

# Research Awards Nationwide 2009-2010

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## **Research Awards Nationwide 2009–10**

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

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## INTRODUCTION

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**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 400,000 Americans die of lung disease, making it the third most frequent cause of death in this country. An additional 33 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.



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## ASTHMA

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**C**lose to 22.9 million Americans have asthma, and 12.3 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 4,000 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, 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. Other Network projects are evaluating the effectiveness of educational programs in controlling asthma.

## American Lung Association Scholar: Asthma



**LIN-FENG CHEN, PhD**  
**University of Illinois at Urbana-Champaign**

Inflammation is the body's response to damage or infection. It can help the body heal, and trigger an immune system response against foreign pathogens. Normally, the immune system automatically turns off the inflammation once the danger is past. But in some diseases, such as asthma, the inflammation doesn't turn off.

Lin-Feng Chen, PhD, is studying a protein called NF-kappa B, which controls genes that cause inflammation. This protein acts like a molecular switch that can be turned on and off as needed. When it is turned on, it moves into the cell's nucleus and sets off proteins that cause inflammation. With the help of an American Lung Association Biomedical Research Grant, Dr. Chen has identified a molecular code that controls the activity of NF-kappa B. With chronic asthma, and with some cancers, NF-kappa B is continuously activated. "It can't be turned off—the signal is on all the time," says Dr. Chen. "This causes the chronic inflammation seen in asthma."

Dr. Chen's team found that by adding small chemical groups to the protein, it is degraded, and the inflammation signal turns off. This process is called post-translational modification. "Using these chemical groups is very important in fine-tuning the immune response and inflammatory response of NF-kappa B," he says. He is trying to identify different chemical groups that could modify NF-kappa B, and determine what kinds of effects they are having on the protein. He plans to study how post-translational modifications affect NF-kappa B activity both under normal and diseased conditions. Understanding how to turn off the protein could lead to new therapies to treat the underlying inflammation in asthma.

With the American Lung Association grant, Dr. Chen was able to continue to support a post-doctoral researcher for his lab. He says, "Without the grant, we wouldn't have been able to keep him in the lab, and we wouldn't have made so much progress so quickly."

To see a complete description of Dr. Chen's research project, please go to page 9.

**LIN-FENG CHEN, PhD**

University of Illinois at Urbana-Champaign, Champaign, IL  
*Biomedical Research Grant* • Funded by the American Lung Association

**Targeting Protein That Causes Inflammation In Asthma And COPD*****Regulation And Functions Of Reversible Acetylation Of NF-kappa B In Lung Inflammation.***

Lung inflammatory diseases, including chronic obstructive pulmonary disease (COPD) and asthma, are characterized by an increased production of genes that cause inflammation. These genes are mainly controlled by a protein called NF-kappa B. Blocking this protein could be a novel treatment in these diseases. Many currently used anti-inflammatory drugs for asthma and COPD, such as steroids, indirectly inhibit NF-kappa B. The researchers will investigate how NF-kappa B is regulated, learn about its role in inflammation, and identify targets for treatment that would inactivate the protein.

**JASON S. DEBLEY, MD, MPH**

Children's Hospital and Regional Medical Center, Seattle, WA  
*Biomedical Research Grant* • Funded by the American Lung Association

**Changes In Airway Wall Can Provide Insight Into Childhood Asthma**

***Airway Epithelial Cell Cytokine Profiles Of Children With And Without Asthma.*** Studies following children with wheezing and asthma into the teenage years and adulthood suggest that lung function in children who ultimately develop persistent asthma is normal at birth, with lung function deficits starting before 6 years of age. Studies also suggest that children with asthma have significantly lower lung function during childhood and at age 35 years compared with children without a history of asthma. This suggests that the asthmatic airway undergoes significant structural changes early in the course of asthma, which may result in permanent lung function deficits. The researchers will study the epithelium, the cells that line the airways, to gain a better understanding of the development of asthma. They will explore how these cells respond to inflammatory signals and viral infection, and study the role of the epithelium in airway remodeling—the changes that occur in the airway wall due

to inflammation. This work could lead to identifying new therapeutic targets to prevent these airway changes. It also could lead to a new approach to the diagnosis of asthma in young children.

**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.

**OCTAVIAN HENEGARIU, MD**

Yale University, New Haven, CT  
*Biomedical Research Grant* • Funded by the American Lung Association

**Could Anti-Diabetic Drugs Be Promoting And Reducing Asthma At The Same Time?**

***Changes In Th2 Responses And Lung Inflammation In Mice With Conditional PPARG Deletion In CD4 T Cells.*** Certain white blood cells,

called T helper (Th) cells, help other immune cells to mount responses by producing and secreting immune growth factors called cytokines. The immune system produces Th1, Th2, Th17 and regulatory T- cells, and all are needed for an effective immune response. People susceptible to allergic asthma, however, often mount potent Th2 responses. The researchers are studying whether a commonly used class of anti-diabetes drugs called thiazolidinediones (TZD), may promote Th2 responses in the immune system. TZD drugs bind to a protein called PPARG that is present in many cells, including cells of the immune system. TZD agonist drugs promote PPARG function and lead to a better control of the number of harmful activated immune cells, as well as a reduction in the release of pro-inflammatory cytokines, thus decreasing inflammation. Several studies have shown that the anti-inflammatory action of TZD is beneficial in treating asthma. But the researchers think that in addition to inhibiting PPARG, TZD may also be activating asthma-promoting Th2 cells, and the effects are being obscured by the drug's anti-inflammatory effect. They will use a mouse in which PPARG is deleted from some T-cells to investigate the effect of TZD on asthma-promoting cells in the immune system. They hope to discover whether using TZD in asthma has a long-term harmful effect, due to its Th2 activation.

#### **FERNANDO HOLGUIN, MD, MPH**

University of Pittsburgh, Pittsburgh, PA  
*Clinical Patient Care Research Grant* • Funded by the American Lung Association

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#### Can Diabetes Drug Improve Breathing In Obese Asthmatics?

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***A Randomized Placebo-Controlled Study Of Pioglitazone For The Treatment Of Asthma In Poorly Controlled, Moderate To Severe Obese Asthmatics.*** Asthma and obesity are intimately related. Being significantly overweight or obese increases the risk for developing asthma. For people who already have asthma, obesity increases the risk that their asthma will worsen and be more difficult to control. Compared with leaner asthmatics, obese people with asthma have more frequent asthma flare-ups and are less likely to achieve control with inhaled steroids, which are the main

treatment for asthma. Obesity affects levels of fat-related hormones, which are present in the airways and may influence asthma severity. Pioglitazone, an anti-diabetic drug, may be able to reverse the effect that obesity has on fat-related hormones. This study will test whether treatment with pioglitazone can improve asthma control, airway “twitchiness” and breathing symptoms in poorly controlled obese asthmatics. Study subjects will receive either pioglitazone or a placebo, and will be evaluated after three months for asthma control, asthma-related quality of life and lung function. The results will be critical in determining whether pioglitazone could be an alternative medication for obese asthmatics not fully controlled on standard asthma medications.

#### **JASON LANG, MD**

Nemours Children's Clinic, Jacksonville, FL  
*Clinical Patient Care Research Grant* • Funded by the American Lung Association of the Southeast

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#### Can Antioxidant Therapy Help Obese Asthmatics?

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***Antioxidant Therapy In Lean and Obese Asthmatics.*** Asthma and obesity are both growing crises that may be interrelated for many patients. Obesity increases the risk for asthma, and increases the severity of existing asthma. The mechanism(s) for this association are unknown. Currently there is conflicting evidence about whether or not antioxidant supplementation reduces asthma severity. The researchers will study whether obesity-related asthma is due in part to excess blood and airway injury that can be improved with supplemental antioxidants. Specifically, they will study the process of oxidative injury, the destruction caused by free radicals (also called oxidants), which are molecules responsible for aging, tissue damage and possibly some diseases. The researchers will examine whether obesity-related oxidant injury creates greater airway injury and greater asthma severity. They will conduct a 6-week study in adolescents and young adults with asthma to investigate whether supplementation with antioxidants may significantly reduce airway inflammation and oxidative injury, and lead to improved lung function and asthma control.

**MARGOT PAULICK, PhD**

Stanford University, Stanford, CA

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

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**Family of Enzymes May Play Important Role in Asthma Inflammation**

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***Investigation of the Roles of Cysteine Cathepsins in Asthma Pathology.*** Asthma is characterized by inflammation of the lungs and airways. During an asthma attack, proteases, enzymes that degrade other proteins, are released by inflammatory and immune cells to modulate the inflammation associated with asthma. The cysteine cathepsins are a family of proteases that may play important roles in the inflammation associated with asthma. The researchers will explore the contributions of the cysteine cathepsins to the asthmatic response in mouse models of asthma. This research will answer the questions of where, when, and how these proteases impact the overall inflammation associated with asthma. Ultimately, this research will provide a more detailed understanding of the roles of the cysteine cathepsins in asthma pathology and may lead to the development of new drugs to treat and prevent asthma by preventing lung inflammation.

