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**Research Awards Nationwide**  
**2003-2004**



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# MISSION

The mission of the  
American Lung Association is  
to prevent lung disease and  
promote lung health  
through research, advocacy,  
and education.

The 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 344,000 Americans die of lung disease, making it the third most frequent cause of death in this country. An additional 35 million of us are living with chronic lung diseases such as asthma and emphysema.

The mission of the American Lung Association is to prevent lung disease and promote lung health 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 Research Initiative included three National Asthma Research Centers, which conducted basic asthma research through 2001. Our Asthma Clinical Research Centers Network consists of 19 Centers and a Data Coordinating Center that conduct clinical studies around the country on patients with asthma.

The American Lung Association also 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. And research is the key that will unlock the door to a better tomorrow for all people with lung disease.

# INTRODUCTION



More than twenty million Americans have asthma, and 12 million of them have had an asthma attack in the past year. Asthma is the leading serious chronic illness of children. Medical professionals continue to be alarmed and mystified by the dramatic increase in numbers of asthma sufferers over the past two decades, during which asthma prevalence has 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 close to 4,500 Americans each year.

There is reason for optimism despite these bleak facts. Research on asthma offers a real chance for dramatic success, as it is to a great extent a reversible disease. The American Lung Association supports extensive research in asthma in a number of critical areas. Since asthma often runs in families, investigators are studying the genes associated with the disease. New theories about the role infections play in causing asthma are being tested. Cellular and molecular mechanisms of the *allergic and inflammatory responses* involved in asthma are being studied. Emphasis is now being placed on the role of the development of the immune system in early childhood. The role of environment, such as proximity to hog farms and the workplace, is also being evaluated. New asthma treatments are being examined, and promising new methods for managing the disease are being sought.

Other areas of importance being studied include the mechanisms by which asthma attacks may be induced by exercise and the ways in which indoor and outdoor pollutants may trigger airway inflammation.

# ASTHMA

## SEEMA ACEVES, MD, PHD

University of California San Diego,  
San Diego, CA

*Research Training Fellowship* • Funded by the American Lung Association of California

### Are New Blood Vessels In The Lungs Linked To Chronic Asthma?

#### *The Role Of Angiogenesis In Chronic Asthma.*

As the lung damage in asthma progresses, the lungs change in structure, a process known as remodeling. The airways thicken and make more mucous, more blood vessels develop, and the lungs fail to function properly. People with chronic asthma have higher levels of chemical factors that promote angiogenesis, the growth of blood vessels, which suggests that these new blood vessels may play an important role in the development of the disease. The new vessels may be leaky, allowing cells that would not normally penetrate lung tissue to enter it and cause damage. This group is investigating whether angiogenesis is a significant component of chronic asthma, and determining how it is promoted in asthma, with the hope that their findings may lead to new asthma treatments.

## OMID AKBARI, PHD

Stanford University, Stanford, CA

*Research Grant* • Funded by the American Lung Association of California

### Using The Body's Immune Responses To Protect Against Asthma

#### *Cellular & Molecular Mechanism Of Tolerance That Protects Against The Development Of Asthma.*

Current asthma treatment involves controlling symptoms, rather than converting immune responses that induce asthma into responses that protect against it. These investigators are unraveling the immunology of asthma, which should form the basis for developing future treatments to cure asthma. They are studying the body's protective immune responses and have found that an immune response called T cell tolerance develops naturally and protects against asthma. Characterizing the precise nature and origin of the signals that lead to T cell tolerance and determining how the response develops, the cell types responsible for its effects, and the various substances expressed by these cells will allow the development of new strategies to induce protective immunity against asthma, as well as new strategies to cure it.

## YASSINE AMRANI, PHD

University of Pennsylvania, Philadelphia, PA  
*Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of Pennsylvania

### Unraveling The Mechanisms Of Airway Inflammation

#### *JAK/STAT-1 Modulates TNF $\alpha$ -Induced Synthetic Function Of Airway Smooth Muscle.*

Despite considerable research effort, the cause of asthma remains unknown. New treatment is needed since severe asthma is not well controlled by currently available medications. Advances in understanding the cellular and molecular mechanisms involved will likely lead to more effective treatment. Inflammation of the airways is critically important, and airway remodeling is also a key component, but its underlying mechanisms as well as the types of cells involved are unknown. This group is defining the molecular mechanisms involved in changes in airway smooth muscle mass (ASM) in asthma patients, which may also be involved in airway inflammation. They are currently seeking to characterize a critical signaling pathway that regulates ASM response, which may offer insight into designing novel approaches to treatment.

## MEHRDAD ARJOMANDI, MD

University of California, San Francisco,  
San Francisco, CA.

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

### How Does Air Pollution Affect People Who Have Asthma?

#### *Airway Inflammation In Asthma Following Multi-Day Exposure To Ozone.*

This study is investigating how multi-day exposure to ozone, a major component of air pollution, affects airway inflammation in people who have asthma. Although current scientific understanding is that air pollution may not be a risk factor for developing asthma, it may cause people with previously existing asthma to do less well. Understanding the mechanisms of the effects of air pollution on asthma is important, because both air pollution and asthma are on the rise throughout the developed world. A better understanding of how air pollution affects people who have asthma will help to develop regulations and strategies for preventing respiratory diseases and promoting lung health.

**MICHAEL T. BORCHERS, PHD**

Mayo Clinic Scottsdale, Scottsdale, AZ  
*Research Grant* • Funded by the American Lung Association

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**Preventing Asthma Through A Better Understanding Of How Inflammation Occurs**


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***G Protein Signaling In Allergic Pulmonary Inflammation.*** Asthma is a complex condition involving many genes. Inflammation of the airways is one of its defining characteristics, and it is well known that airway dysfunction is associated with this inflammation. As part of the cascade of events that take place within the body during an episode of inflammation, certain types of white blood cells are activated and migrate to the lungs. The activation of cells, called eosinophils, is thought to contribute to inflammation associated with asthma. These investigators are studying the way allergic inflammation occurs by examining the signaling pathways between cells that are involved in the migration and activation of white cells. They are also studying smooth muscle function when lung inflammation occurs as an allergic response. Their findings may identify possible new molecular mechanisms of asthma that will contribute to scientific understanding, and perhaps prevention, of asthma and other lung diseases.

**STEVEN L. BRODY, MD**

Washington University School of Medicine, St. Louis, MO  
*Career Investigator Award* • Co-Funded with the American Lung Association and the American Lung Association of Eastern Missouri

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**Investigating A Gene That May Contribute To Lung Disease**


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***Characterization Of Molecular Programs For Airway Epithelial Cell Differentiation And Dedifferentiation.*** Epithelial cells that line the airways are highly specialized, performing critical functions in defending the body against outside invaders. These cells have cilia, tiny hair-like structures that move mucus, pus, dust and other debris out of the lungs into the windpipe where it can be coughed up. They also regulate salt and water to maintain normal mucus. Several major lung diseases, including asthma, bronchitis, cystic fibrosis, and respiratory virus infections, are characterized by abnormalities in epithelial cells that impair

their function. These researchers are studying a gene that may be involved in alterations in normal airway epithelial cell function. Their goal is to add to our knowledge of the mechanisms required for normal function, and the way gene expression is altered in disease, information that is critical for the development of new means of treatment.

**MARK A. BROWN, MD**

University of Arizona, Tucson, AZ  
*Career Investigator Award* • Funded by the American Lung Association of Arizona/New Mexico

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**Mother May Not Always Know Best: Shaping The Immune Response Before Birth May Influence Lifelong Asthma Risk**


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***Maternal Influences On Early Human T-Cell Differentiation.*** Asthma has its genesis in early childhood, as documented by studies showing that even people who appear to develop it as adults had asthma symptoms in early childhood. It has also been established that an unborn baby's immune response is generated as early as the fifth month of pregnancy. The maternal environment in which this occurs may exert crucial influence not only over the immune response at the time, but also in shaping the character of that individual's immune response for a lifetime, including the risk for asthma and other allergic disorders. The goal of this project is to better understand the role of the earliest environmental influence, and its interaction with genetic predisposition, in decreasing or increasing the risk of these diseases. Clarifying the molecular interactions between the environment and the immune system may help to identify ways to reduce the risk of asthma and other allergic diseases.

**CHRISTIANA DIMITROPOULOU, PHD**

Medical College of Georgia, Augusta, GA  
*Research Grant* • Co-funded with the American Lung Association and the American Lung Association of Georgia

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**How Does Estrogen Protect Against Asthma?**


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***Molecular Basis Of Estrogen Action In Airway Smooth Muscle.*** There is increasing evidence that both the incidence and severity of asthma in women are influenced by fluctuations in estrogen levels, and women with elevated estrogen levels are known to have

increased resistance to asthma. This raises the possibility that estrogens affect the way that airway smooth muscles function, preventing the hyperresponsiveness that is characteristic of asthma. These researchers are investigating the molecular mechanisms that are responsible for estrogen-induced relaxation of airway smooth muscle. Their findings will help identify molecular targets for new drugs to help manage both asthma and chronic obstructive pulmonary disease (COPD).

## **SAKSHI DUA, MD**

University of North Carolina at Chapel Hill, Chapel Hill, NC

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

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### **Turning The Tables On A Receptor That Contributes To Asthma**

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**Prostaglandin D2 Receptor – DP2 In Allergic Pulmonary Inflammation.** These studies aim to enhance understanding of the mechanism that causes chronic inflammation of the airways to develop in asthma. Knowing more about the complex pathways by which inflammatory changes occur is essential to gaining better control over this multifaceted disease which has such a powerful negative impact on health, productivity and quality of life for so many people. Prostaglandin D (PGD2) is a substance derived from various inflammatory cells, and is known to play a central role in inflammation in asthma. Its biological effects are mediated through two receptor subtypes, one of which, called DP2, has been recently described. This group is examining how DP2 mediates PGD2, to clarify its role in setting up chronic airway inflammation. They expect the DP2 receptor will be implicated in the development of asthma; if so, future work could focus on developing treatments to reverse its injurious effects.

## **N. TONY EISSA, MD**

Baylor College of Medicine, Houston, TX  
*Career Investigator Award* • Co-Funded with the American Lung Association and the American Lung Association of Texas

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### **Seeking New Ways to Treat Airway Inflammation**

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**Regulation Of Nitric Oxide Synthesis By Inducible Nitric Oxide Synthase (iNOS): Molecular Mechanisms Of iNOS Degradation.** This project is aimed at developing information that can be used to create new means of treatment for the airway inflammation that is characteristic of asthma. Asthma continues to be a public health problem of epidemic proportions in this country, at a cost of about \$14 billion a year. It accounts for nine million visits to health care providers, over 1.8 million emergency room visits, and over 465 thousand hospitalizations annually. It is known that overproduction of nitric oxide by a process called inducible nitric oxide synthase contributes to airway inflammation in people with asthma. The investigators are studying how this process is regulated, with the goal of developing ways to control and thereby reduce or eliminate airway inflammation.

## **STEVE N. GEORAS, MD**

Johns Hopkins University School of Medicine, Baltimore, MD

*Career Investigator Award* • Co-Funded with the American Lung Association and the American Lung Association of Maryland

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### **Studying Proteins That Play A Key Role In Asthma**

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**Epigenetic Regulation Of IL-4 And IL-13.** Inflammation of the airways is asthma's major underlying feature. In most cases it results from the immune system's response to an allergen, a substance that induces an allergic response. White blood cells called lymphocytes play a very important role in the inflammatory process by releasing proteins called cytokines. A subset of these proteins known as Th2 cytokines is very important in asthma, and the researchers are investigating why Th2 cytokine expression is increased at the molecular level in people with asthma. The goal is to gather information that can be used to develop new drugs that will specifically inhibit Th2 cytokines without undesirable side effects.

**CAROLINE L.S. GEORGE, MD**

University of Iowa Hospitals and Clinics,  
Iowa City, IA

*Research Grant* • Co-funded with the American Lung Association and the American Lung Association of Illinois-Iowa

**Why Does The Immune System Allow Asthma To Develop?**

*Immune System Alterations Due To Early Life Environmental Exposures, And The Development Of Childhood Asthma.* Despite recent advances in treatment, the incidence of asthma in children continues to increase. Although medical experts know and understand the disease process of asthma and how to treat it, the reasons why the body's immune system fails to protect against asthma in some children are far less clear. This group is studying how exposures early in life to certain substances in the environment are linked to a reduced risk of developing asthma later in life. Knowing more about how early life exposures affect the onset and evolution of asthma may make it possible to predict which child is at risk for developing it, and eventually to prevent asthma from starting in such children.

**JONATHAN M. GREEN, MD**

Washington University School of Medicine,  
St. Louis, MO

*Career Investigator Award* • Co-Funded with the American Lung Association and the American Lung Association of Eastern Missouri

**Understanding How T-Cells Work Could Lead To New Treatments For Lung Disease**

*T-Cell Survival And Differentiation In Response To Allergen.* Many lung diseases, include asthma, are due in part to an inflammatory process in the lungs. A particular type of cell, the T- lymphocyte, is central to the regulation of the inflammatory response. T-lymphocytes recognize and respond to foreign "intruders" in the body, such as allergens or viruses, and coordinate efforts to control the infection or rid the lung of the allergen. The goal of this project is to gain a greater understanding of precisely how the T-cells respond to foreign substances. A variety of experiments are being performed to determine the basis by which an important protein on the T- cell, called CD28, influences how the T-cell functions. The effect of manipulating this protein on a laboratory

animal model of asthma is also being studied. Elucidating the way normal T-cells work, and what goes wrong in the disease, will make it possible to design new strategies for treating a number of different lung diseases.

**ANGELA HACZKU, MD, PHD**

University of Pennsylvania, Philadelphia, PA  
*Research Grant* • Co-funded with the American Lung Association and the American Lung Association of Pennsylvania

**Using One Of The Body's Proteins To Treat Allergic Asthma**

*Regulation Of The Innate Immune Molecule SP-D In Aspergillus Fumigatus Induced Allergic Airway Inflammation By Th2-Type Cytokines.* Asthma that is triggered by an allergic reaction is one of the most common chronic and debilitating diseases, affecting as much as 10 percent of the population. The number of people who have allergic asthma continues to rise, while treatment remains less than perfect. Corticosteroid drugs are the mainstay of treatment, but in addition to their potentially serious side effects, they merely suppress the immune system rather than curing the disease. This project is investigating the novel concept that a protein in the body called SP-D plays a protective role in the lungs by helping to inhibit the allergic response that leads to airway inflammation. The results should yield information on the potential for using SP-D to treat asthma inflammation that is induced by allergic reactions.

**TEAL S. HALLSTRAND, MD, MPH**

University of Washington, School of  
Medicine, Seattle, WA

*Research Grant* • Funded by the American Lung Association of Washington

**Keep The Exercise, Lose The Asthma**

*Pathogenesis And Treatment Of Exercise-Induced Bronchoconstriction.* Many people who have asthma develop shortness of breath during or following strenuous physical activity, which is called exercise-induced bronchoconstriction (EIB). Unlike other triggers for asthma, avoiding exercise is not desirable because it has so many important health benefits. In fact, exercise can normalize the breathing pattern in people with mild asthma. The mecha-

nism that causes EIB is unclear, particularly the role of inflammation in its development, making the problem difficult to manage. These researchers hypothesize that EIB is triggered by substances known as inflammatory mediators that are released by specific cells in the airways during exercise. They are clarifying precisely how this occurs, and assessing the effectiveness of different treatment options to treat and prevent EIB.

### MARY BETH HOGAN, MD

West Virginia University School of Medicine, Morgantown, WV

*Career Investigator Award* • Co-Funded with the American Lung Association and the American Lung Association of West Virginia

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#### Preventing Permanent Lung Damage From Childhood Asthma

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***Bone Marrow Eosinophil Production In Asthma.*** Asthma remains the third highest cause of hospitalization in children, and more adequate means of controlling it are needed in order to turn this situation around. These studies are focusing on eosinophils, a particular type of cell that accumulates in the lungs of asthmatics and is known to be partly responsible for the coughing, wheezing and shortness of breath that are the hallmarks of the disease. Increased numbers of eosinophils are involved in causing the chronic damage to pulmonary tissue that leads to life-long dysfunction of the airways. A better understanding of the cellular and molecular mechanisms that contribute to the overproduction and accumulation of eosinophils can be used to design new treatments for childhood asthma that can prevent permanent lung damage.

### CLAUDE JOURDAN LE SAUX, PHD

University of Hawaii at Manoa, Honolulu, HI  
*Research Grant* • Funded by the American Lung Association of Hawaii

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#### Preventing Permanent Damage to the Airways in Asthma

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***Involvement Of Interleukin-4 In Airway Remodeling: Activation Of Lung Fibroblasts.*** Although most people with asthma who receive proper care do well, a subset of individuals develop airway obstruction that cannot be reversed, as well as remodeling of the airways.

These complications result from smoldering allergic inflammation that fails to respond to treatment, and has a severe impact on quality of life. This study is concentrating on the functional mechanisms that lead to airway remodeling, particularly mechanisms that are set in motion by the body's allergic inflammatory response. The researchers are seeking to clarify the role played by substances called cytokines. There is evidence that the increased expression of cytokines with pro-inflammatory effects is related to the progression of fibrosis, or scarring of the airways. A better understanding of how this process impacts airway remodeling may lead to specific treatments to prevent the development of fibrosis and reduce the number of people who experience severe asthma and its irreversible effects.

