial for providing oxygen to the blood. The fully functional epithelial cells that form the alveoli originate from cells called epithelial progenitor cells in the embryonic lung. The researchers will test whether FGF9 and Pitx2 are important for the process of maturation and proliferation of these epithelial progenitor cells. This research may ultimately lead to urgently needed treatments for premature infants with breathing problems.

**MATTHEW GIANNANDREA, PhD**

University of Rochester, Rochester, NY  
 Senior Research Training Fellowship • Funded by the  
 American Lung Association

---

Seeking Protection From Lung Infection in Babies  
 Receiving Oxygen Treatment

---

***Effects of Neonatal Oxygen Supplementation on the Response of CD8+ T-cells to Influenza Virus Infection.*** Currently, more than one out of every 10 babies born in the U.S. are premature. Premature infants with low birth weight often have under-developed lungs and require supplemental oxygen treatment in order to survive. While this

life-saving treatment is effective, these infants are often diagnosed with a chronic lung disease called bronchopulmonary dysplasia (BPD). Infants that survive with BPD experience decreased lung function in addition to an increased susceptibility to respiratory infections, which is particularly dangerous during the flu season. In order to devise appropriate treatments, more information is needed to explain why babies with BPD have an increased risk of lung infection. The researchers previously studied how oxygen supplementation at birth affects susceptibility to a respiratory infection using a mouse model. Their preliminary data indicated that the production of immune cells called killer T-cells that are specific to the influenza virus are impaired in mice exposed to oxygen at birth. The researchers will further study how these killer T-cells in mice exposed to oxygen at birth work against virus-infected cells. The findings will help guide drug and vaccine design that could ultimately help limit susceptibility to infection in human survivors of BPD.

**ANDERS HAKANSSON, PhD**

State University of New York at Buffalo, Buffalo, NY  
 Biomedical Research Grant • Funded by the American Lung  
 Association

---

Protein Complex in Breast Milk May Fight Pneumonia

---

***The Use of a Human Milk Protein Complex, HAMLET, to Treat Pneumococcal Pneumonia.*** Streptococcus pneumoniae (pneumococcus) is the most common cause of bacterial pneumonia and a common complication of influenza and measles virus infections. Pneumococci, like so many other bacterial pathogens, have become resistant to common antibiotics used to treat these infections and currently 30% of strains isolated in the U.S. are not susceptible to penicillin. During the researchers' investigations of the antibacterial activity of breast milk, they discovered a protein complex called HAMLET with potent killing activity against S. pneumoniae and other respiratory tract pathogens that cause pneumonia. HAMLET kills pneumococci that are resistant to common antibiotics, and no resistance against HAMLET has been observed. The researchers will investigate the ability of HAMLET to kill bacteria growing

in biofilms (the form of growth encountered during infection) and prevent and treat pneumococcal pneumonia in established mouse model systems, which closely resemble human disease. This research has the potential to lead to the development of more effective therapeutic agents against pneumococcal disease, with less risk for resistance development.

#### **SUIL KIM, MD, PhD**

University of California at San Francisco, San Francisco, CA  
*Biomedical Research Grant* • Funded by the American Lung Association

---

Research into Overproduction of Mucus Could Lead to New Lung Treatments

---

***Role of Cyclooxygenase-2 Feedback Pathway in Epidermal Growth Factor Receptor-Dependent Mucin Production.*** In healthy airways, cells produce small amounts of mucus as part of a defensive response to remove inhaled “invaders” (such as bacteria and viruses) from the airways. However, exaggerated defensive responses may result in the overproduction of mucus, causing mucous plugging of small airways. If extensive, these may be deadly in people with acute asthma and may require lung transplantation in people with advanced COPD and cystic fibrosis. There are presently no proven effective therapies for excess secretion of mucus. Therefore, novel therapies that target mechanisms involved in mucous hypersecretion are urgently needed. The most important constituents of mucus are substances called mucins. The researchers previously discovered a pathway that leads to mucin production in airways. This pathway involves signals from a molecule on the cell surface called epidermal growth factor receptor (EGFR). They will study how the normal EGFR pathway for mucin production is altered, leading to overproduction of the substance in lung disease. This research could lead to drugs that prevent mucous hypersecretion in COPD, cystic fibrosis and acute asthma.