**BEATRIZ QUINCHIA-RIOS, PhD, DDS**

University of Wisconsin, Madison, WI

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

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**Airway Remodeling Research May Benefit Patients With Asthma**

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***Role of the IL-5 Activated Eosinophil In Airway Remodeling Through Modulation Of Bronchial Fibroblasts Activation Of A Fibrotic And Secretory Phenotype.*** The persistence of asthma may lead to progressive changes in the airway that affect air intake, worsen asthma symptoms and irreversibly damage breathing function. These structural changes in the airway are collectively known as airway remodeling. Treatment with anti-inflammatory drugs such as corticosteroids can improve asthma symptoms but has a limited long-term effect on airway remodeling; therefore, it is important to investigate the factors that trigger and perpetuate airway remodeling in order to create better therapies to control or prevent these changes. One of the major inflammatory cells involved

in the allergic asthma reaction and recently linked to some features of airway remodeling is the eosinophil. This cell is activated by the presence of an inflammatory protein, IL-5, and its activation may affect the behavior of the resident cells causing remodeling. The researchers will study the role of IL-5-primed eosinophils in altering the resident cells and causing airway remodeling. This research will contribute to our understanding of the causes as well as the process of airway remodeling, and should be important for the design of more specific medications and treatment strategies to control and perhaps prevent airway remodeling, including anti-IL5 agents.

**MARINA REZNIK, MD**

Montefiore Medical Center, Bronx, NY

*Clinical Patient Care Research Grant* • Funded by the American Lung Association

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

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***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.

## **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.

### **MeCIS: METHACHOLINE BRONCHOPROVOCATION: INFLUENCE OF HIGH POTENCY INHALED CORTICOSTEROIDS**

Core American Lung Association Study

Methacholine bronchoprovocation test is a widely used clinical test to evaluate bronchial hyperreactivity for diagnosis and confirmation of asthma. The test has been recognized to have high sensitivity, which is the proportion of positive diagnosis correctly identified as such. However, there is some question as to whether overtime, the sensitivity of the methacholine challenge may change, especially with the use of high potency inhaled corticosteroids. This clinical trial will measure whether or not methacholine challenge remains a sensitive diagnosis test for 140 subjects ages 12 to 70 (70 control and 70 with stable asthma) or whether the use of high potency inhaled corticosteroids alters methacholine responsiveness.

The next two studies have recently been co-funded by the National Institutes of Health's National Heart, Lung and Blood Institute and are planned to start within the next few months:

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

The study will determine if the treatment of chronic sinusitis and rhinitis with nasal steroids improves asthma control. 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)**

The study is looking at whether a dietary supplement of soy protein helps control asthma inflammation. 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.

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:** Have not been released.

#### *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.

## Asthma Clinical Research Centers (ACRC) Participants

**Michael Busk, MD**  
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Baltimore, MD

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

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**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. 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.

Finally, to clarify how water movement across the lungs is regulated, basic studies are exploring the role of the lung membranes in transporting water and salts. Such studies are critical in understanding the mechanisms of and developing treatments for pulmonary edema and pulmonary arterial hypertension.

At the same time, studies are being done to understand the huge toll on the human psyche of having loved ones treated for ARDS in intensive care units.

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



**JEAN-FRANCOIS JASMIN, PhD**  
**Thomas Jefferson University**

Jean-Francois Jasmin, PhD, wants to improve survival rates for people with pulmonary arterial hypertension (PAH), a disease of high blood pressure in the arteries of the lungs. PAH is progressive and life-threatening because the pressure in a patient's pulmonary arteries rises to dangerously high levels, putting a strain on the heart. None of the current drugs cure or halt the progression of this disease.

"Novel diagnostics and treatments are desperately needed for this serious illness," Dr. Jasmin says. The prognosis for PAH patients is poor. Currently, approximately 50 percent of people diagnosed with PAH die within five years.

Dr. Jasmin is studying the effect of Caveolin-1 on PAH. Caveolin-1, or Cav-1, is a membrane protein that has recently been shown to be involved in the regulation of PAH. Decreases in Cav-1 have been reported in patients with severe PAH.

In 2006, Dr. Jasmin published a paper showing that in hypertensive rats, injections of a Cav-1-mimetic peptide prevented the development of PAH and the enlarged right heart ventricle that accompanies it.

While preventing PAH is also a goal in humans, it will be difficult to achieve, Dr. Jasmin notes. "Because symptoms develop very gradually, most cases of human PAH are usually advanced by the time of diagnosis," he said.

With help from an American Lung Association Biomedical Research Grant, Dr. Jasmin will test whether he can reverse the course of PAH. He is treating hypertensive rodents at various stages of the disease with a Cav-1-mimetic peptide to see at which point the treatment may decrease pressure in the arteries and improve survival. "This grant will help us push forward," he says. "It's a key study in the development of treatment for PAH. We showed we can prevent the disease, and now we need to prove we can reverse it, and then show that in different models. This funding from the American Lung Association is a good platform for us to go further in our research."

To see a complete description of Dr. Jasmin's research project, please go to page 17.

**HYUNG CHUN, MD**

Stanford University, Stanford, CA

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

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**Novel Signaling Pathway May Yield Clues to Pulmonary Hypertension**

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***Characterization of Apelin Signaling in Pulmonary Hypertension.*** Pulmonary hypertension, or high blood pressure in the pulmonary arteries, is a rare disorder of the lung. Pulmonary hypertension can lead to right-sided heart failure, which in turn may lead to severe fluid retention, severe shortness of breath, shock, and death. Although with the development of new treatment options the survival and quality of life of patients have improved, the disease inevitably progresses. There remains an important need to further understand the mechanisms of the disease, and identify novel therapeutic targets. The researchers will study a novel signaling pathway involving the molecule apelin that potentially has an important role in pulmonary hypertension. The results of this research may lead to a novel therapeutic target, resulting in new treatments that could improve the lives of patients with pulmonary hypertension.

**JEAN-FRANCOIS JASMIN, PhD**

Thomas Jefferson University, Philadelphia, PA

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

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

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***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 Caveolin-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.

**ERIN KROSS, MD**

University of Washington, Seattle, WA

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

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**Understanding Post-Traumatic Stress Disorder After Loved One's Death In ICU**

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***Understanding The Mechanism Of PTSD And Depression Among Family Members After Critical Care.*** Post-traumatic stress disorder (PTSD) and depression are common conditions that can occur after critical illness. Both conditions have significant consequences, often with inability to work or return to prior levels of functioning, as well as increased costs to society associated with these symptoms as a result of increased health care costs. Approximately 20% of people in the United States die after a stay in an intensive care unit (ICU). The goal of this proposal is to study the mechanisms behind the development of symptoms of PTSD and depression among family members of those who die in the ICU. Survey data collected from family members of patients who died in 11 intensive care units at both academic and community hospitals will be utilized for this project. The researchers will investigate family and patient factors, such as age, gender, type of illness and family relationship to the patient, as well as aspects of the ICU experience that may be associated with PTSD and depression. With this information, the researchers hope to be able to guide future programs to decrease the likelihood of family members' experiencing these symptoms following death of their loved ones.

**ANNE LIPKE, MD**

University of Washington, Seattle, WA

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

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 Understanding Effect of Fever in Lung Injury  
 May Guide Treatment
 

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***Mechanisms of Enhanced Lung Epithelial Injury in Febrile Hyperthermia.*** Acute lung injury (ALI) is a devastating and common illness in critically ill patients. Fever is also common in the critically ill and frequently coexists with ALI. Previous studies suggest that febrile-range temperatures may worsen critical illness-related organ damage, including ALI. However, the mechanisms by which fever worsens lung injury are poorly understood. Moreover, fever helps the body fight infection. The researchers will examine the mechanisms by which febrile-range temperature augments ALI. They will study whether fever can worsen lung injury through the activation of pathways in the lungs that lead to “programmed cell death,” or apoptosis, of the cells lining the air sacs of the lung. This research will improve understanding of the effect of fever on lung injury and will clarify the necessity to treat fever in patients with lung injury. Understanding how fever affects lung injury may allow the development of interventions that block the injurious effects of fever on the lung, while still allowing patients to benefit from the enhanced defense mechanisms from fever during infections.

**PATRICK A. SINGLETON, PhD**

University of Chicago, Chicago, IL

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

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 Knowing Why Cell Barrier Is Disrupted May Lead To  
 ARDS Treatment
 

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***HABP2/CIINH Regulation Of Acute Lung Injury.*** Acute lung injury (ALI) and the more severe acute respiratory distress syndrome (ARDS) are types of severe, acute lung dysfunction affecting all or most of both lungs that occur as a result of illness or injury. ALI/ARDS afflicts over 190,000 people a year in the U.S., resulting in 74,500 deaths. Despite recent progress in treatment of ALI, there is still no satisfactory strategy to reduce lung damage and tissue injury in this condition.

The hallmark of ALI is inflammation-induced disruption of the cells called endothelial cells that line the pulmonary blood vessels, linking to one another with cell-cell junctions to form a physical barrier between the airways and the blood vessels of the lung. This disruption results in leakage of fluid, protein, and cells into the airspaces of the lung. The researchers seek to understand the mechanisms of the endothelial cell barrier disruption in an attempt to develop novel strategies to treat ALI/ARDS.

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## COPD, SMOKING, AND AIR POLLUTION

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**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 19.8 percent of the adult population in 2007, and in accomplishing important reductions in air pollution during the same time frame. Nevertheless, over 43 million adults still smoke; until recently, teenage smoking has been on the rise; and the American Lung Association estimates that over 186 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. Now studies look at the role of nicotine itself in promoting lung disease. Patient-centered studies are addressing such problems as the best way to assess and ensure quality of care. Other investigations are exploring genetic susceptibility to lung damage by cigarette smoke at the molecular level.