### CHRISTOPHER L. KEPLEY, PHJD

Virginia Commonwealth University, Richmond, VA

*Research Grant* • Funded by the American Lung Association of Virginia

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#### Preventing Allergic Asthma Episodes

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***ITIM Receptors As Potential Therapeutic Targets For Allergic Asthma.*** Allergic asthma is increasing at an alarming rate, and this project has the goal of identifying a new target for treating it. The investigators are attempting to identify novel ways to interrupt the chain of events within the body that triggers an asthma episode, and to prevent them from occurring. They are focusing specifically on turning off the responses of a class of cells called mast cells, which play a key part in initiating the allergic response in most people with asthma. If this effort is successful, it could be a uniquely beneficial way to stop allergic asthma before it starts.

### CARISSA M. KRANE, PHD

University of Dayton, Dayton, OH

*Research Grant* • Co-Funded with the American Lung Association and the Asociación Puertorriqueña Del Pulmón

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#### Studying The Water Channel Gene May Offer New Asthma Treatments

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***Genetic Analysis Of The Aquaporin 5 Gene For Potential Asthma-Predisposition Alleles In Human Asthma Patients.*** Asthma is a complex disease that is brought on by a combina-

tion of genetic and environmental factors. Scientists believe several genes interact with each other and with the environment to cause asthma symptoms. Many of the factors that contribute to this process have been identified and their roles have been pinpointed, yet much remains to be learned about how asthma develops in each afflicted individual, and how best to customize treatment for a particular person. These researchers have identified a gene that had not been studied previously and that may play a key role. This factor is a water channel that normally helps control the fluid environment around the cells of the airways, but when mutated results in the bronchial hyperreactivity that is characteristic of asthma. The investigators are now studying the water channel gene, with the goal of providing information that could be critical in developing new treatments for both acute and chronic diseases in which fluid regulation in the lungs is abnormal.

**ROBERT J. LAUMBACH, MD, MPH, CIH**

UMDNJ-Robert Wood Johnson Medical School, Piscataway, NJ

*Clinical Research Grant* • Funded by the American Lung Association of New Jersey

**Understanding The Respiratory Effects of Low-Level Chemical Exposures**

**A Model Of Chemical Sensitivity.** Low levels of irritating chemicals may be found in the air indoors at home or at work. Although the mechanisms involved remain unknown, breathing these air contaminants has been implicated as a possible cause of respiratory symptoms and a trigger for asthma. Ozone and terpenes, chemicals commonly found in cleaners and household products, react in the air to form a number of compounds, including fine particles that are believed to be highly irritating. This study is examining mechanisms of airway inflammation that may mediate the toxic effects of these ozone-terpene reaction products. The ultimate goal is to find measures of response that will be useful for assessing the effects of breathing these air contaminants on both healthy people and others who have asthma or other forms of low-level chemical sensitivity.

**AILI L. LAZAAR, MD**

University of Pennsylvania, Philadelphia, PA  
*Career Investigator Award* • Co-funded with the American Lung Association and the American Lung Association of Pennsylvania

**Why Do Airway Cells Grow Abnormally In People With Severe Asthma?**

***Vascular Endothelial Growth Factor And Human Airway Smooth Muscle Cell Function.***

In severe asthma, the airways become inflamed, and airway smooth muscle cells (ASM) grow abnormally. There is growing evidence that the obstruction and remodeling of the airways caused by these events is not reversible in many people with chronic, severe asthma, but little is known about how the different cell types within the airways contribute to this process. The investigators are studying vascular endothelial growth factor, or VEGF, which is known to alter the way other cell types function. They believe that VEGF plays a part in controlling ASM cells and are defining the mechanisms by which VEGF can promote airway remodeling. Knowing more about the basic cellular abnormalities that contribute to airway remodeling could make it possible to develop new treatments.

**JAMES J. LEE, PHD**

Mayo Clinic Scottsdale, Scottsdale, AZ  
*Research Grant* • Funded by the American Lung Association of Arizona/New Mexico

**How Do Destructive Enzymes Contribute To Asthma Onset?**

***Lung Pathologies Mediated By Eosinophil-Derived LPLase.***

The goal of these studies is to clarify the process by which allergic inflammation contributes to the onset of asthma. The scientists are focusing on enzymes called LPLases which alter the function of surfactant, a mixture of lipids and proteins that reduce the work of breathing by helping to keep the airspaces of the lung open. The origin of these potentially destructive enzymes is not yet defined, but it is thought that a type of cell called an eosinophil may be a source of LPLase activity in the lungs of asthma patients. The investigators hypothesize that eosinophils release LPLases into the airspaces of the lung, leading to surfactant breakdown and lung dysfunction. They are seeking to identify and characterize the LPLase gene and determine the role of eosinophil-derived LPLase activity in an experimental mouse model of allergic airways disease.

## JUNE H. LEE, MD

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

### Pinpointing The Bad Guys: Which Genes Are Responsible For Damaging The Airways?

**Gene Regulation By IL-4 And IL-13 In Airway Cells.** The molecular mechanisms that are responsible for the airway hyperresponsiveness and airway remodeling so characteristic of asthma are not well understood. These investigators are studying certain mechanisms that have been implicated as central mediators of asthma to gain insight into how they affect gene expression, and how specific genes and cell types contribute to causing asthma. Characterizing the genes that are regulated by these mechanisms will allow scientists to determine which genes are more likely to play a part in airway remodeling, fibrosis (scarring) and hyperresponsiveness. Identifying these genes and cell types may also shed light on the causes of a broad spectrum of other lung diseases. Eventually, a clearer understanding of airway hyperresponsiveness and remodeling will lead to designing new and targeted treatments for asthma and other airway diseases.

## ELIZABETH A. LYNCH, MD, MS

Boston University Medical Center,  
 Boston, MA

*Research Training Fellowship* • Co-funded with the American Lung Association and the American Lung Association of Greater Norfolk County

### Seeking A New Way To Stop Inflammation In Asthma

**Differential Immunodilation Of Th1 And Th2 Cells by IL-16 In An Asthma Model.** To provide the best care for asthma, medical scientists need a better understanding of the basic abnormalities that drive the disease process. This research concentrates on defining and elucidating the mechanism by which a substance called Interleukin-16 (IL-16) inhibits the characteristic inflammation that is a hallmark of asthma. Understanding this mechanism will serve as the foundation for advances in asthma treatment, using IL-16 to prevent inflammation from developing in the airways.

## ADAM P. MATSON, MD

University of Connecticut Health Center,  
 Farmington, CT

*Research Training Fellowship* • Funded by the American Lung Association of Connecticut

### If A Mother Is Allergic, Will Her Baby Acquire The Same Tendency?

**The Impact Of Maternal Allergy On Development Of Allergic Airway Disease In Offspring.** Despite numerous advances in understanding asthma and how to treat it, **asthma prevalence in children has increased at an alarming rate.** The reasons for this increase are unclear, but the trend parallels increases in allergic sensitization during the last two decades. The goal of this project is to elucidate significant factors that contribute to eliciting an immune response in early life, which can ultimately dictate a person's susceptibility to allergic airway disease and asthma. The researchers are exploring how maternal allergy to a model protein antigen called ovalbumin (OVA) affects the development of immune responsiveness to the same antigen in offspring. An antigen is a substance that provokes the formation of antibodies by the immune system to repel what is perceived to be a foreign invader, leading to an allergic reaction. Based on what is learned from these studies, the investigators hope to determine the conditions under which early allergic sensitization can occur either before birth or in early life during breast feeding. This information will provide a fundamental concept of how asthma begins, and may shed light on other inflammatory diseases as well.

## ELIZABETH L. MCQUAID, PHD

Brown University School of Medicine,  
 Providence, RI

*Career Investigator Award* • Funded by the American Lung Association

### Improving the Odds: Better Ways To Get Children To Take Their Asthma Medications

**Enhancing Pediatric Asthma Education To Improve Adherence.** Asthma in children has increased at an alarming rate over the past twenty years and is now the most common chronic illness of childhood. Asthma treatment strategies can be complex and may include taking medications several times a day, making compliance difficult. The researchers have pre-

viously shown that children typically take less than half of their prescribed medications for preventing asthma. The present study seeks to determine whether adding a brief behavioral intervention to a standard asthma education program will improve adherence to medication schedules. The intervention involves electronically monitoring the medications of children in the study and providing objective feedback on their adherence, offering problem-solving strategies to help overcome barriers to adherence, and creating a behavioral contract to increase adherence. Another group of children is receiving a standard asthma education program without the behavioral intervention. The two groups will be compared to determine whether behavioral intervention improves adherence, lessens activity limitation due to asthma, and reduces the number of health care visits.

**MARIA C. MIRABELLI, MPH**

University of North Carolina at Chapel Hill, Chapel Hill, NC

*Lung Health Research Dissertation Grant* • Funded by the American Lung Association

**Can Going To School Near A Hog Factory Affect Lung Health?**

***In-School Exposure To Industrial Swine Farm Emissions And Asthma Symptoms In Adolescents.*** This research focuses on environmental health conditions in public schools and asthma symptoms among students. Little information exists about the health impact of attending a school located near an industrial hog factory, but preliminary findings suggest that neighbors of such enterprises may experience adverse health effects including respiratory irritation. This project evaluates the relationship between attending school near a hog factory, which occurs in rural areas of North Carolina, and asthma symptoms that are common among children living in these areas. The research will shed new light on the respiratory health of students in agricultural communities by estimating their exposure to livestock and investigating the association between estimated exposure and asthma symptoms.

**KATHLEEN M. MORTIMER, MPH, PHD**

University of California, Berkeley, Berkeley, CA

*Research Grant* • Funded by the American Lung Association and Supplemented by the American Lung Association of California

**Who Is Most Susceptible To Lung Damage Caused By Air Pollution, And How Can They Be Protected?**

***The Influence Of Life-Time Exposure To Air Pollution On The Natural History Of Asthma.***

This study is examining the role that specific air pollutants and other environmental factors play in both acute asthma episodes and in the long-term natural history of asthma. The goal is to clarify which groups of people may be more sensitive to the short and long-term effects of air pollution. Identifying these groups may lead to a clearer understanding of the mechanisms by which air pollution damages the lungs. The information developed by these studies will also support American Lung Association's efforts to advocate for more effective and timely regulation of air pollution, and should contribute to public education programs by identifying susceptible groups of people and making recommendations for how to protect them.

**KRISTEN PAGE, PHD**

Cincinnati Children's Hospital, Cincinnati, OH  
*Research Grant* • Funded by the American Lung Association

**How Do Cockroaches Contribute To Asthma, And What Can We Do About It?**

***Cockroach-Induced Pro-Inflammatory Responses In Human Airway Epithelium.***

Asthma is on the rise in inner cities, where overcrowding and low-income status can result in infestation of homes with cockroaches. This causes high levels of cockroach allergens to accumulate, which sensitize some people, who become allergic to cockroaches. Allergic reactions to cockroaches have been strongly associated with asthma, with up to 60 percent of asthma patients in some cities in the United States known to be allergic to cockroaches. Other studies suggest that cockroach allergens may promote sensitization through their ability to cause inflammation in the airways. The goal of these studies is to understand the means by which cockroach proteins exert a direct pro-inflammatory effect on cells from the lining of

the bronchial tubes. This will provide insight into the mechanisms by which foreign proteins can cause airway inflammation, which may lead to new ways of treating asthma.

## **DUANQING PEI, PHD**

University of Minnesota School of Medicine, Minneapolis, MN

*Career Investigator Award* • Co-Funded with the American Lung Association and the American Lung Association of Minnesota

### **Slowing Down Eosinophils, The Migrating Cells Involved In Asthma**

**The Role Of Leukolysin In Asthma.** These researchers are studying leukolysin, a powerful proteinase or type of enzyme that is expressed by eosinophils, specialized cells that are known to be involved in asthma. Their goal is to clarify whether the presence of leukolysin allows eosinophils to migrate into the airways and the lungs, where they play a part in causing tissue damage. If this is the case, it may be possible to develop medications that slow down this infiltration of eosinophils and thereby provide medical professionals with a more effective strategy for promoting lung health and preventing asthma.

## **ALAN PENMAN, MD**

Mississippi State Department of Health, Jackson, MS

*Clinical Research Grant* • Funded by the American Lung Association of Mississippi

### **Learning More About High Risk Groups For Severe Asthma**

**Pilot Project To Develop A Surveillance System For Severe Asthma In The Jackson, MS Tri-County Area.** This project involves establishing and evaluating a limited asthma surveillance system, based on asthma-related emergency room visits and hospitalizations in the main hospitals of metropolitan Jackson, Mississippi. The purpose is to describe the frequency and distribution of asthma in this area, and to identify groups who are at risk of more severe disease that requires emergency treatment and/or hospitalization. The resulting data will contribute to supporting and evaluating asthma prevention programs and strategies in Mississippi.

## **RAYMOND B. PENN, PHD**

Wake Forest University Health Science Center, Winston-Salem, NC

*Career Investigator Award* • Funded by the American Lung Association of Pennsylvania

### **Understanding How Receptors Are Regulated Could Open The Door To New Asthma Treatments**

**Regulation Of G Protein-Coupled Receptors In Airway Myocytes.** The overall objective of this research is to identify the mechanisms and the key regulatory molecules involved in desensitizing two important receptors in smooth muscles of the airways. In an asthma episode, contraction of airway smooth muscle causes wheezing, and sometimes can leave a person gasping for breath. Clarifying how these receptors are regulated will provide a better understanding of how they contribute to asthma attacks, and also foster development of new asthma treatments. Developing therapies that preserve the responsiveness of receptors that relax airway smooth muscle could improve the effectiveness of several current anti-asthma drugs, meaning that a lesser amount of drug would be required to prevent or reverse asthma symptoms.

## **GUIRONG WANG, PHD**

The Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, PA

*Research Grant* • Funded by the American Lung Association of Pennsylvania

### **How Are Surfactant Proteins In The Body Involved In Asthma?**

**Surfactant Protein Innate Immunity On Pollen Allergic Asthma.** Asthma is a complex genetic disorder that can be triggered by exposure to a variety of substances in the environment, such as plant pollen. Two proteins normally present in the body, surfactant protein A and D (SP-A and SP-D), are involved in the immune system's defense against such outside invaders, playing a part in regulating inflammatory processes in the lung which occur in asthma episodes. These researchers are investigating the means by which SP-A and SP-D variants modulate susceptibility to asthma, and are seeking to clarify how SP-A is involved in certain specific mechanisms of pollen-induced allergic asthma.

**MICHAEL E. WECHSLER, MD**

Brigham and Women's Hospital, Boston, MA  
*Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of Massachusetts

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**Studying Genes That Cause Inflammation of Blood Vessels**


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**Identification Of Sequence Variants In Genes Of Eosinophil Function And Regulation In Churg-Strauss Syndrome Patients.** Churg-Strauss syndrome (CSS) is associated with asthma that is characterized by eosinophilic vasculitis, or inflammation of the blood vessels involving a type of white blood cell called eosinophils. CSS has been increasing in incidence over the last several years, but very little is understood about the underlying mechanism responsible for its development. Multiple genetic and environmental factors are involved, with dysregulation of eosinophil production and/or function probably playing a fundamental role. This is likely to be caused by mutations of genes that regulate eosinophils. The researchers are studying genes involved in eosinophil production in patients with CSS to gain a better understanding of the genetics of the syndrome, and greater knowledge about the mechanisms of CSS and other eosinophilic lung diseases, including asthma. Such knowledge could lead to more targeted treatment, and perhaps to new genetic tests to determine who is susceptible to these diseases.

**STEVEN R. WHITE, MD**

University of Chicago, Chicago, IL  
*American Lung Association of Metropolitan Chicago and the Blowitz-Ridgeway Foundation Research Grant* • Funded by the American Lung Association of Metropolitan Chicago and the Blowitz-Ridgeway Foundation

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**New Role For An Important Class Of Asthma Drug**


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**Regulation Of Airway Epithelial Apoptosis By Beta-Adrenergic Agonists.** When asthma damages the airway epithelium or lining of the bronchial tubes, other structures in the airways also become inflamed. These scientists have found that a class of drugs called beta-adrenergic agonists, currently a major drug treatment for asthma, may have a previously unrecognized role in fighting the disease. They are examining how these drugs protect the airway

epithelium both from inflammation and from the potential side effects of other asthma drugs. Since beta-adrenergic agonists are particularly important in treating childhood asthma, the data being gathered may lead to new ideas for suppressing inflammation in children with asthma while also preventing airway damage. It will also set the stage for further investigations to examine how beta-adrenergic agonists and corticosteroids work together to heal asthmatic lungs.

**MICHELLE ZEIDLER, MD**

University of California, Los Angeles, Los Angeles, CA  
*Clinical Research Grant* • Funded by the American Lung Association of California

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**Can A New Formulation Of An Old Standby Offer Better Asthma Treatment?**


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**The Effect Of Extra-Fine Inhaled Corticosteroids On Distal Lung Inflammation In Asthma.** These scientists are measuring changes in inflammation in the small airways of the lungs after treatment with a new, extra-fine hydrofluoroalkane formulation of inhaled corticosteroids (ICS). ICS drugs have long been the mainstay of asthma control, but their large particle size does not allow the medication to reach the small airways of the lungs, which may explain why some people with asthma continue to do poorly despite adequate treatment. Asthma has traditionally been defined as a disease that affects the large airways of the lungs, but accumulating evidence now suggests that inflammation extends beyond the large central airways into the distal small airways. This study will determine the potential of extra-fine ICS to reduce inflammation in the small airways, which may ultimately improve asthma control.