#### **WLADIMIR LABEIKOVSKY, PhD**

The Rockefeller University, New York, NY  
*Senior Research Training Fellowship* • Funded by the American Lung Association

---

Sidestepping a Roadblock in Developing Treatments for Cystic Fibrosis

---

#### ***Structure and Mechanism of Bacterial ATP-Binding Cassette Proteins Resembling CFTR.***

Cystic fibrosis (CF) is a genetic disease that causes chronic bacterial infections and inflammation in the lung. CF is a rare but life-shortening disease; the average life expectancy of a person diagnosed with CF is around 35 years. To date, available therapies against CF are aimed almost exclusively at reducing symptoms, and there is no cure yet. CF is caused by mutations in the gene called CFTR. Most people with CF have a mutation in the CFTR gene that results in the misfolding and premature degradation of the protein encoding the gene. There are a number of research efforts underway to develop CF therapies, all of which would benefit from a thorough understanding of CFTR’s molecular mechanism. Efforts in attaining this information have been hindered largely by the difficulties in obtaining sufficient amounts of stable, purified CFTR protein. The researchers aim to side-step this difficulty by studying bacterial proteins that resemble CFTR. This research should shed light on the structure and mechanism of CFTR.

#### **ARNE RIETSCH, PhD**

Case Western Reserve University, Cleveland, OH  
*Biomedical Research Grant* • Funded by the American Lung Association

---

Unraveling Workings of Bacteria that Cause Lung Infections in CF Patients

---

#### ***Type III Secretion-Mediated Intoxication of Lung Cells by the Opportunistic Pathogen *Pseudomonas aeruginosa*.***

*Pseudomonas aeruginosa* is one of the most common bacteria that infect critically ill patients and cause ventilator-associated pneumonia. It is also the number one pathogen responsible for the chronic lung infections in patients with cystic fibrosis and is responsible for the majority of the illness and death in this patient group. One of the problems with *P. aeruginosa* is that infections are difficult to treat due to the high

antibiotic resistance of the organism. New targets for treatment are sorely needed. The researchers are studying one of the main systems that *P. aeruginosa* uses to cause disease, a syringe-like appendage that allows the bacterium to directly inject toxins into host cells. They hope to better understand how these molecular syringes function, information that potentially could be used to treat *P. aeruginosa* infections.

### **CATERINA TIOZZO, MD, PhD**

Children's Hospital of Los Angeles, Los Angeles, CA  
*Senior Research Training Fellowship* • Funded by the American Lung Association

---

Gaining Better Understanding of Enzyme's Role in Development of BPD

---

#### ***Role of PTEN in Lung Vasculogenesis.***

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that affects 10,000 premature infants in the United States every year. BPD is believed to result from arrested lung development and irregular development of the blood vessels. Proper development of the lung's blood vessels is needed in order for the blood to receive enough oxygen. The researchers are studying Pten, an enzyme involved in several cellular functions, which also may be involved in interfering with blood vessel growth in the developing lung. They will investigate whether the absence of Pten in the embryo's lung connective tissues causes the blood vessel abnormalities seen in BPD. Gaining a better understanding of Pten will be helpful in determining the cause of BPD and identifying molecular targets for its prevention and treatment.

### **ALBERT SENFT, PhD**

Lovelace Respiratory Research Institute, Albuquerque, NM  
*Biomedical Research Grant* • Funded by the American Lung Association

---

How Does RSV Circumvent the Immune System?

---

#### ***Viral Modulation of Lung Phagocyte Functions.***

Respiratory syncytial virus (RSV) is a common respiratory virus that causes severe illness in the

very young and elderly. A large collection of evidence suggests that RSV is adept at circumventing the immune system. This results in an increased risk for developing chronic asthma, as well as severe illness caused by secondary bacterial infection. The mechanisms by which RSV circumvents the immune system are currently unclear. Currently there is no vaccine against RSV and available treatments against the virus are minimally effective. Lung macrophages are specialized white blood cells that are critical for clearing inhaled particles and pathogens from the lung and also regulate the immune system's ability to recognize specific pathogens. The researchers conducted preliminary studies that indicate that RSV impairs macrophage functions that are required for the killing and clearance of pathogens. The researchers will now study how RSV impairs macrophage function. This research may lead to novel therapies to treat and limit RSV-induced disease.