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



**CAROLYN BAGLOLE, PhD**  
**University of Rochester**

While most cases of chronic obstructive pulmonary disease (COPD) are caused by cigarette smoke, not all smokers develop the disease. “There is a lot of speculation that genetic factors play a role in determining which smokers get COPD,” says Carolyn Baglole, PhD. “Even though quitting smoking significantly reduces the likelihood of developing COPD, it does not guarantee that chronic inflammation and lung damage associated with long-term tobacco use will not progress to lung disease.”

Dr. Baglole is using an American Lung Association Biomedical Research Grant to help her understand the molecular basis of how cells regulate damage caused by cigarette smoke. The findings may one day lead to a better treatment for patients with COPD.

Her research focuses on how a cell receptor called the aryl hydrocarbon receptor (or AhR) can prevent inflammation and death in lung cells called fibroblasts in response to cigarette smoke. Fibroblasts are structural cells linked to chronic inflammation that is associated with the development of COPD. Death of these cells also may account for the loss of air sacs in the lungs associated with emphysema.

Dr. Baglole’s previous research found that fibroblasts that are deficient in the AhR are very sensitive to cigarette smoke, and increase key inflammatory mediators. Her current research focuses on understanding how the AhR prevents fibroblasts from undergoing a death process known as apoptosis.

“If we can understand the molecular mechanism by which AhR can prevent inflammation and cell death in COPD, we may be able to find a way to increase this receptor’s ability to impede or even prevent the progression of lung diseases associated with cigarette smoke,” said Dr. Baglole, who hopes this research grant will help her apply for a larger government-funded grant. “COPD is currently incurable. With the knowledge that there are 80 million current and former smokers today in the U.S. alone and that there hasn’t been a single major advance that has produced a significant increase in the lung disease survival rates, this research is long overdue.”

To see a complete description of Dr. Baglole’s research project, please go to page 21.

**CAROLYN BAGLOLE, PhD**

University of Rochester, Rochester, NY

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

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**Understanding How Cigarette Smoking Leads to COPD**

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***The Aryl Hydrocarbon Receptor and RelB Attenuate Cigarette Smoke-Induced Cell Death and Lung Injury.*** Cigarette smoking is the main risk factor for developing COPD, accounting for almost 90% of COPD cases. COPD is associated with chronic inflammation and loss of the air sacs in the lungs where oxygen is exchanged; this damage is irreversible. Lung cells called fibroblasts are linked to chronic inflammation that is associated with the development of COPD. Death of these cells may also account for loss of air sacs associated with emphysema. Little is known about how the body regulates inflammation and structural cell death in response to tobacco smoke, information that would be invaluable in developing new and more selective treatments to prevent or limit cigarette smoke-induced lung injury. This research is aimed at understanding how fibroblasts regulate inflammation and survive repeated exposure to toxic substances such as cigarette smoke. This research has the potential to lead to new approaches that would block some of the untoward health consequences of tobacco smoke.

**CYNTHIA D. BROWN, MD**

University of Virginia, Charlottesville, VA

*Clinical Patient Care Research Grant* • Funded by the American Lung Association

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**New Device Could Improve Sleep In COPD Patients**

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***Treatment Of Sleep-Disordered Breathing With Nocturnal Nasal Insufflation In COPD.*** Sleep problems often accompany chronic obstructive pulmonary disease (COPD). But much remains unknown about the causes of poor sleep in COPD. The researchers hope to better understand these underlying causes and to study a new treatment that may improve sleep quality. They will look at changes in the upper airway muscles during sleep in people with COPD, which result in decreased muscle tone and cause resistance to inhaling. They will investigate how a new device that uses a nasal

tube, or cannula, to deliver warm, humidified air at a high flow rate affects breathing during sleep in COPD patients. Preliminary evidence suggests that this device can improve breathing during sleep in COPD patients by applying a small amount of air pressure to the back of the throat during sleep to minimize difficulty with inhaling. Participants will be asked to use the device nightly at home for six weeks, and they will be tested every two weeks to see how sleepy they are. At the end of the study participants will return for an overnight sleep study to see if their overall quality of sleep has improved.

**LIN-FENG CHEN, PhD**

University of Illinois at Urbana-Champaign, Champaign, IL

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

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**Targeting Protein That Causes Inflammation In Asthma And COPD**

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***Regulation And Functions Of Reversible Acetylation Of NF-kappa B In Lung Inflammation.***

Lung inflammatory diseases, including chronic obstructive pulmonary disease (COPD) and asthma, are characterized by an increased production of genes that cause inflammation. These genes are mainly controlled by a protein called NF-kappa B. Blocking this protein could be a novel treatment in these diseases. Many currently used anti-inflammatory drugs for asthma and COPD, such as steroids, indirectly inhibit NF-kappa B. The researchers will investigate how NF-kappa B is regulated, learn about its role in inflammation, and identify targets for treatment that would inactivate the protein.

**SUN KIM, PhD**

University of Massachusetts, Worcester, MA

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

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**Finding Effective Ways To Get Korean Americans To Quit Smoking**

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***Predictors Of Readiness For Tobacco Dependence Treatment Among Korean Americans.***

Korean male immigrants in the United States have the highest rate of current smoking and the highest rate of cancer deaths caused by smoking; however, this is also one of the groups studied least in

regards to smoking and smoking cessation. Many Asian Americans, including Korean Americans, tend not to seek treatment for smoking cessation that is available in public health care settings due to language and cultural differences. In an effort to prevent lung diseases caused by smoking, this study will identify psychological, social, cultural, and behavioral factors that may predict Korean Americans' willingness to quit smoking and to seek cessation treatment, and to explore their experiences with the treatment, particularly regarding actual and perceived difficulties accessing the treatment. Information from the study will lead to further understanding of Korean Americans' willingness to quit smoking and receive treatment for smoking cessation. This information will also help other researchers identify ways to develop a smoking cessation program that is more acceptable to and receptive by members of this ethnic minority group.

#### **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

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

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***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.

#### **DEVON NOONAN, MPH, FNP-BC**

University of Virginia, Charlottesville, VA  
*Lung Health Dissertation Grant* • Funded by the American Lung Association

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#### Predicting Why College Students Use Waterpipes

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***The New Trend in Tobacco: Predicting Waterpipe Use Among US College Students.*** College students experiment with a wide range of tobacco products in addition to cigarettes, which increases their susceptibility to developing lifelong lung ailments as well as nicotine addiction. Waterpipe smoking is a new trend among college students and young adults and is associated with multiple health problems, including lung diseases. In this study the researcher will examine the potentially modifiable predictors of waterpipe smoking among college students. Understanding the modifiable factors underlying this behavior, such as attitudes and perceptions of norms, will help health care providers target individuals at risk for waterpipe smoking. This research will also provide important information to tailor tobacco prevention programs geared towards preventing waterpipe use and lung diseases associated with tobacco use.

#### **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

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

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***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.

#### **LISA SHAH, MD**

The University of Chicago, Chicago, IL  
*Social Behavioral Research Grant* • Funded by the American Lung Association

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Is Non-Adherence an Issue for Minority Smokers Using Tobacco Cessation Medication?

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***Evaluating Medication Adherence to Varenicline in a Population of Underserved Minority Smokers.*** The United States Public Health Guideline Recommendations for smokers advise several steps for physicians to help patients quit smoking, including assisting patients with quitting through medication or nicotine replacement. Quitting smoking is especially important for underserved minority patients, as they share a disproportionate burden of smoking-related disease. But members of these communities are less likely than the general population to participate in intensive tobacco cessation interventions. Medication non-adherence has been shown to be a barrier to successful asthma treatment in low-income and minority populations, and may also be a barrier for smoking patients in attempting to successfully quit. The researchers will evaluate adherence to varenicline, a recommended tobacco cessation medication for smokers, and assess potential predictors of non-adherence. The results can be used to develop future studies to target increasing medication adherence in smokers, overcoming specific barriers to participating in tobacco cessation interventions, and decreasing tobacco-related lung disease.

#### **JANET THOMAS, PhD**

University of Minnesota, Minneapolis, MN  
*Social Behavioral Research Grant* • Funded by the American Lung Association

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Comparing Two Methods To Encourage Home Smoking Bans

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***Documenting Child Exposure To Environmental Tobacco Smoke (ETS) Carcinogens: A Novel Approach To Motivate Families To Adopt Home Smoking Bans.*** Exposure to secondhand smoke contributes to about 50,000 deaths in the United States each year and is a recognized cause of respiratory disease in children. Yet 36.1% of children in the U.S. live in a home where people regularly smoke cigarettes. One way to reduce children's secondhand smoke exposure is by limiting or banning smoking in the home. The researchers will evaluate two methods to motivate families to adopt home smoking restrictions. One group will receive a home visit by a counselor who will provide a brochure documenting the health impact of home exposure to secondhand smoke. The second group will receive the same brochure and will be given more education from the counselor about the health risks of home smoking and the importance of a home smoking ban. The second group will also receive the results of a lab test conducted on the urine of a child in the home that will document cotinine (a byproduct of nicotine use) and NNAL, a known cancer-causing agent found only in tobacco. Three months later, the researchers will return to see if the method the smokers received changed their home smoking policies and if the treatment had any effect on their smoking behaviors.