**ZHOU ZHU, MD, PHD**

Yale University, New Haven, CT  
*Research Grant* • Co-funded with the American Lung Association and the American Lung Association of Connecticut

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**Studying A Newly Identified Enzyme Involved In Asthma Inflammation**


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**Characterization Of Molecular Mechanisms Of Acidic Mammalian Chitinase In Mediating IL-13 And Th2 Inflammation.** A sub-

stance called chitin is an integral component of the walls of parasites, crustaceans and fungi, where it has protective effects. An enzyme called chitinase degrades chitins and is an essential part of the immune system's response to parasites and infectious agents in lower forms of life. One such enzyme, called Acidic Mammalian Chitinase (AMCase), has recently been described in humans as well as in mice, but nothing is known about its role in mammals. These researchers have shown that AMCase is prominently induced and is a critical mediator in Th2 inflammation, a type of inflammation that is a key factor in the development of asthma. Their current investigations are aimed at studying the molecular mechanisms of AMCase and defining its biologic functions in mammals. This work should provide valuable insights into how the Th2 inflammatory response occurs, which will help to clarify how it contributes to asthma.

# DISORDERS OF THE LUNG'S BLOOD VESSELS

Acute lung injury (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 150,000 Americans are affected with ARDS each year and is often the major complication of extensive surgery, trauma, chemotherapy, and lung transplantation as well as inhalation of noxious agents. No effective treatment yet exists.

Pulmonary 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 severe lung disease with various causes and also in a "primary" form that is without known cause. Pulmonary edema is a condition in which excess fluid leaks from the blood to the lungs.

American Lung Association researchers are attacking the problem of ARDS on several levels. Basic research is exploring the cellular mechanism by which high levels of inhaled oxygen promote and enhance the condition. Patient-oriented studies focus on the prolonged mechanical ventilation that is often required to treat the syndrome. Areas being investigated range from the cellular mechanisms that lead to lung scarring to problems of breathing disorders during sleep, cognitive impairment and end of life decision-making, which are all part of the experience of prolonged mechanical ventilation. The mechanisms of pulmonary hypertension are being studied from several perspectives with emphasis on nitric oxide. This small molecule is a major component of air pollution. Paradoxically, in small amounts it serves as a key player in the system by which the body regulates the circulation within the lungs. 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.

## AND ACUTE LUNG INJURY

# DISORDERS OF THE LUNG'S BLOOD VESSELS...

## **ELLIOTT D. CROUSER, MD**

The Ohio State University Medical Center,  
Columbus, OH

*Career Investigator Award* • Co-Funded with the American Lung Association and the American Lung Association of Ohio

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### **Searching For Ways To Prevent Blood Poisoning**

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***Sepsis-Induced Heart Failure: The Role Of Mitochondria.*** Sepsis is a common and significant complication of acute illness, often leading to a progressive and catastrophic condition called multiple organ dysfunction syndrome (MODS), the most common cause of death in medical intensive care units. While the cause of MODS is unknown, these researchers have gathered information suggesting that mitochondria, a component of the body's cells and the major source of energy in most cells, appear to play a major role in organ dysfunction during severe acute illnesses. They hypothesize that mitochondrial injury is involved in causing sepsis-induced heart failure. The relationship between mitochondrial damage and organ failure during sepsis, and the sequence of events that causes mitochondrial damage, are being investigated. A clear understanding of how such damage occurs may shed light on how to prevent it and protect against organ failure. These investigations have important implications for managing and treating MODS in critically ill patients.

## **ELAMIN M. ELAMIN, MD, MS**

Southern Illinois University School of  
Medicine, Springfield, IL

*Clinical Research Grant* • Funded by the American Lung Association of Illinois-Iowa

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### **Improving The Outcome When A Breathing Machine Must Be Used To Treat Severe Asthma**

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***Ketamine vs. Fentanyl: Effects On Hemodynamics And Length Of Stay In The ICU.*** Many people with severe asthma develop breathing problems and must be placed on mechanical ventilation (MV), using a breathing machine. While this procedure can be lifesaving, it can also lead to serious complications such as pneumonia, and can injure lung tissue. Most patients on MV require sedation, but currently there are few drugs that can provide pain relief and sedation, and that also have the ben-

eficial effect of relaxing the airways. This group is studying a drug called ketamine that has been used successfully to treat severe bronchospasm, which occurs in an asthma episode when airway smooth muscle contracts and interferes with breathing. They believe ketamine may also be valuable for rapidly inducing and maintaining anesthesia in asthma patients on MV. If so, and if using ketamine makes it possible to discontinue MV in a shorter time, then complications due to MV are likely to decrease, and lung health and overall health will improve.

## **JERRY EU, MD**

Duke University Medical Center, Durham, NC  
*Research Grant* • Funded by the American Lung Association

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### **How Does The Body Defend Itself By Controlling Blood Flow To The Lungs?**

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***Ryanodine Receptor In Hypoxia-Induced Pulmonary Vasoconstriction.*** A phenomenon called hypoxia-induced vasoconstriction (HPV), in which blood vessels constrict when oxygen levels decrease, is unique to the blood vessels of the lungs. HPV diverts the flow of blood away from diseased segments of the lungs to segments that are healthier. This adaptation by the circulatory system is critical to maintaining an adequate oxygen supply in people who have respiratory and cardiac diseases. The cellular components of HPV are not well understood, but they are likely to be injured or overwhelmed when a person experiences respiratory failure due to hypoxemia (insufficient oxygenation of the blood). In an ironic example of the cure being worse than the disease, placing a person on mechanical ventilation with a breathing machine also may injure the cellular components of HPV and actually sustain respiratory failure. This research hopes to gain a better understanding of HPV, so as to improve treatment for patients with respiratory failure due to hypoxemia.

## **XIAOHUI FANG, MD**

University of California, San Francisco,  
San Francisco, CA

*Research Training Fellowship* • Funded by the American Lung Association and Supplemented by the American Lung Association of California

### **Why Do Abnormal Amounts Of Fluid Sometimes Accumulate In The Lungs?**

#### ***Role Of CFTR Chloride Channel In Fluid Transport Across Alveolar Epithelial Cells.***

These investigators are clarifying the basic mechanisms that regulate the removal of salt and water from the furthest reaches of the lungs. This information is important to improving scientific knowledge of lung fluid balance in patients who experience respiratory failure because abnormal amounts of fluid accumulate in their lungs, a life-threatening condition known as pulmonary edema. These studies will also provide vital clues to developing new treatments that could treat pulmonary edema more effectively. The researchers have developed a new model for laboratory studies of cells from the lining of the lungs that will allow them to measure fluid transport by these cells. Their findings should provide an integrated understanding of this process that is relevant to what occurs in patients with pulmonary edema.

## **RANDALL S. FREY, PHD**

University of Illinois, Chicago, Chicago, IL

*Research Grant* • Funded by the American Lung Association of Metropolitan Chicago and the American Lung Association of Illinois-Iowa

### **Understanding What Triggers ARDS, An Often Fatal Lung Disease**

#### ***Signaling Of Oxidant Production And NF-kB Activation In Endothelial Cells.***

Acute respiratory distress syndrome (ARDS) is a catastrophic form of acute respiratory failure, in which the lungs become inflamed, and their air sacs and the spaces in between them fill up with inflammatory fluids. ARDS is fatal in 30 to 40 percent of all cases, with the direct cause of death usually due to multiple organ failure and infection of the blood (sepsis). The lung inflammation responsible for ARDS is believed to be caused by substances called mediators that promote the production of oxidants, which generate a cascade of signaling that activates proinflammatory genes. Despite growing evidence of the importance of oxidant signal-

ing in causing the series of events that results in ARDS, little is known about the signaling pathways that are involved. The goal of these studies is to determine the specific signaling pathways that lead to lung injury. These studies are of great significance to understanding the process by which life-threatening damage is done.

## **MARION K. GORDON, PHD**

Environmental and Occupational Health Sciences Institute and Ernest Mario School of Pharmacy, Rutgers University,  
Piscataway, NJ

*Career Investigator Award* • Funded by the American Lung Association of New Jersey

### **Reversing Fatal Pulmonary Hypertension: Could Mountain Climbers Offer Clues To The Answer?**

#### ***Regulation Of Vessel Remodeling In Primary Pulmonary Hypertension.***

Primary Pulmonary hypertension (high blood pressure affecting the pulmonary arteries) is a rare disease that affects women age 20 to 40. The cause is unknown and it is usually fatal within three to five years of diagnosis. A related kind of pulmonary hypertension occurs in high mountain climbers, due to the lower amount of oxygen in the air. Their blood pressure increases because the walls of pulmonary blood vessels thicken and remodel. Unlike primary pulmonary hypertension, this condition is reversible: when the climber returns to a lower altitude and breathes air with higher oxygen content, the vessels return to normal and blood pressure comes down. These studies are seeking information about how vessel remodeling occurs in reversible pulmonary hypertension, since little is known about the mechanisms that control this process. The results will clarify how pulmonary hypertension develops and what events favor its reversal, helping to identify new targets for intervention for primary pulmonary hypertension. The results may also improve understanding of systemic arterial hypertension, the more common type of high blood pressure.

# DISORDERS OF THE LUNG'S BLOOD VESSELS...

## REN-FENG GUO, MD

University of Michigan Medical School,  
Ann Arbor, MI

*Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of Michigan

### Studying The Pathway That Allows Lung Injury To Become Life-Threatening

**Neutrophil Trafficking In Lung During Sepsis.** Acute respiratory distress syndrome (ARDS) is a catastrophic, often fatal, form of acute respiratory failure that affects some 150,000 people in the United States every year. The air sacs of the lungs and the spaces in between them, known as the interstitium, fill up with inflammatory fluids, causing the air spaces to collapse and impairing the exchange of oxygen. These studies are focusing on lung injury associated with sepsis, or infection of the blood, which can result in ARDS. Neutrophils, a type of white blood cell that moves into the lungs under certain conditions, play a pivotal part in the development of acute lung injury induced by sepsis. The researchers are seeking to determine the roles of substances known as b1 and b2 integrins in this process, and to discover the pathway that is used to recruit neutrophils and permit them to migrate into septic lungs. Identification of this pathway will be an important step forward in developing treatment strategies to control the progression of lung injury associated with sepsis.

## MANU JAIN, MD

Northwestern University, Chicago, IL

*Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of Metropolitan Chicago

### Which Patients Are Likely To Develop Lung Scarring From Using A Breathing Machine?

**Mediators Of Fibroblast Proliferation In ARDS.** These researchers are studying the mechanisms that lead to fibrosis, or scarring, of the lungs following acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Nearly 150,000 people in this country suffer from ALI and ARDS annually. About 40 percent of them die, and those who survive have significant health problems. Many of the deaths and the continuing problems brought on by ALI and ARDS are the result of complications associated with prolonged mechanical

ventilation, or being placed on a breathing machine, which affects how the lungs heal after an acute injury. The results of these studies should make it possible to identify patients who are likely to develop lung fibrosis. Future studies are planned to identify medications that may interrupt progression to fibrosis after ALI and ARDS, thus making it possible for more patients to survive with fewer debilitating complications.

## DREW G. JONES, MD

Virginia Commonwealth University,  
Richmond, VA

*Research Training Fellowship* • Funded by the American Lung Association of Virginia

### How Blood Vessels Are Damaged In Severe Lung Disease

**Regulation Of IL-8 In Re-Oxygenating Microvascular Endothelium.** This research seeks to clarify current understanding of the mechanisms that produce injury to the small blood vessels that is characteristically seen in lungs affected by acute respiratory distress syndrome (ARDS). The work will study how blood vessel lining cells manufacture critical inflammatory proteins once the lung's tension is disrupted and then restored. The research will shed new light on severe lung injury typically associated with chest trauma, lung transplantation and pulmonary embolism, a condition brought on by occlusion of blood vessels from blood clots that lodge in the pulmonary artery circulation. These studies will provide new insight into development of effective drug therapy to reduce illness and death from these conditions.

## JUDD LANDSBERG, MD

University of California, San Diego Medical Center, San Diego, CA

*Research Training Fellowship* • Funded by the American Lung Association of California

### Fine-Tuning Treatment By Better Understanding Why It Works

**Effects Of Nitric Oxide And Prostacyclin On TRPC6 Gene Expression.** Severe pulmonary hypertension, or high blood pressure affecting the lungs, is a life-threatening condition. It occurs when the blood vessels in the lung inappropriately narrow due to the abnormal growth

## DISORDERS OF THE LUNG'S BLOOD VESSELS...

of smooth muscle cells that normally form the center of the artery wall. This abnormal pulmonary artery smooth muscle cell (PASMC) growth has been linked to the increased expression of a gene essential for normal PASMC growth, the TRP gene. Severe pulmonary hypertension can be successfully treated with nitric oxide (NO) and/or prostacyclin (PGI<sub>2</sub>), but little is known about how these agents achieve their beneficial clinical results. This project is investigating the effects of NO and PGI<sub>2</sub> on TRP gene expression and PASMC growth. Understanding the molecular mechanisms of these successful therapeutic agents may provide insight into new treatment strategies for this potentially fatal medical problem.

### **MEHRAN MANDEGAR, MD**

University of California, San Diego Medical Center, San Diego, CA

*Research Training Fellowship* • Funded by the American Lung Association of California

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#### **What Goes Wrong In The Body In A Fatal Disease?**

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***Role Of tandem Pore K<sup>+</sup> Channels In Primary Pulmonary Hypertension.*** Primary pulmonary hypertension (high blood pressure involving the medium and small arteries serving the lungs) is a progressive disease that leads to right sided heart failure and death. Understanding the molecular basis that leads to its development is a key step toward developing new means of treatment and prevention. This project is gathering data that will make a substantial contribution to elucidating the molecular mechanisms that contribute to primary pulmonary hypertension, which will permit more specific and effective approaches to controlling and preventing it.

### **H. ROBERT MASURE, PHD**

University of Kansas Medical Center, Kansas City, KS

*Research Grant* • Funded by the American Lung Association of Kansas

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#### **Breathing Freely After Mechanical Ventilation**

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***Molecular Analysis Of The Oxidative Stress Response In Diaphragmatic Fatigue.***

Critically ill patients with respiratory problems may need breathing assistance by mechanical ventilation to save their lives. Some of these

patients experience difficulty when they are weaned from the breathing machine, caused partly by respiratory muscle fatigue. One third of patients are not successfully weaned on the first attempt at liberating them from mechanical ventilation, resulting in pain, discomfort, longer hospital stays and higher health care costs. This study is investigating two antioxidant compounds that may protect against the muscle fatigue that helps to create the problem. The end result may be potential new treatments to help people breathe freely on their own again.

### **SHAKEEB H. MOOSAVI, PHD**

Harvard School of Public Health, Boston, MA  
*Research Grant* • Funded by the American Lung Association

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#### **When Every Breath Is a Desperate Effort**

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***Mechanisms Of Dyspnea Relief by Inhaled Furosemide.*** Dyspnea is the sensation of “shortness of breath” or difficult or labored breathing, such as the distressed breathing that can be caused by heart disease, or when the lungs cannot inhale and exhale freely. It can seriously affect quality of life for people with heart and lung disease, making every breath a desperate effort. More treatment options are needed to provide better relief for these individuals. The investigators in this project are studying the effectiveness of inhaling a substance called furosemide in combating dyspnea. By comparing the usefulness of inhaled furosemide versus furosemide injections they hope to better understand the mechanisms by which inhaled furosemide works, and to determine when furosemide treatment is most valuable.

### **JUDITH E. NELSON, MD, JD**

Mount Sinai School of Medicine, New York, NY

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

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#### **Helping People Make Informed Decisions About Breathing Machines**

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***When Critical Illness Becomes Chronic: Decision-Making In The Setting Of Prolonged Respiratory Failure.*** Prolonged dependence on mechanical ventilation is the hallmark of chronic critical illness, a major lung health problem that is estimated to affect close to 1,000,000

## DISORDERS OF THE LUNG'S BLOOD VESSELS...

Americans annually. The typical patient is an older adult with multiple health problems, including chronic lung disease. The prognosis is poor, hospital stays are usually lengthy, health care costs are extremely high, and many patients never recover sufficiently to breathe without a ventilator. The researchers are seeking to identify what information patients, families and health-care professionals consider relevant and important to the process of making decisions about treating this devastating condition, and how such information is communicated and comprehended. The goal is to empower patients and their loved ones to make informed decisions through meaningful discussion with professional caregivers, which will improve the quality of care.

### **CAROLINE A. OWEN, MD, PHD**

Brigham & Women's Hospital, Boston, MA  
*Career Investigator Award* • Funded by the American Lung Association of Massachusetts

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#### **Enzymes Behaving Badly Contribute To Lung Injury**

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***Roles Of Membrane-Bound Serine Proteinases On PMN In Lung Injury.*** Enzymes called serine proteinases are involved in the development of several chronic lung diseases, but how they mediate lung injury remains unclear, since the lung contains effective proteinase inhibitors. These investigators have shown that serine proteinases are expressed on the cell surface of neutrophils, a type of white blood cell, and that cell surface-bound serine proteinases cannot be inhibited by lung proteinase inhibitors. They are now testing the hypothesis that the cell surface-bound forms of serine proteinases play important roles in lung injury. Their studies may provide new insights and facilitate the design of new treatment strategies for lung disorders in which serine proteinases make a significant contribution to the development of disease.

### **SAIRAM PARTHASARATHAY, MD**

Loyola University Medical Center,  
Maywood, IL

*Research Grant* • Funded by the American Lung Association of Metropolitan Chicago

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#### **Avoiding Sleep Disruption For Patients On Breathing Machines**

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***Effect Of Ventilatory Modes Sleep Quality In The Intensive Care Unit.*** Over one million people nationwide need to be placed on a breathing machine (mechanical ventilation) every year. These intensive care unit (ICU) patients spend about 30% of their time asleep, but their sleep is severely disrupted when they are aroused by alterations in breathing patterns. These arousals can lead to a chain of events involving nervous system reactions that may ultimately result in higher rates of disease and mortality, particularly in people with congestive heart failure. This study is examining how two different modes of mechanical ventilation affect the sleep patterns of patients in the ICU. The goal is to identify the ventilator strategy that results in the best sleep quality and helps prevent cardio-respiratory complications due to sleep disruption.