---

## GLOSSARY

---

**acute**

A condition that progresses quickly and continues for a short time.

**adenovirus**

One of a group of viruses causing upper respiratory disease, including colds.

**AIDS**

(Acquired Immunodeficiency Syndrome) A disease in which the cellular immune system is disabled. It is caused by infection by the human immunodeficiency virus (HIV). HIV destroys a specific white blood cell, the helper T lymphocyte or T cell. Without this T cell, the cellular immune system cannot function properly. AIDS is diagnosed in a patient with HIV infection who has a major complication, such as *Pneumocystis carinii* pneumonia.

**airway**

The route for passage of air into and out of the lungs.

**allele**

Mutually exclusive forms of the same gene, occupying the same locus on homologous chromosomes, and governing the same biochemical and developmental process.

**allergen**

A substance capable of inducing allergy or specific hypersensitivity, such as pollen.

**alveolar**

Relating to the alveolus (singular) or alveoli (plural), the terminal, tiny saclike structures in the lung where gas exchange takes place.

**angiogenesis**

The formation and differentiation of blood vessels.

**antigen**

Any molecule that provokes the synthesis of an antibody.

**antioxidant**

A substance that hinders oxidation. In the lungs, oxidant molecules are suspected of contributing to a variety of serious conditions; antioxidants can be an important defense.

**apoptosis**

A genetically determined process of cell self-destruction, marked by the fragmentation of nuclear DNA, is activated either by the presence of a stimulus or by the removal of a stimulus or suppressing agent. It is a normal physiological process, eliminating DNA-damaged, superfluous, or unwanted cells (as immune cells targeted against the self in the development of self-tolerance or larval cells in amphibians undergoing metamorphosis); and when halted (as by genetic mutation) may result in uncontrolled cell growth and tumor formation.

**Aspergillus**

A genus of fungi with black, brown, or green spores that includes many common molds such as *clavatus*, *flavus*, *Aspergillus fumigatus*, *nidulans*, *niger*, and *terreus*.

**asthma**

A syndrome caused by chronic inflammation of the airway canal, characterized by increased reactivity of the airways to a variety of stimuli, which results in reversible airway swelling, spasm, and increased mucus production characterized by coughing, wheezing, and shortness of breath.

**autoimmune disease**

A disease that results when the immune system attacks elements of its own body.

**bacteremia**

The usually transient presence of bacteria in the blood.

**bacterium**

(bacteria) A single-celled, microscopic organism existing in many forms, some of which cause disease.

**beta-adrenergic agonists**

Any of various drugs that combine with and activate receptors which exist on cell surfaces of some effector organs and tissues. This explains the specificity of certain adrenergic agents in activating or blocking only some sympathetic activities (as vasodilation, increase in muscular contraction and beat of the heart, and relaxation of smooth muscle in the bronchi and intestine).

**biochemistry**

The chemistry of living organisms.

**BPD**

(Bronchopulmonary Dysplasia)

A condition of the lungs in infants and children that may follow the treatment of respiratory distress syndrome in infants. It is characterized by distortion of the airways and scar formation.

**bronchiectasis**

A chronic inflammatory or degenerative condition of one or more bronchi or bronchioles marked by dilatation and loss of elasticity of the walls.

**bronchiolitis obliterans**

Extensive scarring (fibrosis) of the small airways.

**bronchitis**

Inflammation of the bronchial tubes.

**bronchoconstriction**

Reduction in the caliber of a bronchus or bronchi.

**calcium channels**

Pores that allow calcium to get inside of a cell.

**cancer**

A disease involving abnormal, uncontrolled growth of a group of cells. Damage may be caused by local growth or spread throughout the body.

**caveolar kinases**

Enzymes that catalyze the transfer of phosphate groups from a high-energy phosphate-containing molecule (as ATP or ADP) to a substrate in small vesicular invaginations of the cell membrane.

**cell**

The basic subunit of any living organism; the simplest unit that can exist as an independent living system. There are many different types of cells in people, each with specific characteristics. The lung has more than 25 different types of cells.