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## TUBERCULOSIS

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**T**uberculosis (TB) remains an important disease in the United States and a worldwide epidemic that kills approximately 1.7 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.

Studies are being done to discover 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, studies are being done to understand how latent TB progresses to active disease and how the TB organism develops resistance to commonly used drugs.

## American Lung Association Scholar: Tuberculosis



**PUSHPA JAYARAMAN, PhD**  
**Brigham & Women's Hospital**

Pushpa Jayaraman, PhD, is studying a novel mechanism to kill *Mycobacterium tuberculosis*, which causes pulmonary tuberculosis. Her research is centered on immune system cells called macrophages that are the first line of defense against airborne pathogens. They engulf the *M. tuberculosis*, bringing it to white blood cells called T cells, which should kill the TB germ. However, *M. tuberculosis* is able to take refuge in macrophages by diverting some host defense mechanisms. This hijacking of the macrophages defense system interferes with the ability of the immune system to protect people from disease. "A clear understanding of the interactions between *M. tuberculosis* and the immune system at the cellular level is crucial to our attempts at developing novel drug targets and vaccines," she says.

Dr. Jayaraman, who is from India, has seen the high toll TB has taken in her country. "It's a very big public health problem, and we need better treatments to control infection," she says.

With the assistance of an American Lung Association Senior Research Training Fellowship, Dr. Jayaraman is studying how recently discovered molecules called Tim3 on the surface of T-cells regulate the macrophage response to *M. tuberculosis*. "We see that Tim3 expression levels on T cells increase following *M. tuberculosis* infection, and we think it plays an important role in immunity to *M. tuberculosis*," she says. She is studying a novel way in which Tim3 on T-cells can activate *M. tuberculosis*-infected macrophages by binding to a receptor on the macrophages. This receptor sends a signal into the macrophage and activates it, allowing it to efficiently kill *M. tuberculosis*.

Dr. Jayaraman has been encouraged by her findings that mice infected with TB who were treated with the Tim3 protein experienced a dramatic reduction in the TB bacteria in their lungs. "Tim3 might one day become an important treatment option that we could use to reduce tuberculosis," she says.

Currently, TB is treated with a nine-month regimen of drugs. Many people don't finish the treatment, which contributes to the growing problem of drug resistance. "Medications that directly activate macrophages to kill *M. tuberculosis* could bypass the problem of drug resistance. Understanding how Tim3 activates macrophages to kill *M. tuberculosis* will lead to the development of medications that can similarly activate macrophages regardless of drug resistance," she says. More immediately, she plans to treat mice with Tim3 before they have been infected with TB, to see if the protein can prevent the infection.

"It is a great honor to receive the American Lung Association grant," she says. "In addition to the funding, the grant acknowledges that our work is significant."

To see a complete description of Dr. Jayaraman's research project, please go to page 28.

**ANDREA COOPER, PhD**

Trudeau Institute, Saranac Lake, NY

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

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

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***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.

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**Discovering New Drugs To Fight Mycobacteria**

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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*.

**CELIA GOULDING, PhD**

University of California, Irvine, Irvine, CA

*Biomedical Research Grant* • Funded by the American Lung Association with support from the Mary Fuller Russell Research Fund

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**Targeting Tuberculosis Bacteria's Need For Iron Could Lead To Novel Treatment**

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***Does Heme Uptake Contribute To TB Latency?***

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* (*Mtb*), which kills 1.7 million people worldwide every year. One of the difficulties in controlling TB stems from *Mtb*'s ability to allow a fraction of cells to persist in the face of anti-TB drugs. *Mtb* also can survive the body's immune system defenses, living in the body without causing disease, a condition called latent TB. Approximately one-third of the world's population is infected with the TB bacillus that can develop into the active form of the disease. The factors that control *Mtb* are poorly understood. The researchers will focus on *Mtb*'s need for iron, an essential metal for all forms of life. Most bacteria, including mycobacteria, must import iron from their host to survive through so-called iron acquisition pathways. These pathways could be potential anti-TB drug targets. The researchers will study a novel iron acquisition pathway, with a goal of discovering targets for the development of new drugs against TB, as well as possible applications for diagnosing latent infections.

**PUSHPA JAYARAMAN, PhD**

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

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**Learning How Immune System Defends Itself Against TB Bacteria**

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***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.

**FARAHNAZ MOVAHEDZADEH, PhD**

University of Illinois, Chicago, IL  
*Biomedical Research Grant* • Funded by the American Lung  
 Association

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**Genes May Provide Insight About Latent Tuberculosis**

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***The Biological Function Of Genes Essential For Latency In M. Tuberculosis.*** Mycobacterium tuberculosis (Mtb) causes tuberculosis (TB), which kills 1.7 million people worldwide every year. TB can reside latently in the human body for many years, but once active, it attacks the respiratory system. Anti-TB therapy is complicated, involv-

ing combinations of antibiotics taken over 6-12 months. In certain parts of the world, the rates of drug resistance are increasing rapidly. Thus, there is an urgent need to identify new anti-TB drugs. The ability of Mtb to enter a latent state is considered to be the key to its success as an infectious agent. The researchers will study the mechanism of the genes which are important in maintenance of the latent state of Mtb. Determining the functions of such genes will be key to finding targets for new anti-TB drugs that eliminate latent TB infection and/or shorten the duration of treatment of active TB.

**ANIL OJHA, PhD**

University of Pittsburgh, Pittsburgh, PA  
*Biomedical Research Grant* • Funded by the American  
 Lung Association with support from the Mary Fuller Russell  
 Research Fund

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**Uncovering How TB Bacteria Persist Against Current Drug Treatments**

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***Determination Of the Genetic And Environmental Factors That Control Biofilm Development In Mycobacterium Tuberculosis.*** One of the reasons that tuberculosis (TB) kills millions of people worldwide each year is that it has the extraordinary ability to persist against current drug therapy, which requires multiple anti-TB drugs to be administered for up to 12 months. Patients often don't complete their treatment, which results in the re-emergence of infections with multi-drug resistant or extremely drug resistant strains of the bacteria. A shorter treatment course is essential for an improved control of TB. However, development of new-generation antibiotics for a shorter treatment of TB requires a better understanding of the TB bacteria's ability to withstand drug treatment. The researchers have found that the TB bacteria, Mycobacterium tuberculosis (Mtb), is able to form a complex drug-tolerant cellular structure called biofilm, but much is still unknown about this structure and the development of drug tolerance behavior. The researchers plan to investigate the factors that control the development of M. tuberculosis biofilm and study its role in persistence against drug therapy. The study may lead to knowledge that can be used to design new strategies that can shorten the duration of treatment.

**SARAH K. PARKER, MD**

University of Colorado Health Sciences Center, Denver, CO  
*Biomedical Research Grant* • Funded by the American Lung Association

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**Tuberculosis Bacteria ‘Steal’ Lipids From Human Host To Grow**

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***Investigation of M. Tuberculosis Phospholipase A Cell Wall Activity.*** Mycobacterium tuberculosis (Mtb), the bacteria that causes tuberculosis, has the unique ability to survive within its human host for decades. The researchers will investigate the bacteria’s ability to manipulate human lipids, or fats, which are present in all cells and especially rich in the lungs. These lipids are essential to Mtb’s highly successful cell wall and its survival within the human host. Enzymes called phospholipases act directly on lipids, and may be a key in the mycobacterium’s ability to build and change its cell wall, or scavenge lipids from its human host for its own use. The researchers have discovered a novel phospholipase in Mtb, and have found it is present in the mycobacterium’s cell wall, where it could manipulate the wall or have access to its host. They will investigate the contributions of the enzyme to the growth, development and survival of Mtb through a variety of techniques, including deletion of the genes that make the enzyme. This project has the potential to lead to new drug or vaccine targets for mycobacteria, including Mtb.



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## OTHER LUNG INFECTIONS

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**L**ung infections are common and often deadly. Influenza (flu) and pneumonia-related illnesses are responsible for more than 60,000 deaths annually. Studies are being done to understand human susceptibility to the most dangerous flu viruses. American Lung Association researchers continue to study a bacterium called pseudomonas, which affects the injured lungs of people who have chronic obstructive pulmonary disease (COPD) and cystic fibrosis, hoping to find a new means of prevention.

American Lung Association researchers are studying a wide variety of other lung infections at the basic level in the quest for better ways to prevent and heal them. Among those being investigated are respiratory syncytial virus (RSV) infection—which is a major problem in children and the elderly—and fungal infections. How bacterial infections complicate the flu and COPD is receiving renewed attention.

Much work is being done at the cellular and genetic levels in order to understand susceptibility to fungal infections in a variety of circumstances.

## American Lung Association Scholar: Lung Infections



**CARLOS SEREZANI, PhD**  
**University of Michigan**

Immune cells called alveolar macrophages (AM) are on the front line of defense against microbes that cause pneumonia. These cells are responsible for recognizing and killing infectious-causing agents. Carlos Serezani, PhD at University of Michigan is studying how these cells work, with the hope that the results will lead to better treatments for pneumonia.

Pneumonia-causing bacteria are present in some healthy throats. When body defenses are weakened in some way, by illness, old age, malnutrition, general debility or impaired immunity, the bacteria can multiply and cause serious damage. Usually, when a person's resistance is lowered, bacteria work their way into the lungs and inflame the air sacs.