### **ANTHONY P. PIETROPAOLI, MD**

University of Rochester Medical Center,  
Rochester, NY

*Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of Finger Lakes Region

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#### **Manipulating Nitric Oxide In The Blood Could Have A Major Impact On Serious Lung Diseases**

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***In Vitro Measurement Of Nitric Oxide (NO) Equilibrium And Diffusion In Blood And Lung Tissue.*** The most basic function of the lungs is delivering oxygen to the body's tissues. Hemoglobin, a component of red blood cells, is essential to oxygen transport and its flow to the tissues depends upon the size and resistance of blood vessels, or vascular tone. These researchers hypothesize that nitric oxide (NO) is a major controller of vascular tone and are elucidating the way NO interacts with blood. Their findings may lead to new treatments for a variety of lung disorders. Manipulating NO-blood interactions to promote release of NO in the circulating blood during hypoxia, or oxygen deprivation, could

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have a major impact on Chronic Obstructive Pulmonary Disease (COPD) and pulmonary fibrosis, in which oxygen delivery is poor. Manipulating NO in the blood could also be useful in treating pneumonia and other acute respiratory diseases. It might even serve to prevent conditions that cause pulmonary hypertension, or high blood pressure in the circulatory system of the lungs.

### **MARGARET A. PISANI, MD**

Yale University School of Medicine,  
New Haven, CT

*Clinical Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of Connecticut

#### **Improving Care For Elderly Patients**

*Prevalence Of Preexisting Cognitive Impairment And Its Impact On Use Of Interventions And Outcomes In Older ICU Patients.* Cognitive impairment is common in the elderly, increases with age, and predisposes the individuals it affects to pneumonia and respiratory failure. Fifty percent of admissions to Intensive Care Units (ICUs) in hospitals are people over the age of 65, and the majority of these admissions are primarily due to respiratory problems. This study will determine the prevalence of preexisting cognitive impairment in older ICU patients, heightening awareness of the problem and paving the way for further research on its impact. The ultimate goal is to improve critical care for elderly patients.

### **RENLI QIAO, MD, PHD**

University of Southern California,  
Los Angeles, CA

*Research Grant* • Funded by the American Lung Association of California

#### **Gene Therapy To Clear Excess Fluid From The Lungs**

*Augmentation Of Na Pump Activity In The Alveolar Epithelial Cells Via Lentiviral Gene Transfer.* This project is attempting to find a new treatment for pulmonary edema, the accumulation of fluid in the lungs as a result of acute lung injury. There is presently no effective treatment for this condition, which is a major cause of hypoxemia, or insufficient oxygen levels in the blood. These studies are investigating the feasibility of using gene therapy to

augment fluid clearance from the lungs. If the investigation is successful, the result will be a powerful tool for treating one of the most severe yet common disease processes affecting the lungs. This approach could be valuable for improving the outcome of acute lung injury regardless of its underlying cause.

### **CHARLOTTE A. RICHMOND, PHD, RN**

Mt. Sinai Medical Center & Miami Heart  
Institute, Miami Beach, FL

*Seed Grant Award* • Funded by the American Lung Association of Florida

#### **Evaluating A New Way To Provide Breathing Assistance When Lungs Need Help**

*Comparison Of Noninvasive Motion Ventilation (NIMV) Periodic Acceleration (pGz) To Ventilate Oleic Acid Model Of Acute Lung Injury (ALI).* Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are serious medical problems that are typically treated with a breathing machine, which provides mechanical ventilation when the lungs are unable to function independently. However, mechanical ventilation often creates further lung damage and complications. Noninvasive motion ventilation (NIMV) or periodic acceleration (pGz) is a novel and noninvasive means of breathing assistance, using techniques similar to spontaneous breathing. This group is comparing conventional mechanical ventilation to NIMV in laboratory animals. Their findings will provide preliminary data regarding the potential of NIMV to reduce the sometimes life-threatening complications associated with conventional mechanical ventilation.

### **GEORGE W. RODWAY, MSN, BSN, RN**

University of Pittsburgh, Pittsburgh, PA

*Lung Health Research Dissertation Grant* • Co-funded with the American Lung Association and the American Lung Association of Pennsylvania

#### **What Happens When Breathing Repeatedly Stops While You Sleep?**

*Intermittent Hypoxia: Impact On Cardiovascular Parameters And Oxidative Stress.* Obstructive sleep apnea (OSA) is estimated to affect between 12 and 20 million people in the USA, and chronic obstructive pulmonary disease (COPD) affects between 13 and 24 mil-

# DISORDERS OF THE LUNG'S BLOOD VESSELS...

lion others. Recent evidence shows that even people with mild or moderate OSA or COPD have an increased risk of intermittent hypoxia, in which the individual repeatedly stops breathing for brief periods during sleep. When this occurs, oxygen levels in the blood decrease and carbon dioxide levels rise, increasing the risk of developing other disorders, including high blood pressure, stroke and neurologic problems. This study is examining the significance of periods of intermittent hypoxia on blood pressure and heart rate in people who do not have OSA or COPD, to gain a better understanding of its health effects when it is not complicated by another disease process.

## **ROSS S. SUMMER, MD**

Boston University, Boston, MA

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

### Repairing Life-Threatening Lung Injuries

***The Localization And Characterization Of Lung SP Cells.*** Current treatments for acute lung injuries are limited to supportive care or, in some cases, to treating the lung infection that caused the injury. None of these options address the fundamental consequence of acute lung injury, which is damage to the alveoli. These are the tiny, saclike structures inside the lungs where carbon dioxide is exchanged for oxygen, which is necessary to sustain life. These scientists believe that stem cell therapy offers some promise as a means of replacing or repairing damaged lungs, no matter how severely they are injured. They have identified a unique stem cell within the lungs, called the SP cell. They are presently studying SP cells in greater depth and are seeking to determine whether SP cells can become lung cells as well as non-lung cell types. The information they develop about the precise role of these cells will provide the foundation for designing new treatments for acute lung injury, and for replacing damaged lung alveoli.

## **MAGED TANIOS, MD, MPH**

Tufts-New England Medical Center,  
Boston, MA

*Research Training Fellowship* • Funded by the American Lung Association of Massachusetts

### Timing May Be Everything For Patients Who Need Help Breathing

***Sleep Disruption In Mechanically Ventilated Patients Recovering From Acute Respiratory Failure.*** Clear guidelines are needed regarding the timing for removing critically ill patients from artificial ventilation as their condition improves. Taking a person off a breathing machine too soon can create significant health problems, yet delaying for even one day can create a different set of equally serious problems. Less than perfect timing usually delays healing of the lungs and prolongs the amount of time spent in the intensive care unit (ICU) and in the hospital. The researchers are examining whether the lack of sleep that patients typically experience in the ICU leads to abnormalities in the respiratory control system, which in turn hinders a timely and safe removal from the ventilator. The sleep patterns of patients on ventilators are being evaluated, to determine the relationship between interrupted sleep and removal from the ventilator. This knowledge will be helpful in optimizing sleep in the ICU, and in better managing the crucial decision about when the time is right for each individual to come off the breathing machine.

## **ERCHENG ZHU, MD, PHD**

Southern California Institute of Research and Education, Long Beach, CA

*Research Grant* • Funded by the American Lung Association of California

### Keeping The Respiratory Muscles Active While On A Breathing Machine

***Modes Of Mechanical Ventilation And Diaphragm Contractile Properties.*** Various modes of mechanical ventilation with a breathing machine can be used to treat people with acute respiratory failure. Controlled mechanical ventilation, in which the person's diaphragm is completely inactive, results in a profound reduction in the diaphragm's ability to function. This creates complications and makes it difficult to regain the ability to breathe independently. These researchers are investigating the effects of assist-control mechanical ventila-

## DISORDERS OF THE LUNG'S BLOOD VESSELS...

tion, in which the diaphragm muscle remains partially active. They are seeking to determine whether this method lessens the loss of diaphragm function and reduces the muscle atrophy that occurs with controlled mechanical ventilation. Their findings will provide a better understanding of how to prevent loss of the diaphragm's ability to contract by maintaining partial activity of the respiratory muscles. The results may also lead to further studies of how to prevent muscle atrophy at an early stage of development for those who need prolonged assistance with breathing.



# OTHER LUNG

Lung infections are common and often deadly. *Influenza (flu)* and *pneumonia* related illnesses are responsible for 100,000 deaths annually. American Lung Association researchers continue to study a bacterium called *pseudomonas*, which affects the injured lungs of people who have *COPD* and *cystic fibrosis*, hoping to find a new means of prevention. A common *fungal infection* with the mold *aspergillus* affects the lungs in several ways. One form of the infection is destructive, and the special role of white blood cells in protecting against it is being examined. Scientists are also working to develop a vaccine for susceptible people.

*Sepsis (blood poisoning)* is a body-wide bacterial infection that is a common and often fatal complication in the intensive care units of hospitals. Studies are being pursued on the cellular mechanisms that promote or defend against *sepsis*. The mechanisms and treatment of a variety of common and uncommon pneumonias are under investigation. Other infections being studied are *pertussis (whooping cough)*, *H. parainfluenza* (a complication of *COPD*), *Legionella pneumophila* (the cause of *Legionnaire's Disease*) and *cytomegalovirus* (a complication of organ transplantation). Common viral infections such as adenovirus, respiratory syncytial virus and the flu virus are under study.

# INFECTIONS

## **JASON W. CHIEN, MD**

Fred Hutchinson Cancer Research Center,  
Seattle, WA

*Research Grant* • Funded by the American Lung Association of Washington

### How Do Genes Control The Immune System's Response To Factors In The Environment?

**Genetic Epidemiology Of TLR4 And Gram-Negative Bacteremia.** Major advances in genetics are taking place almost daily, as the scientific community moves toward deciphering the genetic code and applying these findings to medical care. The investigation of genetic factors that determine the immune system's response to factors in the environment is a rapidly moving front in the continuing process of gene discovery. Lung immunology in particular is intricately involved with environmental factors. One major environmental factor called lipopolysaccharide (LPS), a component of the cell wall of all Gram-negative bacteria, is a powerful activator of the immune system. Once it is recognized by the immune system, LPS is responsible for triggering an inflammatory response that is thought to be involved in many diseases, including such lung diseases as acute respiratory distress syndrome, asthma, and occupational lung disease. This group is investigating the potential genetic determinants of an individual's susceptibility to various pulmonary processes that result from tissue damage due to exposure to LPS.

## **ALI A. EL-SOLH, MD, MPH**

State University of New York at Buffalo,  
Buffalo, NY

*Clinical Research Grant* • Funded by the American Lung Association of New York State and the American Lung Association of Western New York

### Finding A Marker To Help Prevent and Treat Pneumonia In Nursing Home Patients

**The Role Of Dental Plaques In Nursing Home Acquired Pneumonia.** The percentage of people aged 65 and older in the United States will soar from 13% of the population in 1995 to 20% by 2030. Since a large portion of older people require long-term care, these figures will have a significant impact on the care and management of respiratory diseases in nursing homes. Pneumonia and influenza are the leading causes of death due to infection in nursing homes, but little has been done to

address the reversible causes of pneumonia acquired in the nursing home. This project is studying the role of dental plaques, a known but overlooked risk factor for pneumonia. The researchers hypothesize that respiratory germs recovered from the lower airways of nursing home patients with pneumonia are genetically identical to those recovered from their dental plaques. If so, this information will be valuable in implementing preventive strategies to reduce the rate of pneumonia and promote the quality of life in institutionalized elders.

## **MARTA FELDMESSER, MD**

Albert Einstein College of Medicine,  
Bronx, NY

*Research Grant* • Funded by the American Lung Association of the City of New York

### Protecting People With Weakened Immune Systems From a Treacherous Fungus

**Aspergillus Fumigatus: Monoclonal Antibodies For Prophylaxis & Study Of Pathogenesis.** The fungus *Aspergillus fumigatus* causes disease in people with severe immune defects and is difficult to treat. When it is inhaled by a susceptible individual, it causes pneumonia. This research seeks to develop antibodies that can be used to prevent lung infection from the fungus. Antibodies are components of the immune system which eliminate or counteract foreign substances (antigens) in the body, such as *A. fumigatus*. The antibodies will also be used to study the mechanisms by which the fungus causes lung disease.

## **WILLIAM O. HARTZELL, MD**

Brigham and Women's Hospital, Boston, MA  
*Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of South Carolina

### New Ways To Prevent Bacterial Infections

**The Role Of Matrix Metalloproteinase-12 In Macrophage Innate Immune Response In Bacterial Infections.** Bacterial pneumonia is a major cause of illness, and a common cause of death in this country. Bacterial resistance to antibiotics is making the treatment of pneumonia more difficult and the search for new therapies more important. This group is studying the role of matrix metalloproteinase-12 (MMP-12) and its ability to kill bacteria. They have found

that MMP-12 is produced by the macrophage, the most prevalent immune cell of the lung, and it is an important mechanism of macrophage killing of bacteria. They have also found that if MMP-12 is absent, macrophages are unable to kill bacteria, leading to bacterial infection. It is possible that stimulating MMP-12 production could bolster the body's immune system and prevent bacterial infection when the body's own defense systems are suppressed. These studies have the potential to add a new therapy against multi-antibiotic resistant bacteria.

#### ALAN R. HAUSER, MD, PHD

Northwestern University, Chicago, IL  
*Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of Metropolitan Chicago

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#### How Do Hospitalized Patients Develop Pneumonia?

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***Pseudomonas Aeruginosa Invasiveness And Persistence In Nosocomial Pneumonia.*** Thousands of people are afflicted each year with nosocomial pneumonia, a type of pneumonia that is acquired in hospital settings. One of its leading causes is a bacterium called *Pseudomonas aeruginosa*, which often resists treatment with antibiotics. These studies are focusing on the means by which *P. aeruginosa* invades the cells of the body, and whether substances called macrolides are capable of killing *P. aeruginosa*. The new information being developed by this group will enhance current understanding of how nosocomial pneumonia develops, and then lead to both immediate and long-term improvements in treating it.

#### MOHAMMAD JAMALUDDIN, PHD

University of Texas Medical Branch, Galveston, TX  
*Research Grant* • Funded by the American Lung Association of Texas

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#### A Common Virus Causes Serious Lung Infections In Children

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***Mechanism For MCP-1 Expression In Respiratory Syncytial Virus Infection.*** Respiratory Syncytial Virus (RSV) is responsible for many respiratory infections, including the common cold and pneumonia. It most often affects young children and can cause severe and sometimes life-threatening disease. RSV infection can occur at any time of year, but

widespread outbreaks are more common during the winter months. No effective antiviral treatment or vaccine is yet available, despite significant progress in understanding how RSV causes lung infections. These studies will provide additional insight into the underlying mechanism by which RSV induces lung infection. The researchers are focusing on the role of a particular molecule that defends the body against infection, and of a cellular pathway that may be involved in summoning it when RSV is present. Understanding this pathway in more detail will make it possible to develop new treatments to control RSV-induced lung disease.

#### RICHARD A. JOHNSTON, PHD

Harvard School of Public Health, Boston, MA  
*Research Training Fellowship* • Co-funded with the American Lung Association and the American Lung Association of Massachusetts

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#### Why Does Obesity Increase The Risk Of Pneumonia?

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***Obesity And Pneumonia.*** Obesity is a risk factor for developing a variety of lung diseases, including pneumonia and asthma. As the numbers of obese people continue to increase worldwide, so do the numbers of people who are susceptible to respiratory disease. The result is a growing and potentially enormous public health problem. These researchers are developing a laboratory animal model that mimics the increased susceptibility to pneumonia that occurs in obese people. They will use the animal model to understand the mechanisms that are responsible for increasing vulnerability to pneumonia, with the ultimate goal of finding new ways to treat the disease, or to prevent it.

#### GEE W. LAU, PHD

University of Cincinnati Medical Center, Cincinnati, OH  
*Research Grant* • Co-funded with the American Lung Association and the American Lung Association of Ohio

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#### Preventing A Deadly Infection In People With Cystic Fibrosis

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***Inactivation Of Vacuolar ATPase By Pseudomonas Aeruginosa Pyocyanin-Relevance To Lung Pathogenesis.*** The objective of this project is to preserve lung function and increase survival in patients with cystic fibrosis (CF)

## OTHER LUNG INFECTIONS

who are infected with an organism called *Pseudomonas aeruginosa*. CF is one of the most common fatal genetic disorders of the Caucasian population in the United States. Its most severe effect is the progressive loss of lung function, which in the majority of cases is caused by chronic lung infection with *P. aeruginosa*. Respiratory failure as a result of this infection is responsible for early death in 80 percent of all CF patients. The organism is a formidable adversary, defying treatment by developing resistance to antibiotics, forming impenetrable barriers, and releasing a great variety of virulence factors. The researchers are studying one of these factors called pyocyanin, a compound that kills bacteria and fungi and injures the body's cells, allowing *P. aeruginosa* to dominate the airways. Little is known about the mechanisms by which pyocyanin does its damage; the goal is to clarify how this occurs, which will provide useful information for developing new and effective treatments to increase long-term survival of people with CF.

### **NELL S. LURAIN, PHD**

Rush Medical College/Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL  
*Clinical Research Grant* • Funded by the American Lung Association of Metropolitan Chicago

### **Protecting Lung Transplant Recipients Against Life-Threatening Infection**

***Pathogenesis Of Cytomegalovirus In Lung Transplantation.*** Cytomegalovirus (CMV) infection is a serious complication of lung transplantation, posing a major threat to long-term survival. The infection is often silent in a person with a normal immune system, but lung transplant recipients are treated with drugs that lower their immunity to prevent the transplanted lung from being rejected. CMV can cause infections that range from mild to life-threatening in such people. Antiviral drugs, while the mainstay of treatment, are costly, may have undesirable side effects, and can lead to the development of drug-resistant strains of the virus. This project is studying lung transplant patients to pinpoint the development of resistance to the antiviral drugs that are typically used to treat CMV infection. The researchers also hope to identify genetic markers to detect strains of the infection that are most likely to cause severe disease, so that only patients who are at greatest risk receive drug treatment.