**chemokines**

Soluble proteins produced and released by a wide variety of cell types during the initial phase of host response to injury, allergens, antigens, or invading microorganisms.

**chromatin**

The genetic material of the nucleus, consisting of basic proteins that are usually dispersed in the interphase and condensed into chromosomes in mitosis and meiosis.

**chromosomes**

The structures of a cell that contain the genes, or hereditary factors, and are constant in numbers in each species.

**chronic bronchitis**

A chronic inflammation of the airways - one of the two conditions which make up COPD.

**clone**

A group of genetically identical cells or organisms asexually descended from a common ancestor. All cells in the clone have the same genetic material and are exact copies of the original. The word is also applied to a single gene. An important biotechnology tool is the ability to isolate and make many copies of (clone) specific genes.

**collagen**

A key fibrous element of supporting tissue. It provides the strength to many organs.

**COPD**

(Chronic Obstructive Pulmonary Disease) Refers to chronic bronchitis and emphysema, common serious diseases which are characterized by irreversible obstruction to flow of air in the lungs.

**corticosteroid**

A drug that has actions similar to the natural cortisone of the body.

**Cryptococcus neoformans**

A species of yeast-like fungi that causes an acute or chronic infection resulting in a pulmonary, systematic, or meningeal infection in humans.

**cystic fibrosis**

An inherited disease that is caused by a defect in transportation of certain salts across biologic membranes. Many organs are affected. In the lungs, a severe form of bronchitis is produced in children and young adults.

**cytokines**

Protein chemical messengers involved in the inflammatory process, usually from white blood or similar cells.

**cytoskeleton**

The network of protein filaments and microtubules in the cells that controls cell shape, maintains intracellular organization, and is involved in cell movement.

**cytotoxic**

Toxic to cells.

**dedifferentiation**

Reversion of specialized structures (as cells) to a more generalized or primitive condition, often as a preliminary to major physiological or structural change.

**desensitizing**

To make (a sensitized or hypersensitive individual) insensitive or non-reactive to a sensitizing agent.

**differentiation**

The development of a discriminating conditioned response with a positive response to one stimulus and absence of the response on the application of similar but discriminably different stimuli. The maturation of cells from premature to specific forms such as lining cells of the airways and blood vessels.

**distal**

Situated away from the point of attachment or origin or a central point.

**DNA**

(deoxyribonucleic acid) The molecule containing hereditary information in all but the most primitive organisms. Genes and chromosomes are composed of DNA.

**edema**

Accumulation of excessive fluid in tissues.

**elastin**

A fibrous element of supporting tissue. It provides the stretchable characteristic of the lungs. Destruction of elastin is thought to be the key step in the production of emphysema.

**emphysema (see COPD)**

A condition characterized by the destruction of the walls of air spaces, which results in permanently abnormally enlarged air spaces. This condition decreases the amount of lung surface available for the uptake of oxygen. The resistance to air flow in the air passages is increased, requiring more breathing effort. Severe emphysema is characterized by a profound sense of breathlessness.

**endothelial**

Cells comprising the inside layer of the walls of certain hollow organs such as blood vessels.

**enzymes**

Proteins that speed up specific biochemical processes in an organism. They are fundamental to virtually all biochemical processes.

**eosinophil**

A white blood cell that contains granules filled with a specific set of chemicals and enzymes that influence inflammatory reactions. They are increased in several classes of disease, including allergic diseases.

**epithelial cells**

Cells lining the walls of certain organs, such as the airways of the lungs.

**fibroblast**

An elongated, flattened cell present in connective tissue, which produces fibrous tissue.

**fibrosis**

The formation of scar tissue; excessive formation of scar tissue throughout the lungs is called “pulmonary fibrosis.”

**gene**

A sequence of DNA in the nucleus of a cell that codes for the production of a specific protein.

**gene therapy**

The introduction of a foreign gene into a cell to make that cell produce a protein that it otherwise would not have produced. The form of gene therapy being studied intensively involves provision of a gene which is lacking or not functioning properly. Very promising research is being conducted to develop gene therapy for cystic fibrosis and the hereditary form of emphysema.

**gland**

An organ that secretes a substance.