With the help of an American Lung Association Senior Research Training Fellowship, Dr. Serezani is focusing on substances called lipid mediators that can enhance or decrease macrophage function during the body's fight against pneumonia. Lipid mediators are produced when the body is fighting an inflammatory condition or an infection. They improve clearance of bacteria and bolster the immune system's response.

He is studying what happens to the AMs of mice infected with *Klebsiella pneumoniae* when they are treated with lipid mediators. He has found that when lipid mediators called leukotrienes are added, they enhance the macrophage's capacity to ingest and clear bacterial infection.

Dr. Serezani is now studying how a lipid mediator called prostaglandin inhibits ingestion and clearance of bacteria.

Both parts of his research have implications for treatment of pneumonia. Drugs that increase leukotriene production, or that inhibit prostaglandin production, might have beneficial effects on pneumonia patients. Since Ibuprofen and aspirin are prostaglandin inhibitors, "there is a great interest in how prostaglandin inhibitors could improve pneumonia treatment," Dr. Serezani said.

He is also planning on studying how leukotrienes affect the inflammatory response caused by infection. "Pneumonia leads to massive inflammation in the lung, which can lead to lung injury," he said. "If you can prevent the inflammation, it may improve patients' outlook."

Dr. Serezani says the American Lung Association grant has been instrumental in his career as a pulmonary researcher. "This grant was essential for me as a scientist, because it helped me to decide which direction to go in as an independent researcher," he said.

To see a complete description of Dr. Serezani's research project, please go to page 34.

**ANN CHEN, MD**

University of Washington, Seattle, WA  
 Senior Research Training Fellowship • Funded by the  
 American Lung Association

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**Protein That Regulates Inflammation Could Help Fight Influenza**


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***Role Of Epithelial-Derived Stromelysin-2 In Host Defense Against Influenza.***

Influenza viruses are responsible for a wide spectrum of diseases, ranging from a simple sore throat and cough, to severe pneumonia and complete respiratory collapse. The human body has developed ways to fight such organisms. The airways of the lungs are lined by specialized cells called epithelial cells, which link to one another with tight junctions, forming a physical barrier. When attacked by infectious organisms, these cells secrete various molecules, and coordinate an inflammatory response. Inflammation is a highly regulated process, with the purpose of recruiting white blood cells to the site of infection, in order to fight off the attacking organism. The researchers will study a protein secreted by epithelial cells, called stromelysin-2, which regulates inflammation in response to infections. Their preliminary data shows that mice without stromelysin-2 sustain far more damage in their lungs and have a higher death rate in response to influenza infection, compared with mice with stromelysin-2. This suggests stromelysin-2 is an important regulator of inflammation. By studying stromelysin-2's function and mechanism of action in the body's defense against viral infection, the researchers hope to find data that could be used to develop more effective treatments for influenza.

**ANDERS HAKANSSON, PhD**

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

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


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***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 com-

mon 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.

**TAEG SU KIM, PhD**

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

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**Deciphering How The Immune System Fights Influenza**


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***Regulation Of T Cell Responses By Dendritic Cell Subsets In A Pulmonary Viral Infection.***

Each year, more than 226,000 people in the U.S. are hospitalized and about 36,000 people die from influenza (flu) infection and its complications, thus making the flu syndrome produced by the virus the eighth leading cause of death in the United States. The researchers will study the immune system's response to infection with the flu virus, focusing on cells called dendritic cells. These cells present the viral flu invaders to immune-system fighter cells called cytotoxic T lymphocytes, which migrate to the lung and promote virus clearance. The knowledge gleaned from this study could lead to the development of better vaccines to protect against lung infection and potential new treatments for other illnesses in the respiratory tract.

**GIRISH S. KIRIMANJESWARA, PhD**

Albany Medical College, Albany, NY

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

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**Attacking 'Stealth' Organisms In The Lungs**

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***Mechanism Of Antibody-Mediated Protection Against Intracellular Respiratory Pathogens.***

Several organisms that cause severe lung disease have adapted a unique lifestyle of hiding inside a host cell, including those that are otherwise capable of killing them. By hiding, these organisms become inaccessible to the effect of antibodies and are difficult to eradicate. The researchers have previously reported that one such disease-causing organism, *F. tularensis*, could be eliminated from the body by treating the host with specific antibodies. They found that this elimination requires a potent immune-system fighter molecule called IFN-gamma. They also found that cells that attack hiding bacteria could be armed to rapidly kill the bacteria by treating them with antibodies and IFN-gamma. The researchers will now further investigate the combined effect of antibodies and IFN-gamma on such killer cells. The results will not only advance knowledge of how our body fights stealth organisms, they will also provide clues that could be used to design better vaccines and therapeutics against a broad range of organisms that cause disease in the lungs.

**ALBERT SENFT, PhD**

Lovelace Respiratory Research Institute, Albuquerque, NM

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

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

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***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 avail-

able 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.

**CARLOS SEREZANI, PhD**

University of Michigan, Ann Arbor, MI

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

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**Gathering Facts About Inner Workings of Lung's Immune System**

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***Modulation Of Alveolar Macrophage Antimicrobial Functions By Eicosanoids: Role Of Lipid Rafts And Signaling Molecules.***

More than four million people die from pneumonia each year worldwide, and in the United States, pneumonia is the number one cause of death from infection. This problem is further compounded by the increasing number of people with compromised immune systems and the growing number of infections caused by multi-drug resistant organisms. A type of immune cell called the alveolar macrophage (AM) is the resident defender of lung sterility, patrolling and clearing invading organisms by releasing compounds that affect ingestion and kill bacteria in the lung. In the absence of intact AM clearance, otherwise innocuous bacterial infections become lethal. The researchers will study an important cell-signaling mechanism that affects AM function, focusing on lipid mediators called eicosanoids. Understanding how these mediators affect the AM's defense against microbes may lead to development of treatments that could be of significant use in preventing pneumonia in people with damaged immune systems or enhancing the effectiveness of antimicrobial therapies.

**JIE SUN, PhD**

University of Virginia, Charlottesville, VA

Senior Research Training Fellowship • Funded by the American Lung Association

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**Tamping Down Overactive Immune Responses to Influenza**

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***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.

**KEER SUN, PhD**

Albany Medical College, Albany, NY

Senior Research Training Fellowship • Funded by the American Lung Association

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**Preventing the Influenza-Pneumonia One-Two Punch**

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***Influence of Influenza Infection on Alveolar Macrophage Anti-Bacterial Activity.*** Influenza virus and *Streptococcus pneumoniae* are the two pathogens that cause the majority of the respiratory infections in humans. Co-infection with both these pathogens ultimately causes many, if not the majority of excess deaths during human influenza pandemics, including the 1918 pandemic. The re-

searchers will study the mechanisms of increased susceptibility to secondary bacterial infections that occurs during recovery from viral respiratory infection, with the ultimate goal of prevention of these severe lung diseases. The researchers previously found that a protein chemical messenger called IFN-gamma produced during immune-system responses to influenza infection in mice inhibits initial bacterial clearance from the lung by specialized cells called alveolar macrophages. This leads to enhanced susceptibility to secondary pneumococcal infection. The researchers will study the effect of influenza and pneumococcal infection on alveolar macrophages. The research may ultimately provide a new therapeutic approach for protection against secondary bacterial infection during influenza pandemics and reduce dependency on antibiotic treatment.



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## LUNG CANCER

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**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. Among the new approaches to treatment being investigated are hormone therapy, drugs developed for treatment of arthritis, gene splicing, and the manipulation of the cellular immune system.

In addition, the quest to find tests that will identify lung cancer in an early curable stage continues, as are studies of the all-important issue of why lung cancer becomes resistant to chemotherapy.

## American Lung Association Scholar: Lung Cancer



**MICHAEL A. TAINSKY, PhD**  
**Wayne State University, Karmanos Cancer Institute**

If lung cancer is found relatively early, treatment—surgery, radiation, drug therapy or a combination of these approaches—is often effective. Unfortunately, most cases of lung cancer are found at an advanced stage, when treatment is much less effective.

Michael Tainsky, PhD, is developing a noninvasive blood test designed to detect early stage lung cancer. He is focusing on a type of lung cancer called adenocarcinoma in women. “It’s becoming clear that there are subsets of lung cancer with different molecular characteristics,” said Dr. Tainsky, whose research is supported through a Lung Cancer Discovery Award, funded in partnership between the American Lung Association and the LUNGevity Foundation. “Right now we are looking for specific serum antibodies in women with this type of lung cancer, because such a blood test could be more accurate than a test that would look for all types of lung cancer in all patients.”

The blood test takes advantage of the body’s immune system, which recognizes cancer as foreign, and produces antibodies against it. These antibodies are not present in the blood of people without cancer or with noncancerous lung diseases. The blood screening test looks for antibodies to cancer-associated proteins. Some inflammatory diseases of the lung may produce similar antibodies, so the researchers are working to distinguish between the antibodies of those with lung cancer and those with noncancerous lung conditions, such as asthma or COPD.

They are using sophisticated computer programs to decipher which are the most accurate markers of cancer. Dr. Tainsky would then like to test his findings on blood samples of patients before and after they were diagnosed with lung cancer, to see whether the test accurately picked up the cancer in the “before” samples.