### **DANIEL W. MARTIN, PHD**

Brody School of Medicine at East Carolina University, Greenville, NC  
*Research Grant* • Funded by the American Lung Association

### **Analyzing A Gene That Plays A Key Role In Potentially Fatal Legionnaire's Disease**

***Analysis Of A Novel Legionella Virulence Factor: An Inducible Peptide Synthetase Required For Growth In Ameba.*** This group is studying and analyzing HigA, a gene they have identified as playing a key part in the development of virulence in *Legionella pneumophila*. This is the organism that causes Legionnaires' disease, a potentially fatal type of pneumonia. Although it is treatable with antibiotics, Legionnaires' disease still carries a significant mortality rate, especially among people who become infected while in the hospital. The HigA gene contributes to the virulence of Legionnaire's disease. When it is disrupted by mutation, *L. pneumophila* is no longer highly infectious in laboratory experiments. Currently, the researchers are determining whether HigA is required for virulence in human peripheral blood monocytes, a type of white blood cell. This line of research may uncover additional factors that play a significant role in causing disease. Analyzing such genes and their products may make it possible to develop better prevention and treatment approaches to *L. pneumophila*.

### **JORDAN P. METCALF, MD**

University of Oklahoma, Oklahoma City, OK  
*Career Investigator Award* • Funded by the American Lung Association of Oklahoma

### **How Does A Common Virus Cause Inflammation In Lung Cells?**

***Signal Transduction And Cytokine Activation By Adenovirus.*** These studies are designed to answer a basic question about how a common virus causes inflammation in the lung. Adenovirus can cause illness, infections and pneumonia in such diverse groups as military recruits, children, patients undergoing organ transplantation, and people with weakened immune systems. It has also been implicated in some forms of chronic lung disease and persistent inflammatory disease, including treatment-resistant asthma in children. To complicate matters even further, adenovirus is also used to

deliver gene therapy. Understanding how adenovirus stimulates cells to produce proteins that are known to cause inflammation is essential to unraveling how this inflammation occurs, and will provide the first step toward defining the best way to manage the disorders that are associated with contact with the virus.

**JESSICA G. MORELAND, MD**

University of Iowa, Iowa City, IA

*Research Grant* • Co-funded with the American Lung Association and the American Lung Association of Illinois-Iowa

**Getting A Grip On How The Immune System Responds To Bacteria That Cause Pneumonia**

***Organism-Specific Neutrophil-Endothelial Cell Interactions In The Pathogenesis Of Pneumococcal Pneumonia.*** Bacterial pneumonia caused by an organism called *Streptococcus pneumoniae* is an extremely common illness, with more than 500,000 cases a year occurring in the United States alone. This group is studying the way in which the disease develops, seeking to gain important insights into how the body's immune system responds to the invading organism. They are examining how the disease-causing bacterium interacts with the lining of the lungs, and what impact those interactions have on the immune system's recruitment of neutrophils to the lungs. Neutrophils are specialized white blood cells that play an important part in protecting against disease. The goal is to identify more precisely how the immune system responds, and the specific bacterial components that are required to trigger that response. Gathering this information may help with future studies directed toward making the response more effective.

**RAJU C. REDDY, MD**

University of Michigan, Ann Arbor, MI

*Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of Michigan

**Strengthening Defenses Against Bacteria In The Lungs**

***Peroxisome Proliferator-Activated Receptor-Gamma Regulates Sepsis-Induced Alveolar Macrophage Deactivation.*** Patients with sep-

sis, or blood poisoning, are highly susceptible to developing infections while they are hospitalized, particularly bacterial infections of the lungs. Increasing resistance to antibiotics and a growing number of people with compromised immune systems, including the elderly, are creating a burgeoning problem. The exact mechanisms that contribute to the development of sepsis-related suppression of the immune system, allowing bacterial organisms to invade the body and cause disease, remain unclear. A number of functional defects in leukocytes, a type of white blood cell, have been identified in sepsis patients. The investigators are seeking to identify a strategy for reversing these changes and improving the functioning of the immune system. The knowledge gained could point the way to new treatments for patients with sepsis that would strengthen lung antibacterial defense.

**YOLANDA SANCHEZ L.-BOADO, PHD**

Wake Forest School of Medicine,  
Winston-Salem, NC

*Research Grant* • Funded by the American Lung Association

**Could Tiny Proteins Called B-Defensins Become A New Kind of Antibiotic?**

***The Role of Matrilysin In The Pathogenesis Of Lung Infection.*** Bacterial infection is a major health concern, partly because new infectious agents that are resistant to currently available antibiotics continue to emerge. However, to date there is no evidence of resistance to defensins, antimicrobial peptides (small proteins). A class of these peptides called b-defensins is expressed by the epithelial cells that line the lungs, where they help defend against infection in the airways. The b-defensins can kill both gram-positive and gram-negative bacteria, as well as yeast and virus infections. The researchers are studying how the anti-infectious activity of these molecules is regulated and generated. These molecules are potentially significant as antibiotics in a variety of situations, including infectious lung diseases. Researchers are focusing on the role of a protein called matrilysin that normally is involved in defending against infections but in cystic fibrosis and other inflammatory diseases may cause damage instead.

## OTHER LUNG INFECTIONS

### TEIJI SAWA, MD, PHD

University of California, San Francisco,  
San Francisco, CA

*Research Grant* • Funded by the American Lung Association and Supplemented by the American Lung Association of California

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#### Developing a New Vaccine To Prevent Bacterial Pneumonia

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##### *Development Of A V-Antigen Vaccine To Prevent Pseudomonas Aeruginosa Infection.*

Despite continuing improvements in available medications and supportive care, bacterial pneumonia is still a major cause of death. These researchers are developing data that may lead to a new vaccine against *Pseudomonas aeruginosa*, the bacterium responsible for many cases of pneumonia. *P. aeruginosa* infection often leads to septic shock and has a higher death rate than other types of pneumonia. These studies are delineating how septic shock associated with *P. aeruginosa* occurs at the molecular and cellular level so that methods can be devised to prevent it through immunization.

### GARY R. WHITTAKER, PHD

Cornell University College of Veterinary  
Medicine, Ithaca, NY

*Career Investigator Award* • Funded by the Northeastern New York Division of the American Lung Association of New York State and the American Lung Association of Central New York

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#### New Ways To Ward Off The Influenza Virus Role Of The Actin Cytoskeleton

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##### *During Influenza Virus Entry Into Polarized Epithelial Cells.*

These studies focus on the influenza virus, one of the most common and potentially deadly lung infections. Influenza is responsible for 20,000 deaths annually in the United States, and new strains of the virus frequently emerge. As is the case with all viruses, influenza first has to enter target cells to cause infection in an individual. The researchers are investigating the entry process of the virus into cells that serve as a model for lung epithelium, or lining. Their results will enhance scientific understanding of the basic biology of the influenza virus. They may also identify potential new targets for anti-influenza treatment that can be used alongside existing drugs and vaccines.

### TODD A. WYATT, PHD

University of Nebraska Medical Center,  
Omaha, NE

*Career Investigator Award* • Funded by the American Lung Association of Nebraska

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#### Preventing The Loss of Cells That Line The Airways Due To Viral Infection

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##### *Protein Kinase C Epsilon: A Regulator Of Ciliated Bronchial Epithelial Cell Attachment.*

Respiratory syncytial virus (RSV) infects almost all children during the first two years of life and is the most frequent cause of bronchiolitis, a condition that is strongly linked with asthma. Viral factors are known to cause worsening of asthma, and RSV is one of the top viruses detected in worsening of childhood asthma. A functional mucociliary apparatus lining the airways is essential for trapping inhaled particles and infectious agents, and clearing them from the lungs. Damage to the epithelial cells that line the airways occurs in many chronic airways diseases, and ciliated bronchial epithelial cells are shed after exposure to virus. It has been shown that RSV induces these ciliated cells to detach. These studies are concerned with understanding the mechanisms that control ciliated cell detachment during viral infection. The information being gathered could make it possible to develop treatments to prevent damage and loss of airway epithelial cells during viral infection in both children and adults. Maintaining the integrity of the airway epithelium could reduce the impact of germs and other toxic substances in the environment.

### AILIANG XIE, MD, PHD

University of Wisconsin – Madison,  
Madison, WI

*Research Grant* • Funded by the American Lung Association of Wisconsin

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#### Does Blood Flow To The Brain Play A Part In Breathing Abnormalities During Sleep?

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##### *Cerebrovascular Mechanisms For Breathing Instability During Sleep.*

Breathing abnormalities during sleep are an important public health problem, due to the high prevalence of sleep apnea in people who are apparently otherwise healthy. Sleep apnea is a condition that involves repeated arousals from sleep because breathing has been momentarily interrupted. It has been identified as a risk factor for high

blood pressure and other cardiovascular diseases. This study is investigating the relationship between brain blood flow regulation and the occurrence of sleep apnea. The researchers are documenting how blood flow to the brain and the brain's responsiveness to carbon dioxide in the arteries can affect or be affected by sleep apnea. A series of studies will be performed on normal humans as well as on patients with heart failure who are unusually susceptible to sleep apnea. Understanding the mechanism of these unstable breathing patterns during sleep will allow a more rational approach to treatment.

**JOHN G. YOUNGER, MD**

University of Michigan, Ann Arbor, MI  
*Career Investigator Award* • Funded by the American Lung Association of Michigan

How Do Gram-Negative Bacteria Evade the Lung Defense System and Cause Pneumonia?

***Klebsiella O-Antigen And The Host-Pathogen Interface During Gram-Negative Pneumonia.***

The aim of this project is to better understand how the lungs defend themselves against bacteria that cause pneumonia, and how harmful bacteria evade those defenses and cause disease. The results may lead to new strategies for preventing and treating pneumonia. The researchers are using genetic engineering techniques to reveal how a bacterium called *Klebsiella pneumoniae* disguises itself during the early stages of lung infection. This bacterium is one of a class of organisms called Gram-negative bacteria that are an important cause of pneumonia, especially in hospitalized patients and those with weakened immune systems. Preliminary experiments suggest an important role for a cluster of bacterial genes that enable the bacterium to 'stealth' itself with an unusual carbohydrate coating (the O-antigen), thereby becoming invisible to host defenses. The results of this work may lead to new strategies for preventing and treating pneumonia.

**JING-REN ZHANG, DVM, PHD**

Albany Medical College, Albany, NY  
*Research Grant* • Co-funded with the American Lung Association and the Northeastern New York Division of the American Lung Association of New York State

Preventing The Most Common Cause Of Bacterial Pneumonia

***Molecular Mechanisms Of Pneumococcal Adherence To Human Lung Epithelium.***

The long-term goal of this research is to prevent pneumococcal pneumonia, which is the most common cause of bacterial pneumonia. Treating this disease with antibiotics has become less effective in recent years, as drug-resistant strains of the bacteria have emerged, and currently available vaccines do not protect against all varieties of pneumococcal pneumonia. The infecting bacterium, *Streptococcus pneumoniae*, attaches itself to the lining (epithelium) of the lungs to cause inflammation and damage to lung tissue. Determining how the bacterium adheres to the epithelial cells that make up the lungs' lining is an essential step toward prevention. This group is identifying the bacterial surface proteins called adhesins that allow the bacteria to cling to the epithelium. These adhesins could be the key to developing more effective vaccines for both pneumococcal pneumonia and other pneumococcal infections in the future.



# COPD, SMOKING,

Smoking is the major cause of COPD, and air pollution also makes a significant contribution to its development. 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 22.6 percent in 2001, and in accomplishing important reductions in air pollution during the same time frame. Nevertheless, almost one quarter of adults still smoke, until recently teenage smoking has been on the rise, and the American Lung Association estimates that the air people breathe in 55 percent of counties with ozone monitors throughout the United States is a danger to health.

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. Some projects are focused on the potential roles of anti-inflammatory drugs and antioxidant vitamins. Others are studying the muscles of breathing in COPD, since muscle weakness is thought to be a cause of breathlessness in this disease. Very early basic studies are examining how stem cells may be converted into lung cells, a possible approach to growing new lung. Patient centered studies are addressing such questions as the best way to assess quality of care. Other investigations centered on smoking range from the basic mechanisms of damage by smoke to the way in which secondhand smoke causes respiratory infections in children, plus a wide spectrum of approaches to smoking cessation.

# AND AIR POLLUTION

## ZSUZANNA BEBOK, MD

University of Alabama, Birmingham, Birmingham, AL

*Research Grant* • Funded by the American Lung Association

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### How Does Chronic Inflammation Develop In The Respiratory Tract?

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***Alterations Of Membrane Protein Trafficking In Airway Epithelia By Reactive Oxygen Nitrogen Species.*** These researchers are seeking new insight into the way chronic inflammatory lung diseases develop. Chronic inflammation is an important factor in COPD (chronic obstructive pulmonary disease), which includes emphysema and chronic bronchitis and afflicts millions of Americans. The precise role of inflammation in the development of COPD has not yet been clearly defined, but it is well known that chronic inflammation does irreversible damage to the lining of the respiratory tract (epithelium). The investigators are studying the way in which increased production of nitric oxide in the body, and the resulting formation of compounds called reactive species, may be involved in the inflammatory process. They have shown that reactive species derived from nitric oxide can decrease the levels of a protein known as CFTR. Decreasing CFTR levels alters its ability to regulate the functions of the epithelium. If these studies can clarify the mechanism by which reactive species decrease CFTR and thus alter certain functions of the cells that make up the epithelium, new treatments might be developed to help prevent irreversible damage to the epithelium.

## YIN CHEN, PHD

University of California, Davis, Davis, CA

*Research Training Fellowship* • Funded by the American Lung Association of California

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### Why Do Mucous Cells Run Amok In Airway Diseases?

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***Transcription Profiling In Cytokine-Induced Mucous Cell Hyperplasia/Metaplasia.*** This project is focusing on the underlying mechanism involved in the excessive secretion of mucus that is characteristic of many chronic diseases involving the airways. As with many biological processes, mucous cell hyperplasia (abnormal increase in the number of cells) and metaplasia (change in the type of cell to a form that is not normal) is regulated at multiple

steps, and many genes are involved. Using the latest technology to gather data, the researchers are constructing a panoramic view of changes in gene expression relating to mucous cell hyperplasia/metaplasia. This information will be valuable in developing treatments to reduce or even eliminate mucus hypersecretion in a variety of airway diseases.

## DANIEL L. CLEMANS, PHD

Eastern Michigan University, Ypsilanti, MI

*Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of Michigan

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### Preventing Airway Destruction Caused By Inflammation

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***Haemophilus Influenza Moduline In Chronic Obstructive Pulmonary Disease Airway Inflammation.*** COPD is the fourth most common cause of death in the United States, and its annual toll continues to rise. An organism called Nontypeable *Haemophilus influenzae* (NTHi) is the most common cause of exacerbations of COPD, and can also cause complications in patients with chronic bronchitis and cystic fibrosis. These exacerbations are characterized by inflammation and the accumulation of polymorphonuclear leukocytes (PMN), a type of white blood cell, in the lungs. The mechanisms by which NTHi stimulates the epithelial cells that line the lungs to bring on the inflammatory response, and the sequence of events that leads to progressive destruction of the airways, remain unclear. These researchers are elucidating precisely how inflammation occurs in response to NTHi infection. The insight gained from their laboratory investigations should pave the way for future clinical research, and could lead to more effective treatment strategies that limit NTHi respiratory diseases.

## DAVID S. CRISWELL, PHD

University of Florida, Gainesville, FL  
*Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of Florida

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### Can Vitamin E Help Patients On Breathing Machines?

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***Aging, Oxidant Stress, And Mechanical Ventilation-Induced Diaphragmatic Contractile Dysfunction.*** Mechanical ventilation (MV) with a breathing machine is a life-saving intervention for many critically ill patients. Paradoxically, this procedure causes the diaphragm, which is the body's principal muscle for breathing, to weaken and atrophy. Many MV patients have trouble breathing on their own when the ventilator is removed, due to weakness and wasting of the diaphragm. This research is studying factors that predispose some people to difficulties in coming off the respirator, such as age. The investigators are also exploring the mechanisms that are responsible for MV-induced diaphragm weakness. They are testing the hypothesis that oxidative stress plays a key role in weakening the diaphragm during MV and the normal aging process, and that treating MV patients with the antioxidant vitamin E can prevent oxidative stress. If this proves to be true in laboratory animals, it has important implications regarding antioxidant therapy in MV patients.

## SAMUEL EVANS, MD

University of California, Davis Medical Center, Sacramento, CA  
*Research Training Fellowship* • Funded by the American Lung Association of California

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### How Does Cigarette Smoke In The Environment Trigger Coughing In Children?

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***Chronic Environmental Tobacco Smoke In Young Guinea Pigs Augments Coughing Via Neuroplasticity In The CNS.*** Exposure to cigarette smoke is indisputably responsible for substantial adverse effects on respiratory health in children. Infants and children raised with exposure to environmental tobacco smoke (ETS) have an increased risk of developing respiratory diseases, with coughing as a frequent and prominent symptom. Smoke exposure is also associated with the early development and increased severity of asthma. Yet little is known about the fundamental

mechanisms underlying the association between ETS and increased respiratory disease. These researchers are studying the cough reflex in laboratory animals to better understand its central mechanisms, and to determine precisely how exposure to ETS initiates coughing. This knowledge may open up new lines of inquiry into regulating cough, and new treatment strategies.