**graft vs. host disease**

A serious complication of transplantation in which transplanted donor immune cells recognize the body as foreign and attack the recipient’s cells.

**heat shock proteins**

Also called stress proteins, these proteins are found in all living organisms. They play a central role in the survival of cells under stress, and are activated by heat, radiation, and chemotherapy.

**Histoplasmosis**

An infectious disease caused by inhaling the spores of a fungus called *Histoplasma capsulatum*.

**HIV (see AIDS)**

(Human Immunodeficiency Virus) The agent responsible for causing AIDS. Patients with HIV infection will ordinarily develop abnormal immune systems and are predisposed to infection with organisms such as *Pneumocystis carinii* and *Mycobacterium tuberculosis*.

**hyperoxia**

The use of high concentrations of oxygen. Hyperoxia is commonly used as lifesaving therapy in patients with profound loss of lung function, but prolonged use of hyperoxia can lead to inflammation, fluid accumulation, lung failure, and even death.

**hypoxia**

A pathological condition in which the body as a whole (generalized hypoxia), or region of the body (tissue hypoxia), or the blood is deprived of adequate oxygen supply.

**idiopathic pulmonary fibrosis (IPF)**

A chronic and usually progressive lung disorder of unknown cause.

**immunization**

A medical treatment that imparts immunity to a specific disease. “Vaccinations” and “flu shots” are immunizations.

**immunomodulation**

Changing certain characteristics of the immune system, which may be done as therapy for a disease state.

**inflammation**

A fundamental response to injury or abnormal stimulation, consisting of complex reactions occurring in the affected blood vessels and adjacent tissues. The inflammatory process includes destruction or removal of the material causing the injury and responses that lead to repair and healing, or responses that lead to a variety of acute and chronic disease states.

**interstitial**

The supporting matrix of the lungs, as opposed to the airways or air sacs. May be the site of specific diseases.

**in vitro**

Outside of the living body; in a test tube or glass.

**in vivo**

Inside of the living body of a plant or animal; opposite of in vitro. Scientific studies frequently involve testing concepts in both ways.

**leukocyte**

A white blood cell that constitutes a major component of the immune system.

**lipids**

A general term for molecules that are the building blocks of fats.

**lipoprotein**

A molecule made of a lipid and a protein.

**macrophage**

Specialized cells that engulf and destroy bacteria and foreign particles in the lungs and other organs. In the lungs, these cells are called alveolar macrophages.

**malignant**

Usually refers to the behavior of a tumor that is invasive, destructive, or spreads to other parts of the body.

**membrane**

The surface covering a biologic entity. Example: mucous membranes line the nose and airways.

**metabolism**

The chemical processes of the body.

**metastasis**

The spreading of a disease to another part of the body.

**molecular biology**

A field of biology dealing with the fundamental biochemical organization of living matter, especially the biochemical basis for inheritance. For example, molecular biologists may study genes, DNA, or protein synthesis.

**molecule**

The smallest amount of a specific chemical substance that can exist alone.

**mutation**

Any alteration in the base sequence along the DNA, changing the genetic material.

**myofibroblasts**

Connective tissue cells that are important in normal wound-repair responses. They also play an important role in the development of the air sacs in the lungs, called alveoli.

**neutrophil**

A white blood cell important in the immune process.

**non-tuberculosis mycobacteria**

Microorganisms which belong to the overall TB family but cause a different disease. Non-tuberculosis mycobacterial infection is not transmitted from person to person. It may grow in previously damaged lung (bronchiectasis) or it may affect otherwise normal individuals.

**oxidants**

Molecules that react readily with other molecules in a manner similar to the way in which oxygen reacts. The reaction can be destructive, and the generation of an excess of powerful oxidants is thought to play a role in several disease processes in the lungs.

**peptide**

A sequence of amino acids. Peptides are combined to make proteins.

**phospholipid**

A form of lipid that is combined with the phosphorous molecule. Phospholipids are key elements in the surfactant of the lungs, which prevents the alveoli from collapsing.

**physiology**

The science of living things, dealing with the normal life process.

**pneumonia**

Inflammation of the alveoli and/or supporting structures of the lungs (air sacs). Can be due to infection by bacteria, viruses, fungi, or other microorganisms. Some pneumonias are not infectious.