A major question still to be answered is whether one blood test can be developed for different types of lung cancer, or whether a number of different specific tests will need to be developed for various subsets of lung cancer. Dr. Tainsky also plans to investigate whether there should be separate tests for smokers and nonsmokers. If the blood test becomes available, it would be used in conjunction with a chest x-ray or spiral CT to confirm whether cancer is indeed present in the lung.

The Lung Cancer Discovery Award has provided a significant boost to his research, Dr. Tainsky says. “This is significant seed money that is helping us gather enough data that hopefully will be a springboard to larger grants.”

To see a complete description of Dr. Tainsky’s research project, please go to page 40.

**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

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


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***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 studies 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.

**MICHAEL P. LISANTI, MD, PhD**

Thomas Jefferson University, Philadelphia, PA  
*Lung Cancer Discovery Award* • Funded in partnership between the American Lung Association and the LUNgevity Foundation

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**Replacing Tumor Suppressor Gene May Lead To New Lung Cancer Treatment**


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***Role of CAV-1 In Suppressing Lung Tumor Formation: Therapeutic Implications.*** Tumor suppressor genes function as a “brake” that normally prevents the onset of lung tumors. But these genes are often lost or silenced during the development of human lung tumors. Thus, developing replacements for these genes may be an effective treatment for lung cancers. The researchers will test the effectiveness of replacing a tumor suppressor gene, known as caveolin-1 (CAV-1), using an established mouse model of lung cancer. The research may

lead to the development of novel CAV-1-based therapies for the treatment of human lung cancers.

**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

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


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***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

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


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***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.

#### **GEORGE C. PRENDERGAST, PhD**

Lankenau Institute for Medical Research, Wynnewood, PA  
*Lung Cancer Discovery Award* • Funded in partnership between the American Lung Association and the LUNGevity Foundation

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#### Will Blocking 'Hijacked' Enzyme Shrink Lung Cancer?

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***Genetic Regulation And Therapeutic Correction Of Immune Escape In Lung Cancer.*** Lung cancer remains among the most common and deadliest diseases in the developed world. The researchers have found that a gene called Bin1 acts to prevent the development of lung cancer in mice. They found that Bin1 wipes out cancer by restricting the action of an enzyme called IDO that suppresses the immune system. It appears that IDO is 'hijacked' in cancer and other diseases, and ends up contributing significantly to disease. This suggests that a drug that could inhibit IDO could be particularly useful in treating lung cancer. While evidence already exists that IDO is often switched on in late-stage lung cancer, the researchers want to fill in gaps in knowledge about its relevance and whether blocking IDO may be useful in treating lung cancer. They will use a mouse model of lung cancer to determine if removing the Bin1 and/or IDO genes drives or impedes lung cancer development or progression. They will also study whether

blocking IDO with their drug-like compounds can block or shrink lung tumors.

#### **JULIEN SAGE, PhD**

Stanford University, Stanford, CA  
*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

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#### Targeting A Cell Communication Network In Small Cell Lung Cancer

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***Hedgehog Signaling As A Therapeutic Target In SCLC.*** More than 25,000 new cases of small cell lung cancer (SCLC) are diagnosed each year in the United States. Small cell lung cancer 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. The researchers have developed a mouse model in which the mice are genetically altered so that they develop tumors that are closely related to human SCLC tumors. Using the mouse model, the researchers will test the importance in SCLC of the Hedgehog signaling pathway, which is part of a communication network between cells that regulates different genes and tells the cells of the tumor to proliferate and to survive. They will investigate whether inhibiting these signals leads to suppression of tumor growth. If so, this signaling pathway may serve as a therapeutic target against SCLC.

#### **MICHAEL A. TAINSKY, PhD**

Wayne State University, Karmanos Cancer Institute, Detroit, MI  
*Lung Cancer Discovery Award* • Funded in partnership between the American Lung Association and the LUNGevity Foundation

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#### Developing Noninvasive Blood Test To Detect Early Lung Cancer

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***Autoantibody Biomarkers For The Detection Of Lung Cancer.*** If lung cancer is detected at an early stage, there is a much greater chance that it can be treated. An inexpensive, noninvasive early detection test that could detect early stage lung cancer would reduce deaths from lung cancer. The researchers have developed a strategy for early detection of cancer that takes advantage of the responses of the human immune system to identify cancer-associated proteins that bind to antibodies

present in the blood of cancer patients but not in the blood of healthy subjects or those with non-cancerous diseases. They hope to develop a non-invasive screening blood test for early detection of lung cancer using these cancer-associated proteins. Along with blood from lung cancer patients, the blood from other cancer patients will be tested so that the researchers can identify markers for lung cancer that do not falsely identify other cancers or benign lung conditions as lung cancer.

### **LIN ZHANG, PhD**

University of Pittsburgh, Pittsburgh, PA

*Career Investigator Award* • Funded in partnership between the American Lung Association and the Chest Foundation

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#### Substance That Controls Cell Death May Prove Useful In Lung Cancer Treatment

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***PUMA As A Novel Sensitizer For The Treatment Of Lung Cancer.*** The current treatment options for lung cancer patients produce a low rate of response and virtually no cure. Apoptosis, or programmed cell death, is a normal suicidal process the body uses to selectively remove cells that are no longer needed, are damaged, or dangerous. Apoptosis is fundamental to our health; failure of cells to die leads to initiation and progression of cancer, and makes cancer cells resistant to anticancer drugs. To understand how apoptosis is uncontrolled in cancer cells, the researchers identified PUMA, a novel controller of apoptosis and a target of p53, the gene that is altered in the majority of lung tumors. They found that PUMA is often used by anticancer drugs to kill cancer cells. However, PUMA is frequently interrupted in lung cancer cells due to abnormalities of p53. The researchers aim to use PUMA as a target to encourage selective killing of lung cancer cells. The studies will provide useful information about the molecular mechanisms by which anticancer drugs kill lung cancer cells, and also may provide novel strategies to restore the sensitivity to anticancer therapies in lung cancer cells.

### **YANYAN ZHENG, PhD**

Stanford University, Stanford, CA

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

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#### Lung Cancer Stem Cells May Help Explain Resistance To Chemotherapy

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***Lung Cancer Stem Cells And Cisplatin Resistance.*** Non-small cell lung cancer (NSCLC) is a major type of lung cancer, accounting for approximately 80-87% of cases. Results from the current therapies for NSCLC are poor except in cancers found early that have not spread. In more advanced cancers, chemotherapy plays an important role and can improve survival. However, the long-term survival of patients with chemotherapy is still poor, partly due to cancer relapse from resistance to chemotherapy. Scientists do not know much about the mechanisms responsible for resistance to conventional chemotherapy. Recent evidence suggests that many tumors contain a small population of cells with unique characteristics, called “cancer stem cells” because of their ability to grow a new tumor in transplantation experiments. The overall objective of this research is to test whether the chemotherapy resistance in NSCLC is contributed by a small subset of lung cancer stem cells. The researchers will use a mouse model of lung cancer to determine whether cancer stem cells show increased resistance to therapy. If they find that these stem cells are present, they can then extend this work to human samples and begin to identify new ways of treating patients with NSCLC.



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## THE IMMUNE SYSTEM, INFLAMMATION AND LUNG SCARRING

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**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**



**ANNE-KARINA PERL, PhD**  
**Childrens Hospital Medical Center-Cincinnati**

Anne-Karina Perl, PhD, is investigating how airways regenerate after acute and chronic injury and what causes airway wall thickening, which leads to airway obstruction in COPD. Airway injury and wall thickening also occurs in bronchiolitis obliterans syndrome (BOS), which is the main chronic complication after lung transplantation. Understanding the cause of airway wall thickening may lead to improved treatments for both conditions.

“Despite the importance of COPD as a disease, the mechanisms underlying it are still very poorly understood,” says Dr. Perl. “We want to understand how airway wall thickening is activated and how we can interfere with it.”

With help from an American Lung Association Biomedical Research Grant, Dr. Perl is studying a mouse model of acute and chronic injury of the cells lining the airways, which can lead to airway wall thickening. She is looking at regeneration of the cells after airway injury. Her hypothesis is that epithelial growth factor receptor (EGFR), a substance that is present in the membrane of the lung cells, plays a beneficial role after short-term, or acute injury but has a detrimental role after long-term, or chronic lung injury. In acute lung injury, EGFR sends signals needed for repair of airway cells. But in chronic lung injury, EGFR signaling leads to fibrosis, or scarring of the lungs. “We think that the right balance of EGFR activation is needed to regenerate the lung after acute lung injury, but has a detrimental effect after chronic injury and leads to fibrosis of the airways.” Dr. Perl said.

She plans to test whether a drug called gefitinib (Iressa), used in some countries to treat non-small cell lung cancer, suppresses fibrosis in the lung. Gefitinib targets and blocks an enzyme called tyrosine kinase, part of EGFR signaling.

“I hope the findings from the research I perform with the American Lung Association grant will provide the groundwork for more extensive funding on a national level,” Dr. Perl said.

To see a complete description of Dr. Perl’s research project, please go to page 47.