## VINCENT S. FAN, MD, MPH

University of Washington, Seattle, WA  
*Research Training Fellowship* • Co-funded with the American Lung Association and the American Lung Association of Washington

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### Better Care For Patients With COPD

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***Assessing Quality Of Care In Chronic Obstructive Pulmonary Disease.*** Chronic Obstructive Pulmonary Disease (COPD) is progressive, and treatment primarily involves relieving its symptoms to maintain the best possible quality of life. People with COPD typically require a number of outpatient visits and hospitalizations as their physical ability declines. Death rates continue to increase, especially among women. This project seeks to establish better ways to identify people who have COPD, and to determine which of them have the greatest risk of worsening disease and are most likely to need hospitalization. Establishing more accurate guidelines will lead to improved strategies to minimize the need for hospitalization. It will also provide a framework for assessing how well care is being delivered, and for guiding health professionals in selecting the appropriate medications and dosages.

## RAMZI KAFOURY, MPH

Jackson State University, Jackson, MS  
*Research Grant* • Funded by the American Lung Association of Mississippi

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### Inhaling Ozone And Particulate Matter May Be A Double Whammy For The Lungs

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***Studying The Effect Of Environmental Exposures On Cell Function.*** This study is investigating the interaction of the epithelial cells that form the lining of the lungs with both ozone and particulate matter (PM) in the environment. Exposure to ozone or PM and their effect on the lungs have previously been

addressed as separate problems. However, ozone and PM may be coupled in the ambient air, and the coupling may be an important determining factor of the urban levels of both ozone and PM. Ozone is a major component of smog and is known to adversely affect the lungs when inhaled. Inhaling PM has been reported to cause airway inflammation in animals, and evidence suggests that exposure to PM correlates with increased acute and chronic respiratory illness, and with worsening of asthma. This study will provide important information about the effect of exposure to ozone coupled with particulate matter on epithelial cell function.

## **ULYSSES J. MAGALANG, MD**

State University of New York at Buffalo,  
Amherst, NY

*Research Grant* • Funded by the American Lung Association of New York State

### **Finding New Ways To Treat Breathing Problems Related to Obesity**

***Chemoreceptive Transduction Pathways Mediating Hypoxic Ventilatory Depression In Experimental Obesity.*** Obesity is a chronic disease that contributes to a number of medical conditions, including respiratory problems. It has profound effects on the respiratory system, predisposing obese people to develop a condition called obesity hypoventilation syndrome (OHS), in which a reduced amount of air enters the alveoli, the lungs' tiny air sacs. This group is using laboratory animals to study the reduced response of the respiratory system in obese individuals to acute hypoxia and to excess carbon dioxide in the blood (hypercapnea). New insight into the neurobiological basis of the depressed hypoxic ventilatory response may provide insight into developing new treatment strategies for obesity-related conditions such as OHS.

## **BERND W. MEIBOHM, PHD**

University of Tennessee Health Science  
Center, Memphis, TN

*Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of Tennessee

### **Identifying Which Drug Helps Each Patient The Most**

***Gene Expression Of Molecular Mediators Of Inflammation In COPD.*** Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States, exceeded only by heart attack, cancer and stroke. This project is targeted toward identifying biomarkers that are characteristic of the development and progression of COPD in individual patients, and that will indicate each person's response to anti-inflammatory medication. Using minimally invasive techniques and gene expression profiling the researchers are studying cells from different groups of COPD patients to pinpoint appropriate biomarkers. The biomarkers will be used to identify which individuals will benefit the most from prolonged treatment with anti-inflammatory drugs, and monitoring treatment with biomarkers will allow dose adjustment for optimum results. This approach will result in a more focused and individualized treatment plan, which has the potential to improve lung health, daily functioning and quality of life.

## **ENID R. NEPTUNE, MD**

Johns Hopkins University School of  
Medicine, Baltimore, MD

*Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of South Carolina

### **Studying New Substances For Better Control Of Emphysema**

***Therapeutic Utility Of TGFbeta Antagonism For Murine Models Of Emphysema.*** The number of Americans who suffer from Chronic Obstructive Pulmonary Disease (COPD) is steadily increasing, and so is the number of lives claimed each year by emphysema and chronic bronchitis. COPD is now the fourth-ranking cause of death in this country, surpassed only by heart attack, cancer, and stroke. During the past ten years, few nonsurgical treatments for COPD have been investigated, but during this time scientists have developed

increased understanding of the cause and evolution of emphysema, the most serious form of COPD. This group is studying the role of substances known as Transforming Growth Factor beta (TGFb) in the disease process that leads to emphysema. The data they generate may lead to new treatment approaches involving modulating TGFb signaling to alter the severity of emphysema.

## **WADE A. NICHOLS, PHD**

Illinois State University, Normal, IL  
*Research Grant* • Funded by the American Lung Association of Illinois-Iowa

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### **Keeping COPD Under Better Control**

#### ***The Role Of Haemophilus Parainfluenzae In Chronic Obstructive Pulmonary Disease.***

Chronic obstructive pulmonary disease (COPD) is one of the most common causes of death in the United States and worldwide. Exacerbation, or worsening, of COPD frequently coincides with the presence of bacteria in the airways. The goal of this project is to better understand the interactions with bacteria that occur in people who have COPD, and to delineate their role in COPD exacerbation. It is known that Haemophilus influenzae, the germ that causes flu, can worsen COPD. A related bacterium called Haemophilus parainfluenzae has also frequently been found in COPD patients experiencing an exacerbation. The scientists are studying this bacterium to determine whether it possesses either the ability to bind to the lining (epithelium) of the respiratory tract, or to promote an inflammatory response. The resulting information will be valuable in developing better treatment and prevention that will keep COPD under control.

## **KOLAWOLE OKUYEMI, MD, MPH**

University of Kansas Medical Center, Kansas City, KS  
*Research Grant* • Funded by the American Lung Association of Kansas

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### **Helping The Homeless To Quit Smoking**

#### ***Smoking Cessation Among The Homeless.***

Tobacco use, especially cigarette smoking, is the leading cause of preventable death in the United States. While smoking has declined significantly among adults in this country, smoking rates remain substantially higher among

certain segments of the population, including those below the poverty line. Smoking cessation programs have largely excluded the homeless. The primary goal of this project is to further the understanding of smoking among the homeless and identify acceptable and effective methods for reducing smoking in this population. A series of focus groups with homeless persons is providing data on their perceptions about smoking, barriers to quitting, and treatment preferences for quitting. A pilot study will assess the value of providing nicotine patches combined with counseling to help the homeless quit smoking.

## **THOMAS O'ROURKE, PHD, MPH**

University of Illinois – Champaign, Champaign, IL  
*Research Grant* • Funded by the American Lung Association of Illinois-Iowa

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### **Does A Telephone Quitline Help People Stop Smoking?**

#### ***Tobacco Quitline Study – American Lung Association Of Illinois.***

This study is evaluating the American Lung Association of Illinois Quitline by means of a telephone survey to a random sample of Quitline callers. They will be asked to assess the Quitline, the counselors, the Quit materials, and their smoking behavior. A random sample of people who call within a five month period will be selected, with a goal of 600 completed telephone interviews. Five hundred interviews will be from the general population, and 100 will be from the Veterans Administration population. In addition to the overall assessment, those surveyed will be asked specific questions depending upon whether they are still smoking or have quit.

## **OMOWUNMI Y. O. OSINUBI, MD**

UMDNJ-Robert Wood Johnson Medical School, Piscataway, NJ  
*Clinical Research Grant* • Funded by the American Lung Association of New Jersey

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### **Facing Surgery May Help Motivate Smokers To Quit**

#### ***Smoking In Preoperative Patients: An Intervention Study.***

A fundamental reason smokers give for quitting is concern for their health. Patients about to undergo surgery have an increased level of health awareness, sug-

gesting that such individuals may be more likely to be receptive to smoking cessation counseling than smokers in general. This project will compare two groups of pre-surgical patients, one of which will receive a standard pre-anesthesia evaluation by an anesthesiologist. The other group will receive a counseling intervention based on a physical examination during the pre-anesthesia evaluation. The goal of the intervention is to motivate smokers to quit for 24 hours prior to surgery, and to enroll in a smoking cessation program. The investigators will compare smoking cessation rates between the two groups to assess the impact of the pre-anesthesia motivational intervention on quit rates immediately before surgery, and in promoting long term smoking cessation.

## **HOLGER J. SCHUNEMANN, MD, PHD**

State University of New York at Buffalo, Buffalo, NY

*Research Grant* • Funded by the American Lung Association of New York State and the American Lung Association of Western New York

### **Do Anti-Oxidant Vitamins Help Preserve Lung Function?**

**Clinical Epidemiology Of Pulmonary Function.** Oxidative stress is believed to have a negative impact on lung function, both in the general population and in people who have COPD (chronic obstructive pulmonary disease, including emphysema and chronic bronchitis). Nutritional factors that counteract oxidative stress, such as anti-oxidant vitamin supplements, could be central in preventing impairment of lung function, whereas nutritional factors that increase oxidative stress may have negative effects. This research is examining the links between antioxidant vitamin intake, other lifestyle factors, and lung function and airway obstruction. The results will improve understanding of the role of antioxidant vitamin intake and other factors such as alcohol intake on lung function, and provide a scientific basis for public health information to help prevent lung disease.

## **EDWIN K. SILVERMAN, MD, PHD**

Brigham and Women's Hospital, Boston, MA  
*Career Investigator Award* • Funded by the American Lung Association

### **New Genetic Clues To Identify People At Risk For Emphysema**

#### **Positional Candidate Genetic Association Studies In COPD.**

Chronic obstructive pulmonary disease or COPD, which includes emphysema and chronic bronchitis, is a major cause of illness and death, and it is on the rise. Designing better treatments and preventing its development requires an improved understanding of its causes. It is well known that although cigarette smoking is a major risk factor for developing COPD, many smokers never get this disease, while a small number of non-smokers do get it. One important genetic risk factor for COPD was identified years ago, but no others have been proven. This study is looking at families of individuals who developed severe COPD at an early age, seeking new genetic factors that predispose a person to develop COPD. If such risk factors can be identified, scientific understanding of the mechanisms leading to COPD would improve, new treatments could be developed, and susceptible individuals could be identified, improving both treatment and prevention of this devastating illness.

## **AKSHAY SOOD, MD, MPH**

Southern Illinois University School of Medicine, Springfield, IL

*Clinical Research Grant* • Funded by the American Lung Association of Illinois-Iowa

### **Is A Reactive Telephone Helpline An Effective Tool For Smokers Who Want To Quit?**

#### **Effectiveness Of A Reactive Telephone Helpline For Smokers.**

The American Lung Association of Illinois has launched a telephone line to help smokers quit. These researchers are evaluating the effectiveness of this "reactive" telephone line, in which smokers around the country call the helpline for assistance. Callers are randomly assigned to two groups, with one group receiving self-help literature only and the other group receiving literature plus telephone counseling. The two groups are being compared by means of follow-up calls at regular intervals, to examine rates of abstinence, attempts made to quit,

changes in the extent of smoking, and cost-effectiveness of the program. The results will provide much needed information regarding the public health significance of this type of helpline as a relatively low intensity and low cost tool to assist smokers in quitting. Given the large number of smokers who want to stop, establishing the program's effectiveness is critical to determining its value compared to other smoking cessation approaches, and to clarifying whether committing more resources to expand it is justified.

## **JAGADEESHAN SUNDERRAM, MBBS**

University of Medicine & Dentistry of New Jersey – Robert Wood Johnson Medical School, New Brunswick, NJ

*Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of New Jersey

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### **The First Step Toward Better Treatment Of Deadly Oxygen Deprivation**

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#### ***Role Of Heme Oxygenase In The Cardiorespiratory Adaptations To Chronic Hypoxia.***

Chronic hypoxia, or oxygen deprivation, occurs in a number of chronic lung, cardiovascular and sleep disorders, from chronic obstructive pulmonary disease (COPD) to sleep apnea to sudden infant death syndrome (SIDS). Specific sites in the body sense hypoxia, and cause changes and adaptations to survive for prolonged periods. Defining the basic cellular mechanisms that determine these adaptive responses will increase scientific understanding of how adverse respiratory and cardiovascular consequences occur in some people. The researchers hypothesize that a protein called heme oxygenase (HO-1) is critical in adaptive responses to chronic hypoxia, and that variations in its induction may explain why some people have maladaptive responses. Their goal is to clarify the role of this and other proteins, the first step toward prevention and early detection of lung and cardiac disease involving chronic hypoxia. These studies could lead to the development of screening tools for maladaptive responses, offering the possibility of early treatment, either by replacing the protein or the gene involved in the production of the protein.

## **ROBERT VASSALLO, MD**

Mayo Clinic, Rochester, MN

*Research Grant* • Funded by the American Lung Association

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### **Does Smoking Change The Immune System's Ability To Protect Against Disease?**

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#### ***Effects Of Cigarette Smoking And Nicotine On Dendritic Cell Functions.***

A particular type of cells called dendritic cells have a critical role in the body's immune system and how it responds to disease-causing invaders. This group is examining how cigarette smoking and nicotine alter the function of dendritic cells. Their findings may have significant implications regarding how cancers and other diseases caused by smoking come about. By identifying specific molecular defects in the dendritic cells of smokers, it could be possible to develop new strategies for treating cancer. Information is also being sought about the effect of smoking on dendritic cell vaccines, which are currently being investigated as a new way to treat various kinds of cancer. This project may reveal whether such vaccines are likely to be less effective if the person being treated is a smoker. Information about the effects of cigarette smoking on dendritic cells in the lungs will also be relevant to how asthma develops, as well as to other serious lung diseases related to smoking.

## **PING M. WANG, PHD**

Georgia Institute of Technology, Atlanta, GA

*Research Grant* • Funded by the American Lung Association of Georgia

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### **How Do Lung Cells Respond To Tobacco Smoke?**

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#### ***Microscopic Study Of Effects Of Tobacco Smoke In The Lung.***

The goal of this study is to develop a better understanding of how cells in the lungs respond to tobacco smoke, and to provide a scientific basis for estimating the risk of developing tobacco-induced lung disease at the cellular level. The researchers are using novel microscopic techniques to identify intracellular signals, and to examine the damage sites caused by tobacco smoke in the lungs. They are studying for the first time how cells in the lining of the lungs and inflammatory cells in the lungs respond to the presence of tobacco smoke. The knowledge gained will provide

increased understanding of diseases that result from the presence of tobacco smoke in the lungs. It may also be valuable in clarifying how air pollutants and other products that reach the lungs affect lung cells, and how they are cleared from the lungs.

## **FADI XU, MD**

University of Kentucky College of Medicine,  
Lexington, KY

*Career Investigator Award* • Funded by the American Lung Association

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### **Searching For Better Treatment When The Lungs Fail To Supply Enough Oxygen**

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**Central Interaction Of Respiratory Afferents In Breathing.** The basic function of the lungs is ventilation, which is controlled by the central nervous system and involves the exchange of oxygen and carbon dioxide that is essential to life. Inflammation of the airways decreases the ability of the lungs to supply oxygen, resulting in hypoxia. Patients with airway inflammation and hypoxia frequently have difficulty breathing and can experience respiratory failure. Some patients with chronic bronchial asthma or obstructive pulmonary diseases have abnormalities in control of breathing by the central nervous system, and it is well established that the ventilatory response to hypoxia is significantly reduced in asthmatics. These studies are examining the mechanisms by which the respiratory response is controlled, and elucidating precisely how the interactions involved are mediated by the central nervous system. The results should yield new and important insights that will lead to better treatment of respiratory difficulty in patients with airway inflammation and hypoxia.

## **SERGEY I. ZHARIKOV, PHD**

University of Florida, Gainesville, FL

*Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of Florida

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### **Studying How The Body Regulates Nitric Oxide Production May Offer Clues To Treatment**

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**Regulation Of L-Arginine Transport And Nitric Oxide Production In Lung Endothelial Cells By Caveolar Kinases.** A number of lung diseases, including chronic obstructive pul-

monary disease (COPD) and primary pulmonary hypertension (high blood pressure involving the arteries in the lungs), are characterized by impaired production of a substance called vascular nitric oxide. An important regulatory factor for nitric oxide production has recently been identified, and these researchers are now studying how this mechanism functions. Their investigations may point the way to new treatment possibilities for correcting impaired nitric oxide production.

Tuberculosis remains an important disease in the United States and a worldwide epidemic that kills some 2 million people each year. Since it is relatively easy to transmit and more and more people are immigrating 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 of TB internationally, as the two infections often coexist. There is presently no totally satisfactory means of treating TB.

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. Studies of patients are exploring the genetic basis for increased TB infection and more severe disease in certain ethnic groups. Other studies are seeking to understand how the body's immune system protects against TB and why this defense system sometimes fails, which will provide a solid foundation for developing a better vaccine.

# TUBERCULOSIS

## **SAMUEL M. BEHAR, MD, PHD**

Harvard Medical School, Boston, MA  
*Career Investigator Award* • Funded by the American Lung Association

### The Quest For Better Tuberculosis Vaccines

***CD8+ T-Cells And Their Role In Protective Immunity To Tuberculosis.*** Tuberculosis is currently responsible for 2 millions of deaths worldwide each year, with more individuals now infected than at any other time in the history of the world. One of the factors contributing to this epidemic is the lack of a widely effective vaccine. Using a specialized animal model developed in their laboratory, the researchers are investigating the role of a class of cells called CD8+ T-Cells in providing immunity against tuberculosis. It is known that these cells contribute to immunity, but little information exists about how they function or what antigens they recognize. Antigens are substances that stimulate the formation of antibodies, proteins the body's immune system develops as a protective mechanism. The information generated by these studies may prove useful in the design and testing of better vaccines.