**prostaglandin**

A family of fatty acid derivatives producing a variety of biological effects, including inflammatory responses. Tiny amounts have potent effects.

**proteases**

Enzymes that degrade other proteins.

**proteins**

Organic compounds made up of amino acids; one of the major constituents of plant and animal cells.

**pulmonary arteries**

The arteries that bring oxygen-poor blood to the lungs from the heart.

**pulmonary edema**

Excess fluid in the lungs.

**pulmonary fibrosis**

A condition characterized by diffuse scar formation in the supporting structure of the lungs.

**pulmonary hypertension**

Abnormally high blood pressure in the arteries of the lungs.

**RDS**

Respiratory distress syndrome occurs in premature infants as a result of a lack of adequate surfactant, which makes the air sacs difficult to expand.

**receptor**

In nerves, a specialized nerve ending able to receive and respond to a stimulus in a specific way. Also used to describe the molecule on a cell surface that interacts with a specific chemical messenger.

**sarcoidosis**

A disease that involves a distinct form of diffuse inflammation of the lungs, lymph nodes, and other organs. It is prevalent in African Americans and may lead to pulmonary fibrosis.

**sepsis**

The presence of various pus-forming and other pathogenic microorganisms, or their toxins, in the blood.

**SIDS**

(Sudden Infant Death Syndrome)

The unexplained and sudden death of an infant, one month to one year of age.

**sleep apnea**

One of several common respiratory disorders of adults and children, characterized by periodic cessation of breathing during sleep. It is usually accompanied by loud snoring and results in daytime sleepiness and other severe disabling characteristics.

**smooth muscle**

A lung tissue that plays a key role in airway inflammation and bronchial hyper-responsiveness (airway “twitchiness”).

**streptococcus**

A form of bacteria that may cause pneumonia.

**surfactant**

A surface-tension lowering agent. Pulmonary surfactant is produced by alveolar type II cells, which line the alveolar space. It is essential for normal expansion of the lungs and is abnormal or lacking in premature infants with respiratory distress syndrome and other diseases.

**syndrome**

A specific set of symptoms and/or medical findings that often occur together but are not distinct enough to be thought of as a single disease entity (e.g., sleep apnea syndrome).

**theory**

General principles derived from a body of scientific data to explain a natural occurrence.

**toxicity**

Ability to cause harm.

**tuberculosis**

An infectious disease due to a microorganism called *Mycobacterium tuberculosis*. The disease usually begins in the lungs, but can involve virtually any part of the body. Progression from infection to disease is more likely in patients with an abnormal immune system.

**tumor**

An abnormal collection of cells into a distinct physical entity.

**T cells**

Small white blood cells that orchestrate and/or directly participate in the immune defenses; also known as T lymphocytes, they are processed in the thymus and secrete lymphokines.

**type I cells**

The cells that line the alveoli that produce surfactant.

**vaccine**

An inactivated (noninfectious) preparation of a microorganism that can be injected into a patient to stimulate the production of antibodies in order to protect the patient from infection by the live organism. Also an active but attenuated microorganism which causes a mild form of the disease while stimulating antibody production.

**ventilator**

A device that provides for mechanically assisted breathing.

**virus**

A tiny infectious agent that requires a host cell in order to replicate. It is composed of either RNA or DNA wrapped in a protein coat. Viruses cause a wide variety of diseases.



---

## TOPIC INDEX

---

**Air Pollution**

Estelle Cormet-Boyaka 22, 23  
Kari Christine Nadeau 11, 24

**Allergic Bronchopulmonary Aspergillosis**

Xuexian Li 36

**Allergy**

Oliver Haworth 10, 47

**ARDS**

Kaiser Mohammad Bijli 19  
Anasuya Sarkar 18, 19  
Umapathy Siddaramappa 19

**Asthma**

Scott Alper 9, 23  
Tracey Bonfield 9  
Rebecca Gail Breslow 9  
Ka Young Chung 10  
Oliver Haworth 10, 47  
Shamsah Kazani 10  
Hyun-Hee Lee 11  
Quan Lu 8, 11  
Vera Moiseenkova-Bell 11  
Kari Christine Nadeau 11, 24  
Marina Reznik 12  
Yui-Hsi Wang 12  
Zhong-Xin Wu 12, 25  
Cuneyt Yilmaz 13  
Nives Zimmermann 13