**PETER CHEN, MD**

University of Washington, Seattle, WA

*Biomedical Research Grant* • Funded by the American Lung Association with support from the Mary Fuller Russell Research Fund

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**Why Is Chronic Rejection So Common After Lung Transplant?**

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***Mechanisms Of Matrilysin-Mediated Airway Re-Epithelialization.*** Diseases such as idiopathic pulmonary fibrosis, emphysema and cystic fibrosis destroy the lungs and limit the amount of oxygen the patient can get into his/her body. Some patients must undergo lung transplantation for their debilitating lung disease. Unfortunately, only approximately 50% of these lung transplant patients survive five years after transplantation. Survival is limited by the body's chronic rejection of the transplanted lung. Chronic rejection after lung transplantation is characterized by scarring of the airways called obliterative bronchiolitis (OB), which causes respiratory failure and death. The researchers are studying the molecular mechanisms by which the airways repair themselves after injury to lend insight into why the lung graft is rejected after transplantation. Previous studies in OB have found that the proper repair of the airway epithelium (cells that line the airways) is necessary to prevent transplant rejection. The researchers will study how matrilysin, a protein necessary for repair of the airway epithelium, may participate in the development of OB. This research will contribute to the fundamental knowledge necessary in developing treatments for OB.

**OLIVER HAWORTH, PhD**

Brigham and Women's Hospital, Boston, MA

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

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

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***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.

**OCTAVIAN HENEGARIU, MD**

Yale University, New Haven, CT

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

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**Could Anti-Diabetic Drugs Be Promoting And Reducing Asthma At The Same Time?**

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***Changes In Th2 Responses And Lung Inflammation In Mice With Conditional PPARG Deletion In CD4 T Cells.*** Certain white blood cells, called T helper (Th) cells, help other immune cells to mount responses by producing and secreting immune growth factors called cytokines. The immune system produces Th1, Th2, Th17 and regulatory T cells, and all are needed for an effective immune response. People susceptible to allergic asthma, however, often mount potent Th2 responses. The researchers are studying whether a commonly used class of anti-diabetes drugs called thiazolidinediones (TZD) may promote Th2 responses in the immune system. TZD drugs bind to a protein called PPARG that is present in many cells, including cells of the immune system. TZD agonist drugs promote PPARG function and lead to a better control of the number of harmful activated immune cells, as well as a reduction in the release of pro-inflammatory cytokines, thus decreasing inflammation. Several studies have shown that the anti-inflammatory action of TZD is beneficial in treating asthma. But the researchers think

that in addition to inhibiting PPARG, TZD may also be activating asthma-promoting Th2 cells, and the effects are being obscured by the drug's anti-inflammatory effect. They will use a mouse in which PPARG is deleted from some T cells to investigate the effect of TZD on asthma-promoting cells in the immune system. They hope to discover whether using TZD in asthma has a long-term harmful effect, due to its Th2 activation.

#### **LAURA KOTH, MD**

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

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

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***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.

#### **WILLIAM LAWSON, MD**

Vanderbilt University Medical Center, Nashville, TN  
*Dalsemer Research Grant* • Funded by the American Lung Association

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#### Genetic Mutations May Yield Information On Idiopathic Pulmonary Fibrosis

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***Dysfunction In The Alveolar Epithelium In Pulmonary Fibrosis.*** Idiopathic pulmonary fibrosis (IPF) is a severe lung disease in which patients develop shortness of breath, decreased exercise capacity, lung scarring (fibrosis) and difficulty with oxygen exchange. Once diagnosed, most IPF patients gradually develop respiratory failure and die within 2–4 years. There is no cure for IPF. While most cases of IPF occur in people who do not have family members with the disease, some cases of IPF are found in families, called familial IPF. The researchers found genetic mutations in telomerase in several families with IPF. Telomerase is the enzyme that maintains stability of the end of a chromosome, the region referred to as a telomere, throughout the life of the cell and during cell division. Lack of telomerase can lead to telomere shortening, resulting in cell death. The researchers suspect that telomerase dysfunction in cells lining the alveoli, or air sacs at the end of the airways, is responsible for the development of lung fibrosis in people with IPF with telomerase mutations. They also think that similar processes may be at play in non-familial IPF. They will determine how telomerase dysfunction and telomere shortening affect alveolar cells and impact IPF. These studies will identify key components that may serve as future therapeutic targets in IPF.

#### **RICHARD NHO, PhD**

University of Minnesota, Minneapolis, MN  
*Biomedical Research Grant* • Funded by the American Lung Association of the Upper Midwest

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#### Spotlight On Cell That May Be Responsible For Scarring in Pulmonary Fibrosis

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***A Pathologic Integrin Growth Signaling Pathway Regulates Aberrant IPF Fibroblast Proliferation On Extracellular Matrices.*** Idiopathic pulmonary fibrosis (IPF) is a deadly lung disease of unknown cause. Short of lung transplantation there is no proven effective treatment for the disease process.

IPF is characterized by progressive scarring of the lungs. The primary cell type responsible for the progressive scarring is the lung fibroblast. Recent work suggests that the lung fibroblast in IPF has distinct properties enabling it to abnormally proliferate and survive. However, much is still not known about the differences between the out-of-control growth of fibroblasts in IPF responsible for progressive proliferation and the limited production of normal fibroblasts necessary for proper lung repair. In preliminary studies, the researchers have discovered abnormal changes in chemical pathways that regulate IPF fibroblast proliferation. The researchers will further investigate key differences between normal and IPF fibroblasts that underlie the ability of IPF fibroblasts to proliferate and scar the lungs. These experiments could suggest new therapeutic strategies for this lethal disease.

#### **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

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

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***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.

#### **BEATRIZ QUINCHIA-RIOS, PhD, DDS**

University of Wisconsin, Madison, WI  
*Senior Research Training Fellowship* • Funded by the American Lung Association of the Upper Midwest

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#### Airway Remodeling Research May Benefit Patients With Asthma

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***Role of the IL-5 Activated Eosinophil In Airway Remodeling Through Modulation Of Bronchial Fibroblasts' Activation Of A Fibrotic And Secretory Phenotype.*** The persistence of asthma may lead to progressive changes in the airway that affect air intake, worsen asthma symptoms and irreversibly damage breathing function. These structural changes in the airway are collectively known as airway remodeling. Treatment with anti-inflammatory drugs such as corticosteroids can improve asthma symptoms but has a limited long-term effect on airway remodeling; therefore, it is important to investigate the factors that trigger and perpetuate airway remodeling in order to create better therapies to control or prevent these changes. One of the major inflammatory cells involved in the allergic asthma reaction and recently linked to some features of airway remodeling is the eosinophil. This cell is activated by the presence of an inflammatory protein, IL-5, and its activation may affect the behavior of the resident cells causing remodeling. The researchers will study the role of IL-5-primed eosinophils in altering the resident cells and causing airway remodeling. This research will contribute to our understanding of the causes as well as the process of airway remodeling, and should be important for the design of more specific medications and treatment strategies to control and perhaps prevent airway remodeling, including anti-IL5 agents.



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## DISEASES OF INFANTS AND CHILDREN

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**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 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.

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**




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**ALEJANDRO P. HEUCK, PhD**  
**University of Massachusetts Amherst**

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While people with cystic fibrosis live longer today than in years past, they still succumb to a deadly lung infection, *Pseudomonas aeruginosa*, because of its antibiotic resistance. By studying how *P. aeruginosa* works in the lung, Alejandro Heuck, PhD, hopes to develop a way to block the infection in people with CF.

“In cystic fibrosis, the lungs get infected by pathogens very early, and once they are established it’s very difficult to eradicate them,” Dr. Heuck says. “Ultimately, the pathogen damages the lung and the person with CF dies. We try to delay this as long as possible using antibiotics, but the pathogen rapidly learns how to resist the treatment. We need to find alternative ways to attack the pathogen.”

With assistance from an American Lung Association Biomedical Research Grant, Dr. Heuck is studying the way in which *P. aeruginosa* injects toxins directly into a target cell using a “bacterial machine” resembling a syringe. During toxin injection, this machine pokes a hole in the target cell, allowing the passage of different bacterial toxins. Dr. Heuck is trying to isolate the proteins that poke the holes and see how they work. “Knowing how the protein works to create the hole could allow us to find a way to plug it up and interfere with the bacterial infection,” he says.

So far, he has isolated the proteins involved in the bacterial machine, and identified the segments of the proteins that interact with the membrane of the target cell. The next step is to combine these proteins to see how they work together to engage with the bacterial syringe. This research should provide information on potential targets for new drug therapy that would block *P. aeruginosa* toxin injection in the lung cells of people with CF.

“This was a completely new, and very challenging, research project,” Dr. Heuck says. “In a difficult funding situation, the American Lung Association gave me a chance to train people and collect preliminary data that will now allow me to apply for federal funding to continue the project.”

To see a complete description of Dr. Heuck’s research project, please go to page 52.

**DENISE AL ALAM, PhD**

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

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**Studying Embryonic Lung Development May Lead to Treatment for Breathing Problems**


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***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.

**LIANWU FU, PhD**

University of Alabama, Birmingham, AL  
*Biomedical Research Grant* • Funded by the American Lung  
 Association

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**Blocking Disintegration Of Mutated Gene In Cystic Fibrosis**


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***Regulation Of CFTR Degradation Under Cystic Fibrosis.*** Cystic fibrosis (CF) is an inherited disease that affects the lungs and digestive system of about 30,000 people in the United States. 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. The best way to treat CF is to prevent the mutant gene from degrading, and restore the function of CFTR. The researchers will study the regulation of CFTR degradation in conditions that exist in CF lungs. The information gained will provide critical therapeutic information to treat CF patients by preventing CFTR degradation.