## **MIRIAM S. BRAUNSTEIN, PHD**

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

### Does A Specific Protein Help Tuberculosis Germs Survive And Grow When They Reach The Lungs?

***The Role Of The Accessory Secretion Factor SecA2 In Mycobacterium Tuberculosis Pathogenesis.*** Lung disease is the most common manifestation of tuberculosis, and it is responsible for transmitting *M. tuberculosis*, the bacterium that causes the disease. When someone inhales an airborne substance containing *M. tuberculosis*, the bacteria are deposited in the alveoli, the small air sacs in the lungs. There they are taken up by specialized cells called alveolar macrophages. The ability of *M. tuberculosis* to survive and grow within macrophages is essential to the development of disease. Understanding how it resists attack by macrophages will influence future approaches to controlling tuberculosis. These researchers are examining whether a protein called SecA2

promotes the growth and survival of *M. tuberculosis* in macrophages, and the process by which this takes place. The information generated by their studies will expand scientific understanding of the mechanisms that allow the disease to develop and may help develop new treatment strategies.

## **DAVID CANADAY, MD**

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

### How Do Tuberculosis Germs Hide Inside The Body?

***Antigen Processing Of M.Tuberculosis Infected Human Macrophages: Modulation By Chronic Infection And Cytokines.*** A major obstacle to preventing tuberculosis is that *M. tuberculosis*, the organism that causes it, has the ability to hide from the body's immune system. One of the possible ways it may be able to become latent, lying hidden within a person, is to conceal itself in macrophages, a particular type of cell, thus evading the CD4+ T-Cells of the immune system that protect against invading organisms. These studies are developing a better understanding of how this takes place in chronically infected macrophages. The information being generated could lead to a more rational design of a tuberculosis vaccine.

## **EDWARD D. CHAN, MD**

National Jewish Medical Center, Denver, CO  
*Career Investigator Award* • Funded by the American Lung Association

### Why Does Natural Immunity Against Tuberculosis Sometimes Fail?

***Lipoarabinomannan And Interleukin-4 Re-gulation Of Nitric Oxide.*** Macrophages are white cells in the body's tissues that have the ability to kill *Mycobacterium tuberculosis*, the microbe that causes tuberculosis, or at least to keep it in check. When the macrophages fail to accomplish this, the result is active tuberculosis infection, most often in the lungs. These researchers are examining certain molecules on the outer covering of mycobacteria that can elicit specific responses from the macrophages. They are seeking to determine how nitric oxide, a potent antibacterial agent

produced by macrophages, is induced, and how a substance called interleukin-4 that is produced by the immune system's T-cells inhibits this process. The results of these studies will provide greater understanding of the body's innate immunity against tuberculosis that is conferred by macrophages, and why it sometimes fails. Building on this information, future studies can be designed that will lead to better treatment options.

#### JOHN L. DAHL, PHD

Washington State University, Pullman, WA  
*Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of Washington

#### Investigating The Role Of The *relA* Gene In Suppressing Tuberculosis Germs

***Identifying Mycobacterium Tuberculosis Genes Required For Dormancy Within The Host.*** More people die of tuberculosis today than at any other time in history, despite the fact that for 50 years it has been a detectable and treatable disease. It is responsible for about 2 million deaths each year worldwide and approximately one third of the world's population harbor *M. tuberculosis*, the germ that causes the disease. Many people who are infected do not develop active tuberculosis disease, because the body's immune system keeps the infection under control, and the bacterium remains dormant in their bodies. These studies address the issue of bacterial dormancy, in which *M. tuberculosis* is suppressed but lies in wait for the body's defenses to fail. The researchers have found that a gene called *relA* has a critical role in maintaining bacterial dormancy. They believe the *M. tuberculosis relA* gene performs a similar function, and are seeking to define it and to better understand the molecular mechanisms involved in dormancy. Increased scientific understanding of *M. tuberculosis* dormancy can be applied to finding new targets for treatment, and better vaccines.

#### JOANNE L. FLYNN, PHD

University of Pittsburgh School of Medicine, Pittsburgh, PA

*Career Investigator Award* • Funded by the American Lung Association

#### Designing An Effective Tuberculosis Vaccine

***CD4+ T-Cells In Acute And Persistent Tuberculosis.*** Tuberculosis is responsible for about 2 million deaths worldwide annually, despite the fact that it can be successfully treated with antibiotics. Many people who are infected with the microbe that causes tuberculosis do not have adequate access to treatment, or are unable to comply with a lengthy treatment program that can involve taking as many as four different drugs daily for up to a year. Vaccination against tuberculosis is the only definitive answer to this enormous problem, but the currently available vaccine is not generally effective. The goal of these studies is to elucidate the means by which the body's immune system protects against tuberculosis, which will provide a solid foundation for developing a better vaccine. The researchers are investigating the role and function of the CD4+ T-Cell, an immune system cell that is known to be involved in protecting against tuberculosis. A series of experiments to determine precisely how CD4+ T-Cells perform this function will yield useful knowledge for designing a vaccine against tuberculosis.

#### KURT A. HELDWEIN, PHD

Boston University Medical Center, Boston, MA

*Research Training Fellowship* • Co-Funded with the American Lung Association and the American Lung Association of Massachusetts

#### The Quest For New Ways To Control Tuberculosis When Antibiotics Fail

***Toll-Like Receptors And Host Defense Against Mycobacterium Tuberculosis.*** In recent years, multidrug-resistant strains of tuberculosis have emerged, complicating treatment with the currently available antibiotics that are used against *Mycobacterium tuberculosis*, the microbe that causes tuberculosis infection. These researchers are investigating an immune system-based approach to tuberculosis treatment, which could augment existing antibiotic-based treatment, and may also provide a means to control antibiotic-resistant

tuberculosis. They are studying the immune mechanisms that are critically involved in the body's defense against tuberculosis, in particular the role of a newly discovered class of receptors called toll-like receptor (TLR) proteins. Their preliminary findings suggest that TLR proteins are important in the body's ability to recognize *M. tuberculosis*, and in the way the immune system reacts to this invader. Currently, they are determining precisely how TLR proteins and the cellular responses that depend on them function in immune responses against *M. tuberculosis*.

## RUSSELL K. KARLS, PHD

University of Georgia College of Veterinary Medicine, Athens, GA

*Research Grant* • Funded by the American Lung Association of Georgia

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### Understanding How Tuberculosis Infection Hides Within The Body

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**Regulation Of Mycobacterium Tuberculosis Sigma Factor C and Identification Of SigC-Transcribed Genes.** These studies will provide insight into the factors that contribute to the persistence of *Mycobacterium tuberculosis* in the body following infection. The investigators are examining the role of a secondary sigma factor called SigC in mycobacterial adaptation to host defenses. Understanding of how this occurs could lead to a diagnostic test to identify active or latent tuberculosis infection, and might also pinpoint new targets for treatment.

## DAVID M. LEWINSOHN, MD, PHD

Oregon Health Sciences University, Portland, OR

*Career Investigator Award* • Funded by the American Lung Association

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### How Do Cytotoxic T-Cells Defend Against Tuberculosis?

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**Recognition Of Mtb-Infected Cells By DC8+ T-Lymphocytes.** The most effective strategy for wiping out tuberculosis is to develop an improved vaccine. Scientists know that the bacterium that causes tuberculosis resides within normal immune system cells called macrophages. T-lymphocytes, another component of the immune system, identify the infected cells so they can be eliminated. A precise understanding of how the T-Cells respond to

the presence of the tuberculosis bacterium is of central importance to the quest for a more effective vaccine. This project is studying cytotoxic T-Cells, a type of T-Cell that is essential in immunity against viruses and tumors. Since little is known about their role in defending against tuberculosis, defining the manner in which certain cytotoxic T-Cells recognize cells that are infected with tuberculosis is crucial to the process of developing a better vaccine.

## LAKSHMI RAMACHANDRA, PHD

Case Western Reserve University, Cleveland, OH

*Research Grant* • Co-Funded with the American Lung Association and the Asociación Puertorriqueña Del Pulmón

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### Developing Strategies To Maximize T-Cell Protection Against Tuberculosis

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#### **Mycobacterium Tuberculosis Antigen Processing And Its Inhibition By Live Bacilli.**

Fighting tuberculosis remains a high priority, since between 10 and 15 million people in this country are infected with *Mycobacterium tuberculosis*, the organism that causes tuberculosis. About ten percent of them will develop active tuberculosis infection. Current vaccines are not highly effective, and new vaccination strategies are needed. Developing strategies that maximize the protective responses of T-Cells, a component of the body's immune system, requires understanding precisely how antigens derived from *M. tuberculosis* are processed by cells to activate the immune system. An antigen is a substance that stimulates T-Cells and the formation of antibodies, protein substances that protect against infection. The goal of these studies is to elucidate the mechanisms of mycobacterial antigen processing, and the factors that contribute to inhibiting it. The investigators will clarify the basis of the T-Cell response to *M. tuberculosis* and point the way to new means of eliciting protective T-Cell immunity.

**PETER C. SAYLES, PHD**

Trudeau Institute, Saranac Lake, NY  
*Research Grant* • Funded by the American Lung Association of Central New York and North-eastern New York Division of the American Lung Association of New York State

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**Developing More Effective Tuberculosis Vaccines**


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***Characterization Of ESAT-6 Peptide-Specific T-Cell Recruitment Into The Lung Of Immunized Mice.*** Tuberculosis causes more deaths worldwide than any other infectious disease, and over one-third of the world's population are infected with *Mycobacterium tuberculosis*, the germ that causes the disease. People in many parts of the world have been immunized against tuberculosis with a vaccine called BCG, but its effectiveness has varied widely. Furthering understanding of how immunization works at the cellular level will contribute to lung immunology, which is essential in developing more effective vaccines for tuberculosis and other lung diseases. It has been shown that specific components of the immune system called CD4 T cells are involved in protecting against tuberculosis. These studies are carrying this work a step further by characterizing the response of T cells to a specific antigen, or foreign substance in the body. Their work in elucidating the complexity of the immune system will lead science further down the road to prevention of tuberculosis.

**CHRISTOPHER J. SCHWAB, PHD**

University of New Mexico School of Medicine, Albuquerque, NM  
*Research Training Fellowship* • Co-funded with the American Lung Association and the American Lung Association of Arizona/New Mexico

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**How Do The Body's Dendritic Cells React When They Spot The Germ That Causes Tuberculosis?**


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***Mycobacterium Tuberculosis And Lung Dendritic Cell Interaction: Role Of Toll-Like Receptors And Prostaglandin E2.*** These studies are asking important questions about the way an individual's immune system responds to *Mycobacterium tuberculosis* (Mtb), the germ that causes tuberculosis. The researchers are examining how a class of cells in the body called dendritic cells interacts with the invading germ. They are determining which cells spread

the tuberculosis germ in the body, where the organism is transported, and how the immune system is alerted to its presence. A better definition of this process could lead to targets for developing new drugs for treating or even preventing tuberculosis. The effects of asthma on the dendritic cell response to the tuberculosis germ are also being investigated. Asthma's dramatic rise in this country is occurring at the same time that tuberculosis is reemerging as a significant problem, and knowing more about how these two conditions interact could benefit numerous patients in the future.

**HOLLY M. SCOTT, BS**

University of Pittsburgh School of Medicine, Pittsburgh, PA  
*Lung Health Research Dissertation Grant* • Funded by the American Lung Association of Pennsylvania

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**How Does The Immune System Keep Tuberculosis Infection From Becoming Active?**


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***TNF-Alpha Effects On Cell Migration To The Lung In Tuberculosis.*** The majority of people who are infected with tuberculosis never develop active disease because their immune systems mount an effective response to the invading organism. This response requires the formation of a granuloma, a cellular structure within the lungs that physically contains the germ that causes tuberculosis and allows the immune system to prevent it from growing and spreading. The goal of this project is to determine which chemical signals are necessary for granuloma formation. The scientists hypothesize that a substance called tumor necrosis factor-alpha is an important signal for calling immune cells to the lungs during infection, and are testing this hypothesis in a series of experiments.

**RICHARD F. SILVER, MD**

Case Western Reserve University School of Medicine, Cleveland, OH  
*Career Investigator Award* • Co-Funded with the American Lung Association and the American Lung Association of Ohio

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**How Do White Blood Cells Travel To The Lungs And Eliminate Tuberculosis Germs?**


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***Pulmonary Immune Responses To Mycobacterium Tuberculosis.*** Tuberculosis remains a major threat to international public health and

is the single greatest cause of preventable death in the world today. Even so, the majority of otherwise healthy people who are infected with the microbe that causes tuberculosis never develop active disease. This is due to the immune system's ability to effectively contain the organism and is likely to involve lymphocytes, white blood cells that specifically guard against infection. The investigators are assessing how these protective cells migrate into the lung and how they function to eliminate the infecting organism. These scientific insights are essential to ongoing efforts to develop a more effective vaccine against tuberculosis than the one that is currently available.

## **RONGGAI SUN, DVM, PHD**

Johns Hopkins University School of Medicine, Baltimore, MD

*Research Training Fellowship* • Co-Funded with the American Lung Association and the American Lung Association of Southeast Florida

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### **Could The Germ That Causes Tuberculosis Also Protect Against It?**

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***Studies Of Mycobacterium Tuberculosis Sigma Factor SigC: Genomics, Pathogenesis, And Prevention.*** SigC is a key regulatory gene in *Mycobacterium tuberculosis*, the microbe that causes tuberculosis infection. Because SigC is necessary for virulence, studying it and the genes it controls should yield important data on *M. tuberculosis* virulence mechanisms and how they regulate virulence. Initial data developed by this group suggest that SigC mutants may have valuable properties as a potential new vaccine against tuberculosis.

## **ILDIKO VAN RHIJN, PHD**

Brigham and Women's Hospital, Boston, MA  
*Research Training Fellowship* • Co-funded with the American Lung Association and the American Lung Association of Massachusetts

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### **Better Vaccines To Protect Against Tuberculosis**

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***Memory And Effector Functions Of CD1-Restricted, Mycobacterial Glycolipid-Specific T-Cells In Tuberculosis Patients.*** These studies are providing basic insight into the functions of a class of lymphocytes (white blood cells) that play an important role in the body's

immune system, and that are involved in defending against tuberculosis and other infections. This class of lymphocytes is called CD1-restricted T-Cells. The scientists are studying CD1-restricted T-Cells from tuberculosis patients to define more precisely what these cells do, which should help to point the way toward developing new and more effective vaccines to protect against tuberculosis.

Lung 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 cures in less than 15 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 study how the body regulates lung cancer cell growth, with the hope of defining how it may control cancer at the cellular level. Another promise inherent in the study of cancer genetics is the eventual development of treatment by gene therapy. Basic studies are exploring the genetic abnormalities in lung cancer cells. The mechanisms of radiation injury to the lungs are also being studied. Several studies, primarily at the genetic level, will examine why the risk of developing lung cancer varies among individuals, including the puzzling question of why women appear to be more susceptible than men. Other researchers are examining novel approaches to making current therapies more effective, such as reducing the development of resistance to chemotherapy. Basic cell and molecular biology is being explored, including the mechanisms by which lung cancer spreads to other parts of the body. This spectrum of scientific investigations may ultimately result in new treatments.

# LUNG CANCER

## RAJ K. BATRA, MD

University of California at Los Angeles and The Greater Los Angeles Veterans Administration Healthcare System, Los Angeles, CA

*Career Investigator Award* • Funded by the American Lung Association

### Retooling A Designer Virus For Better Lung Cancer Treatment

**Comparison Of Gene Transfer Efficiency Using Adenovirus (Ad) Versus FGF-Retargeted Ad For Lung Cancer.** Lung cancer is the leading cause of cancer death, killing over 157,000 Americans annually. Even with the best currently available treatment, it can only be cured at its earliest stage, and the five year survival rate is a low 15%. Novel approaches, such as using specially designed viruses to deliver therapeutic genes into cells, could improve the odds for successful treatment. This research is testing a strategy for modifying the virus that is typically used for gene delivery. The virus is being altered to target a particular protein, or receptor, that has been shown to have an increased presence in cancer cells and their blood vessels. The researchers hope to demonstrate that this modification improves gene transfer into cancer cells and their blood vessels.

## XIAOYUAN CHEN, PHD

University of Southern California, Los Angeles, CA

*Research Grant* • Funded by the American Lung Association of California

### A New Approach To Treating Lung Cancer With Radiation

**Vasoactive Intestinal Peptide Receptor Targeted Imaging Of Lung Cancer.** This project is developing a new approach to early detection and treatment of lung cancer, using positron emission tomography (PET scanning). The investigators are studying the effectiveness of molecular imaging with this technology in assessing small, early cancer lesions, pinpointing the dosage of radiation to be delivered, and monitoring the effectiveness of treatment. They are also seeking a more fundamental understanding of lung cancer at the molecular level. Radiation treatment delivered in this way is likely to improve the outlook for lung cancer patients by providing maximum effectiveness with minimal undesirable side effects.

## SONYE K. DANOFF, MD, PHD

Johns Hopkins University School of Medicine, Baltimore, MD

*Research Grant* • Funded by the American Lung Association

### Blocking A Key Receptor Might Prevent Deadly Lung Diseases.

**The Role Of The Transcription Factor, TFII-I, In Pulmonary Endothelial Biology.** Normal lung development, lung tumors, and emphysema all have one thing in common: they share a critical dependence on the expression of a receptor called KDR/flk-1, or vascular endothelial growth factor receptor. The timing and localization of KDR/flk-1 expression is essential in early lung development during gestation. Overexpression can result in several types of tumors, while blocking it can cause a tumor to regress. Emphysema can be caused in laboratory animals by selectively blocking KDR/flk-1. This group is seeking to understand the mechanism that controls KDR/flk-1 expression, with the goal of genetically manipulating it to prevent such deadly diseases as lung cancer and emphysema. They are testing the hypothesis that a transcription factor called TFII-I controls KDR expression in the pulmonary endothelial cells that make up the lining of the lungs, and exploring the consequences of altering the levels of TFII-I expression.