**Bronchopulmonary Dysplasia**

Denise Al Alam 52, 53  
Matthew Giannandrea 53  
Caterina Tiozzo 55

**Chronic Obstructive Pulmonary Disease**

Tracy Adair-Kirk 23  
Scott Alper 9, 23  
Estelle Cormet-Boyaka 22, 23  
Seyed Javad Moghaddam 24, 42  
Anne-Karina Perl 24, 48  
Masahiro Sakagami 25

**Cystic Fibrosis**

Suil Kim 54  
Wladimir Labeikovskiy 54  
Xuexian Li 36  
Arne Rietsch 54

**Histoplasmosis**

Sinem Beyhan 35

**Influenza**

Alina Boesteanu 35  
Mehmet Kesimer 36  
Jie Sun 37

**Lung Cancer**

Ralph Arlinghaus 41  
John Eaton 41  
Ping-Ching Hsu 23, 41  
Teresa Liberati 42  
Matthew Meyerson 42  
Seyed Javad Moghaddam 24, 42  
Emelyn Helen Shroff 43  
Christopher George Slatore 43  
Kwok-Kin Wong 40, 43

**Lung Transplantation**

Anne-Karina Perl 24, 48

**Nontuberculosis Mycobacterial Infections**

Andrea Cooper 29  
Mary Ann De Groot 29

**Pneumonia**

Amal Amer 35  
Anders Hakansson 36, 53  
Xuexian Li 36

**Pulmonary Fibrosis**

Ming-Hui Fan 47  
Charlotte Mitchell 31, 48  
Katsuhide Okunishi 48  
Nathan Sandbo 46, 49

**Pulmonary Hypertension**

Jean-Francois Jasmin 19

**Respiratory Syncytial Virus (RSV)**

Albert Senft 34, 37, 55

**Sarcoidosis**

Laura Koth 47

**Tobacco**

Ping-Ching Hsu 23, 41  
Zhong-Xin Wu 12, 25

**Tuberculosis**

Bouke Catherine De Jong 29  
Evelina Guirado 28, 30  
Pushpa Jayaraman 30  
Joan Mangan 30  
Charlotte Mitchell 31, 48

---

## REVIEWERS

---

The American Lung Association would like to thank the following Research Awards and Grant Reviewers:

**2008-09**

Patrick Arndt, MD  
 David H. Au, MD, MS  
 William Calhoun, MD  
 Patricia Chess, MD  
 Brian Christman, MD  
 Lauren Cohn, MD  
 Margaret Covey, RN, PhD  
 Mark D. Eisner, MD, MPH  
 Benjamin Gaston, MD  
 Mark N. Gillespie, PhD  
 Kelly E. Greene, MD  
 Susan Guttentag, MD  
 Margaret Gyetko, MD  
 Nicola Hanania, MD, MS  
 Leslie A. Hoffman, RN, PhD  
 A. McGarry Houghton, MD  
 Charles Irvin, PhD  
 David Kamp, MD  
 Steven Kawut, MD, MS  
 David Lewinsohn, MD, PhD  
 Rama K. Mallampalli, MD  
 David Moller, MD  
 Alison Morris, MD  
 Marc Moss, MD  
 Patrick Nana-Sinkam, MD  
 Judith A. Neubauer, PhD  
 Lawrence M. Nogee, MD  
 Kristen Page, PhD  
 Robert Paine, MD  
 Richard Pierce, PhD  
 Karen M. Ridge, PhD  
 David Riley, MD  
 John M. Routes, MD  
 Edward Schelegle, PhD  
 Lynn M. Schnapp, MD  
 Lisa M. Schwiebert, PhD  
 Ronald Sorkness, PhD  
 Theodore J. Standiford, MD  
 Chad Steele, PhD  
 Erik Swenson, MD  
 Victor J. Thannickal, MD  
 Angela C.C. Wang, MD  
 Daniel J. Weiss, MD, PhD  
 Christine H. Wendt, MD  
 Mark M. Wurfel, MD, PhD  
 James Yankaskas, MD