**ANDERS HAKANSSON, PhD**

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

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


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***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.

**ALEJANDRO P. HEUCK, PhD**

University of Massachusetts, Amherst, MA

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

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**Blocking Formation Of Channel For Bacterial Infection In Cystic Fibrosis**

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***Identifying New Methods To Block Bacteria From Injecting Toxins Into Lung Cells.*** Patients with cystic fibrosis (CF) have a defect in a gene that allows for proper regulation of salts and water in various tissues. This alteration causes significant problems in the lungs of people with CF. The normal mucus in the lungs becomes thick and dehydrated and ultimately blocks the airway passages, resulting in a predisposition towards chronic bacterial infections and lung disease. One species of bacteria, *Pseudomonas aeruginosa* (PA), causes debilitating lung malfunction, leading to the death of CF patients due to its resistance to antibiotics. The researchers want to find a way to block PA infection in CF patients. They will focus on the way in which PA injects toxins into the target cell using a “bacterial machine” that resembles a syringe. During toxin injection, this machine opens a channel, allowing the passage of different bacterial toxins. Blocking the formation of this channel will interfere with the bacterial infection of the lung. With this information, they can begin to design therapeutic agents to block toxin injection, thereby protecting the lungs of CF patients from the devastating effects of PA infections.

**SUIL KIM, MD, PhD**

University of California at San Francisco, San Francisco, CA

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

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**Research into Overproduction of Mucus Could Lead to New Lung Treatments**

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***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.

**YOHEI NORIMATSU, PhD**

Oregon Health and Science University, Portland, OR

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

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**Study Of Mutated CF Gene Structure Could Lead To More Effective Treatments**

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***Using Chemical Modification To Define A Blocker Binding Site In Cystic Fibrosis Transmembrane Conductance Regulator.*** Cystic fibrosis (CF) is caused by mutations in the CF gene. This gene is responsible for the production of a protein called “the cystic fibrosis transmembrane conductance regulator” (CFTR). A healthy CFTR functions to secrete chloride ions onto the inner surface of the lungs, which helps the lungs to prevent microbial infection. Many mutated CFTRs degrade and disappear before they can function. Even if mutated CFTRs escape degradation, they often do not function well enough to secrete chloride ions. The lack of sufficient chloride secretion can lead to mucus accumulation and microbial infection in the lungs. In the digestive system, lack of chloride secretion by CFTR can result in blockage of pancreatic ducts. Recently, potential drugs have been identified that can help mutated CFTRs to fight against degradation (called “correctors”) and/or help secrete chloride ions better (called “potentiators”). It is currently not known how these potential drugs are helping

mutated CFTRs. This research will study the structure of CFTR using a CFTR blocker and techniques of chemical modification. Information gained in this research is likely to help us understand how the potential drugs are helping mutated CFTRs, and might lead to a better understanding of how to make the drugs more effective.

**ALBERT SENFT, PhD**

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

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

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***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.



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## BREATHING MECHANICS, CONTROL OF BREATHING, AND SLEEP DISORDERED BREATHING

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**W**e all know people who snore and usually consider it an annoyance rather than a problem. However, some people who snore actually stop breathing many times during the night and develop a serious condition called sleep apnea. This is a serious, common problem that has been implicated as contributing greatly to cardiovascular disease, especially in obese individuals and African Americans.

The American Lung Association supports research designed to define the relationship between sleep apnea and disease as well as studies looking at newer, simpler therapies.

Studies are being done of the respiratory central centers in the brain which could help us understand how patients with lung disease may be given narcotics for pain without seriously depressing their breathing.

## **American Lung Association Scholar: Breathing Mechanics, Control of Breathing, and Sleep Disordered Breathing**



**CYNTHIA D. BROWN, MD**  
**University of Virginia**

A survey by the American Lung Association revealed that half of all COPD patients say their condition limits their ability to sleep. But the reason that COPD affects sleep is unknown. Cynthia Brown, MD, says it is frustrating not to be able to offer her COPD patients an effective solution to their sleep difficulties.

With help from an American Lung Association Clinical Patient Care Research Grant, Dr. Brown is investigating the reasons for the problem, as well as a potential treatment. “The patients we have studied tend to have a lot of awakenings at night, but it’s not necessarily related to low oxygen levels caused by COPD, or to sleep apnea,” she says.

Previously, Dr. Brown studied the impact of sleep problems in patients with COPD. “Sleep symptoms have a strong negative impact on their quality of life,” she says. “It affects their energy levels, and how much they’re able to do.” Physicians often don’t ask their COPD patients about their sleep, and even if they do, they don’t have much to offer them to solve the problem, she says. While some doctors prescribe oxygen or continuous positive airway pressure (CPAP), the most common treatment for sleep apnea, neither of these treatments has been shown to have great benefit in improving the sleep problems of COPD patients unless they also have underlying sleep apnea, Dr. Brown says.

In her American Lung Association-supported study, patients with COPD stay overnight in a sleep lab, so researchers can observe their sleep patterns in an attempt to better understand the physiologic mechanisms of sleep disturbances in COPD.

Dr. Brown is also testing a new device called transnasal insufflation, a nasal tube that delivers warm, humidified air at a high flow rate while the person sleeps. Preliminary evidence suggests that this device can improve breathing during sleep in COPD by applying a small amount of air pressure to the back of the throat during sleep to minimize difficulty with inhaling.

Transnasal insufflation is also being studied elsewhere as a possible treatment for sleep apnea. It is currently approved as a treatment for sleep apnea in Europe, but not in the United States.

The next step in Dr. Brown’s research after the sleep lab studies are completed will be to test nasal insufflation in a home setting. “This research wouldn’t be possible without the American Lung Association grant,” she says. “Sleep research is expensive, so this grant is invaluable.”

To see a complete description of Dr. Brown’s research project, please go to page 57.

**CYNTHIA D. BROWN, MD**

University of Virginia, Charlottesville, VA  
 Clinical Patient Care Research Grant • Funded by the  
 American Lung Association

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**New Device Could Improve Sleep In COPD Patients**


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***Treatment Of Sleep-Disordered Breathing With Nocturnal Nasal Insufflation In COPD.*** Sleep problems often accompany chronic obstructive pulmonary disease (COPD). But much remains unknown about the causes of poor sleep in COPD. The researchers hope to better understand these underlying causes and to study a new treatment that may improve sleep quality. They will look at changes in the upper airway muscles during sleep in people with COPD, which result in decreased muscle tone and cause resistance to inhaling. They will investigate how a new device that uses a nasal tube, or cannula, to deliver warm, humidified air at a high flow rate affects breathing during sleep in COPD patients. Preliminary evidence suggests that this device can improve breathing during sleep in COPD patients by applying a small amount of air pressure to the back of the throat during sleep to minimize difficulty with inhaling. Participants will be asked to use the device nightly at home for six weeks, and they will be tested every two weeks to see how sleepy they are. At the end of the study participants will return for an overnight sleep study to see if their overall quality of sleep has improved.

**JONATHAN C. JUN, MD**

Johns Hopkins University, Baltimore, MD  
 National Sleep Foundation Pickwick Award • Funded in  
 partnership between the American Lung Association and the  
 National Sleep Foundation

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**Clarifying The Relationship Between Sleep Apnea And Cardiovascular Disease**


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***Role Of NADPH Oxidase In Chronic Intermittent Hypoxia-Induced Atherosclerosis.*** Obstructive sleep apnea (OSA) is a condition in which breathing is repeatedly interrupted at night as a result of upper airway closure. Not only does OSA lead to sleep deprivation, but it also increases the risk of cardiovascular diseases such as high blood pressure, stroke, and heart attack. There is growing evidence that OSA is associated with advanced

hardening of the arteries (atherosclerosis), which may be responsible in part for its cardiovascular complications. However, the exact reason for these detrimental effects of OSA is unclear. When a person with OSA falls asleep, the upper airway periodically collapses and the body's oxygen levels fall. Safeguards in the central nervous system detect the plummeting oxygen levels and cause the person to awaken, restoring oxygen to the body. This repetitive rise and fall of oxygen levels is called intermittent hypoxia (IH). Prior studies have shown that cells exposed to IH release free radicals, highly reactive particles that can cause disease. When free radicals attack fat in the bloodstream, oxidized lipids are generated, one of the key ingredients of atherosclerosis. The researchers will study the pathways by which IH induces atherosclerosis using a mouse model. The results may have implications for developing new treatments for OSA.

**ZHENXIONG ZHANG, PhD**

Lovelace Respiratory Research Institute, Albuquerque, NM  
 Senior Research Training Fellowship • Funded by the  
 American Lung Association

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**How Can We Use Opiate Drugs For Pain Relief Without Affecting Breathing?**


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***$\mu$ -Receptors Of Chemosensitive Neurons In Medullary Raphe: Role In Breath Control.*** Opiate drugs, such as morphine, are widely used to relieve pain. However, the most adverse effect of opiate drugs, even at therapeutic doses, is the substantial depression of breathing that could be lethal. Opioids exert their life-threatening impact on breathing mainly through activation of micro-receptors in the central nervous system but how this activation occurs remains unknown. The researchers will study the way in which opioids depress breathing. The novel information generated will provide the foundation for developing approaches in which opioids produce pain relief with less impact on breathing.



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## GLOSSARY

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**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 nonre-active 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.

**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.



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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 cigarettes 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.*