**2009-10**

Douglas Arenberg, MD  
 Patrick Arndt, MD  
 David H. Au, MD  
 Michael F. Beers, MD  
 Hubert Chen, MD, MPH  
 Patricia Chess, MD  
 Brian Christman, MD  
 Andrea Cooper, PhD  
 Margaret Covey, RN, PhD  
 David A. Dean, PhD  
 Ognjen Gajic, MD, MSc  
 Benjamin Gaston, MD  
 Samir Ghadiali, PhD  
 Mark N. Gillespie, PhD  
 Kelly E. Greene, MD  
 Nicola Hanania, MD, MS  
 Leslie A. Hoffman, RN, PhD  
 Cory M. Hogaboam, PhD  
 A. McGarry Houghton, MD  
 David A. Kaminsky, MD  
 David Kamp, MD  
 Robert Kaner, MD  
 Steven Kawut, MD, MS  
 David Lewinsohn, MD, PhD  
 Nicholas W. Lukacs, PhD  
 Rama K. Mallampalli, MD  
 Marc Moss, MD  
 Patrick Nana-Sinkam, MD  
 Judith A. Neubauer, PhD  
 Lawrence M. Nogee, MD  
 Kristen Page, PhD  
 Robert Paine, MD  
 Jonathan P. Parsons, MD  
 Richard Pierce, PhD  
 Charles A. Powell, MD  
 Troy D. Randall, PhD  
 Karen M. Ridge, PhD  
 David Riley, MD  
 Edward Schelegle, PhD  
 Lynn M. Schnapp, MD  
 Lisa M. Schwiebert, PhD  
 Ronald Sorkness, PhD  
 Theodore J. Standiford, MD  
 Chad Steele, PhD  
 Erik Swenson, MD  
 Steve Tilley, MD  
 Angela C.C. Wang, MD  
 Daniel J. Weiss, MD, PhD  
 Christine H. Wendt, MD  
 Mark M. Wurfel, MD, PhD

**2010-11**

Douglas Arenberg, MD  
 Patrick Arndt, MD  
 David H. Au, MD, MS  
 Natalie Bauer, MD, MS  
 Aladin Boriek, PhD  
 Ellen L. Burnham, MD, MS  
 Hubert Chen, MD, MPH  
 Patricia Chess, MD  
 Brian Christman, MD  
 Lauren Cohn, MD  
 Andrea Cooper, PhD  
 Margaret Covey, RN, PhD  
 David A. Dean, PhD  
 Anne Fitzpatrick, PhD  
 Samir Ghadiali, PhD  
 Cara Gottardi, PhD  
 Leslie C. Grammer, MD, FAAAAI  
 Mitchell H. Grayson, MD, FAAAAI  
 Susan Guttentag, MD  
 Angela Haczku, MD, PhD  
 Nicola Hanania, MD, MS  
 Leslie A. Hoffman, RN, PhD  
 Cory M. Hogaboam, PhD  
 A. McGarry Houghton, MD  
 David A. Kaminsky, MD  
 David Kamp, MD,  
 Robert Kaner, MD  
 Steven M. Kawut, MD, MS  
 David Lewinshon, MD, PhD  
 Nicholas W. Lukacs, PhD  
 Rama K. Mallampalli, MD  
 Patrick Nana-Sinkam, MD  
 Judith A. Neubauer, PhD  
 Lawrence M. Nogee, MD  
 Kristen Page, PhD  
 Richard Pierce, PhD  
 Lee J. Quinton, PhD  
 David Riley, MD  
 Edward Schelegle, PhD  
 Erik Swenson, MD  
 Steve Tilley, MD  
 Daniel J. Weiss, MD, PhD  
 T. Eoin West, MD, MPH



We will breathe easier when the air over every  
American city is clean and pure.  
We will breathe easier when the air in our public spaces,  
workplaces and children's homes is free of secondhand smoke.  
We will breathe easier when Americans are free from the addictive grip  
of tobacco and the debilitating effects of lung disease.  
We will breathe easier when our nation's children no longer battle  
airborne poisons or the fear of an asthma attack.  
*Until then, we are fighting for air.*