## KITAW DEMISSIE, MD, PHD

UMDNJ-School of Public Health, Piscataway, NJ

*Career Investigator Award* • Funded by the American Lung Association of New Jersey

### A Powerful New Tool To Identify The Cause Of Lung Cancer

**Gene Expression As An Approach To Identifying Asbestos-Related Lung Cancer.** Medical experts have not been able to distinguish between cases of lung cancer caused by exposure to asbestos and lung cancer that is due entirely to smoking. This project is examining gene expression profiles to determine whether they can be used to pinpoint asbestos-related lung cancer among the much larger number of people with smoking-related lung cancer. Specimens of lung tissue are obtained at the time of surgery from three groups of people with primary lung cancer: a group of heavy smokers, a group of non-smokers with no his-

tory of exposure to asbestos, and a group of heavy smokers with a history and X-ray findings that strongly suggest asbestos exposure. Profiles of gene expression in the three groups are being determined. The resulting findings may have significant value in the prevention and treatment of lung cancer.

#### **MARIAM DOHADWALA, PHD**

VA Greater Los Angeles Health Science Center, Los Angeles, CA

*Research Grant* • Funded by the American Lung Association and Supplemented by the American Lung Association of California

#### **Improving The Outlook For People With Lung Cancer**

##### ***Regulatory Pathways In COX-2 Dependent Invasion In Non-Small Cell Lung Cancer.***

Lung cancer patients have a poor prognosis, with fewer than 15 percent surviving for five years following diagnosis, a statistic that has changed only minimally in the last 20 years. Multiple genetic alterations are necessary for cancer to invade the lungs, and it is suspected that elevated expression of a gene known as COX-2 maybe a central element in orchestrating this process. This group has reported that COX-2 is overexpressed in Non-Small Cell Lung Cancer (NSCLC), and that inhibiting it has led to significant reduction of tumors in laboratory animals. They are now studying the regulatory pathways in the sequence of events that follows the overexpression of COX-2 and leads to NSCLC. A more complete knowledge of the part played by PGE<sub>2</sub>, a hormone that is naturally present in the body, could suggest ways to develop more specific treatment for NSCLC.

#### **WEIGUO HAN, MD, PHD**

Health Research, Inc./New York State Department of Health, Albany, NY

*Research Training Fellowship* • Funded by the Northeastern New York Division of the American Lung Association of New York State

#### **Which Smokers Run The Highest Risk Of Lung Cancer, And How Can We Help Them?**

***Tobacco Carcinogen And Hormonal Regulation Of Carcinogen Metabolizing Enzyme Expression.*** The vast majority of lung cancers are associated with cigarette smoking, yet only

about 10 to 15 percent of lifetime smokers develop lung cancer. Since cases of lung cancer are known to cluster in families, and there is evidence that female smokers are at higher risk than males, these researchers hypothesize that individuals differ in their genetic and gender-related susceptibility to lung cancer. They are examining the interplay between the cancer-causing substances (carcinogens) in tobacco, dietary and hormonal factors, and the expression of genes that may affect susceptibility. The results will contribute to current understanding of the molecular and genetic risks for developing lung cancer. This work may eventually make it possible to develop a screening test that identifies high risk individuals. An intensive effort to prevent lung cancer could then focus on these people, employing a combination of smoking cessation, changes in diet, medication and early detection efforts.

#### **AMY S. HEARN, PHD**

University of Florida, Gainesville, FL

*Research Training Fellowship* • Co-Funded with the American Lung Association and the American Lung Association of Florida

#### **Can An Enzyme Called MnSOD Slow Down Or Stop The Growth Of Cancer Cells?**

##### ***Overexpression Of Mutant Human MnSOD***

***Inhibits Tumor Cell Growth In Mice.*** Human manganese super oxide dismutase (MnSOD) is an enzyme that provides the body's primary defense against oxidative damage at the cellular level. Most cancer tumors have decreased or undetectable levels of MnSOD. Conversely, overexpression of this enzyme slows the growth of cancer cells, probably due to increased production of hydrogen peroxide, which has been shown to slow cell growth and even to cause cell death. The researchers have generated mutants of MnSOD that show enhanced activity and may cause elevated levels of hydrogen peroxide in cells. They hypothesize that overexpression of specific mutants of MnSOD in cancer cells will have anti-cancer effects. The goal is to determine whether increasing MnSOD levels and activity can stop tumor cell growth, and to delineate how this effect is mediated at the cellular level. The knowledge gained could prove valuable in developing new treatments for lung cancer.

## **VIDYA R. HEBBAR, PHD**

Rutgers University, Piscataway, NJ  
*Research Training Fellowship* • Funded by the American Lung Association of New Jersey

### **Improving The Body's Defenses Against Lung Cancer**

***Lung Cancer Chemoprevention Via Enhancement Of Cellular Defense Mechanisms.*** These scientists are seeking a better understanding of the cause of lung cancer and how to prevent it. More than 87 percent of lung cancer cases are attributed to cigarette smoking. It is well documented that cigarette smoke contains a number of carcinogens, harmful agents that can cause mutations and lead to lung cancer. Susceptibility to lung cancer among smokers can be the result of several factors, including genetic variations in phase II enzymes that prevent or decrease the metabolism of an important carcinogen called BaP. This project is focusing on the mechanisms involved in enhancing phase II enzymes in normal cells and increasing apoptosis (programmed cell death) of cancer cells. Understanding these molecular mechanisms will provide a basis for intervention that could prevent lung cancer.

## **REBECCA P. HUGHEY, PHD**

University of Pittsburgh School of Medicine, Pittsburgh, PA  
*Research Grant* • Funded by the American Lung Association of Pennsylvania

### **Why Does A "Good" Protein Become A Bad Actor?**

***Mechanism Of MUC1 Antigen Shedding From Lung Tumor Cells.*** MUC1 is a protein that is normally found on the surface of the epithelial cells that line the lungs, where its function is to protect the cell surface. MUC1 is also a diagnostic marker for lung tumor cells. High levels of MUC1 on tumors and in ascites (serous fluid that accumulates in the abdominal cavity) indicate that the tumor is highly likely to spread, with a poor outlook for the patient. The shedding of MUC1, after loss of its normal location on epithelial cell surfaces, also interferes with the body's immune response. These scientists are investigating what causes MUC1 release, and how this unique form of the protein differs from the cell-associated form. This information will be valuable in designing treat-

ments that can either prevent MUC1 shedding to avoid its immunosuppressive features, or better target tumor cell-associated MUC1.

## **ISABELLA IMHOF, PHD**

University of California, San Francisco, San Francisco, CA  
*Research Training Fellowship* • Funded by the American Lung Association of California

### **A Signaling Pathway That Opens The Door To Lung Cancer And Lung Inflammation**

***TACE-Mediated Ectodomain Shedding Of TGF-Alpha.*** These scientists are delineating the biochemical action and the regulation of a substance known as TACE, which plays a key role in lung inflammation and the malignant transformation of cells in the lining of the lungs (epithelium), which results in lung cancer. TACE may also be significantly involved in asthma and other chronic lung diseases. The investigators are characterizing the signaling mechanism that controls the activation of TACE and the subsequent role of transforming growth factor-alpha (TGF-alpha) in the development of cancer. The information gained about this signaling pathway may lead to possible intervention in the progression of lung cancer and inflammatory lung diseases that affect millions of people worldwide.

## **VENKATESHWAR G. KESHAMOUNI, PHD**

University of Michigan, Ann Arbor, MI  
*Research Grant* • Co-funded with the American Lung Association and the LUNGevity Foundation

### **Identifying A New Way To Target Lung Cancer**

***Regulation Of Tumor Progression By Peroxisome Proliferator-Activated Receptor-Gamma In Non-Small Cell Lung Cancer.*** Lung cancer is the leading cause of cancer death in the United States, and non-small cell lung cancer accounts for 80 percent of all lung cancers. Despite advances in understanding how cancer occurs, the five year survival rate for lung cancer still hovers dismally at 15 percent, underlining the need for innovative approaches to treatment. These researchers are studying a substance known as PPAR-?, which could present a new target for cancer treatment. They have demonstrated that it is expressed in high levels in tumor samples from patients with non-small cell lung cancer, suggesting that it

plays a part in the development of these cancers. Understanding PPAR- $\gamma$ 's precise role will eventually offer additional clues for controlling and treating this deadly disease.

#### **SUZANNE L. KIRBY, MD, PHD**

University of North Carolina at Chapel Hill,  
Chapel Hill, NC

*Dalsemer Research Scholar Award* • Funded by the American Lung Association

#### Minimizing The Risks Of Radiation Therapy

***Chemokines In Radiation-Induced Pulmonary Fibrosis.*** Radiation therapy, a valuable treatment tool for lung cancer, unfortunately carries with it the risk of debilitating and potentially lethal lung fibrosis, or scarring of the lungs. People who are or were smokers, or who have a previous history of lung disease, are particularly vulnerable to this complication. The researchers have identified a chemical substance called MIP-1 $\alpha$  they believe to be an important mediator of radiation-induced lung fibrosis. They are seeking to confirm that targeting this mediator and inhibiting it could have a protective effect. They also hope to identify the optimal timing for therapeutic intervention. The knowledge gained by these investigations could improve the ways radiation therapy is used to treat cancer, while also protecting lung health

#### **ROBERT J. KORST, MD**

Weill Medical College of Cornell University,  
New York, NY

*Research Grant* • Funded by the American Lung Association

#### Harnessing The Immune System To Treat Lung Cancer

***Enhancement Of Vaccine-Mediated, CD8+ T-Cell-Specific Antitumor Immunity By In Vivo Manipulation Of The Tumor Cell Surface.***

These studies are evaluating a new approach to treating lung cancer with immunotherapy, in which certain cells in the immune system are augmented in order to kill cancer cells in the body. While this is not a clinical trial for patients with lung cancer, such “translational” research is a key link in the chain of scientific knowledge that begins with laboratory findings and concepts of basic research, and culminates in the ultimate goal of treating patients safely

and successfully. The investigators are testing specific methods of vaccinating laboratory animals to create immunity against lung cancer, to determine whether this represents an effective strategy that might eventually be useful in humans.

#### **DAIQING LIAO, PHD**

University of Florida, Gainesville, FL

*Career Investigator Award* • Funded by the American Lung Association of Florida

#### Understanding A Genetic Change That Leads to Lung Cancer

***Identification Of A C-Terminal Kinase Of Tumor Suppressor p53.*** The mutation or inactivation of a gene called tumor suppressor p53 is known to be one of the most frequent genetic changes that lead to lung cancer. Understanding the biology involved in this phenomenon is of great value in revealing the molecular basis of lung cancer, which is the leading cause of cancer death worldwide. This group has found that a type of enzyme called kinase may play a key role in regulating tumor suppressor p53. They are currently seeking to identify this kinase and study how it regulates the function of tumor suppressor p53. The resulting knowledge has great potential for helping design new treatments for lung cancer. For example, it might be possible to use the kinase to activate tumor suppressor p53 in cancer cells, which could result in tumor suppression.

#### **TAMARA MINKO, MS, PHD**

Rutgers, State University of New Jersey,  
Piscataway, NJ

*Research Grant* • Co-funded with the American Lung Association and the LUNGeVity Foundation

#### Designing A Multifaceted Drug Delivery System To Kill Lung Cancer Cells

***Enhancement Of The Efficacy Of Chemotherapy For Lung Cancer By Simultaneous Suppression Of Multidrug Resistance And Antiapoptotic Cellular Defense.*** Treating lung cancer with chemotherapy is limited by the ability of lung cancer cells to resist treatment, and such resistance often increases during the course of treatment. Cancer cells have two main mechanisms of resistance: they pump the anticancer cells out, and they simultaneously activate defense mechanisms that limit their

own death rate. Suppressing both types of resistance cannot be accomplished using a drug with only one component, and it also requires a complex system of drug delivery to the cancer site. This group is developing and evaluating a new drug delivery system that will induce the death of cancer cells while suppressing both main mechanisms of resistance. The system will include an anticancer drug, a suppressor of the proteins that pump out the drug from cancer cells, and an inhibitor of the defense mechanisms that prevent cell death. If it is successful, the effectiveness of chemotherapy in treating lung cancer will be significantly increased.

## **GEORGE MINOWADA, MD**

Case Western Reserve University,  
Cleveland, OH

*Research Grant* • Co-funded with the American Lung Association and the American Lung Association of Ohio

### Stopping Lung Cancer Cells In Their Tracks

***Role Of Sprouty 2 In Mouse Lung Tumorigenesis.*** More effective drugs are badly needed to increase the current low survival rates in patients with lung cancer. A hallmark of cancer cells is their ability to proliferate and grow out of control. These scientists are studying a family of proteins called Sprouty, which prevent normal cells from excess proliferation by inhibiting a process called growth factor signaling. They want to find out whether a loss of Sprouty tips the balance in favor of uncontrolled growth in a laboratory animal model of lung cancer. If this proves to be the case, then Sproutys would be a candidate target for developing new drugs to keep cancer cells from proliferating. They are also studying whether more tumors develop in the lungs when Sprouty is not present. If so, more Sprouty might increase resistance to lung cancer, which could make it highly useful as a cancer-preventing drug. Such a drug would be desirable for people with COPD (chronic obstructive lung disease) or diseases that cause scarring of the lungs, since these individuals have an increased risk of lung cancer.

## **DAVID REISMAN, MD, PHD**

University of Michigan, Ann Arbor, MI

*Research Grant* • Funded by the American Lung Association of Michigan

### Identifying and Understanding the Subtypes of Lung Cancer

***The Loss of BRG1 And BRM In Human Nonsmall Cell Lung Cancer.*** Although lung cancer is thought of as a single disease, scientists know that it varies at the molecular level. Specific molecular changes have been used to define specific subtypes of disease in other kinds of cancer, and similar information about lung cancer may be highly valuable both to identifying susceptible individuals and to target more effective treatment. The goal of this project is to characterize a novel genetic change at the molecular level, involving the chromatin remodeling complex SWI/SNF. This complex may regulate the expression of thousands of genes in the body and affects the function of many key cellular proteins and pathways that control growth. The loss of the SWI/SNF complex undoubtedly has an impact on the type of cancer tumor that arises in an individual patient, and may also play a role in the evolution of lung cancer. This group is laying the foundation for further investigation that holds promise for better understanding, and one day better treatment, of different types of lung cancer.

## **GLENN D. ROSEN, MD**

Stanford University Medical Center,  
Stanford, CA

*Career Investigator Award* • Funded by the American Lung Association

### Can Triptolide From A Chinese Herb Kill Lung Cancer Cells?

***Triptolide-Mediated Apoptosis In Lung Cancer.*** To increase long-term survival rates in people with lung cancer, these studies are focused on finding novel methods to induce apoptosis, or programmed cell death, in lung cancer cells. The investigators have observed that a compound called triptolide, which is derived from a traditional Chinese herb, induces apoptosis in lung cancer cells and may represent a new approach to treatment. Triptolide also sensitizes tumor cells to apoptosis by chemotherapy by blocking proteins that inhibit the process. A derivative of triptolide has been shown to cause regression of tumors

in laboratory animals. Current studies are examining how triptolide activates cell death pathways in lung cancer cells.

### **DARYA SOTO, MD**

University of California, San Francisco,  
San Francisco, CA

*Research Training Fellowship* • Funded by the American Lung Association and Supplemented by the American Lung Association of California

#### How Do Mast Cells Help Cancer Cells Multiply?

***The Role Of Mast Cells In Angiogenesis Of Pulmonary Carcinoma.*** This project is studying the role of specialized cells known as mast cells in Non-Small Cell Lung Cancer (NSCLC). Mast cells have been shown to reside near various types of tumors, and recent studies of NSCLC patients correlated the presence of mast cells with angiogenesis and poor outcome in the early stage of adenocarcinoma, a type of cancer tumor. Angiogenesis is a process by which tumor cells multiply by stimulating the formation of a network of capillaries (small blood vessels) that nourishes them. The molecular mechanisms by which mast cells secrete a variety of factors connected with angiogenesis are not well understood. These scientists are studying mast cell proteins called Eph receptor tyrosine kinases and ephrins, which mediate changes in cell migration and attachment. Their investigations will provide a clearer understanding of signaling between mast cells and vascular (blood vessel) cells, which may suggest new strategies for anti-tumor therapy in NSCLC.

### **WUFAN TAO, PHD**

University of Minnesota College of Medicine,  
Minneapolis, MN

*Career Investigator Award* • Co-Funded with the American Lung Association and the American Lung Association of Minnesota

#### How Does The Body Prevent Cancer?

***Negative Regulation Of Cell Proliferation By Lats2 Tumor Suppressor.*** Lung cancer is a leading cause of cancer-related deaths in industrialized countries. Several tumor suppressor genes, which play critical roles in preventing cancer, have been shown to be involved in lung cancer, with laboratory analyses suggesting that many others remain unidentified. The

researchers are studying the Lats2 gene, a member of the lats tumor suppressor gene family, and their preliminary data suggest that it may also be important in preventing lung cancer from developing. They are now investigating the mechanism by which Lats2 negatively regulates the cycle by which cells proliferate. This should improve scientific understanding of how cancer development is controlled and may eventually lead to treatment strategies that target cell cycle check points in human lung cancer cells without affecting normal cells.

### **KOUNOSUKE WATABE, PHD**

Southern Illinois University School of  
Medicine, Springfield, IL

*Research Grant* • Funded by the American Lung Association of Illinois-Iowa

#### Slowing Down Lung Cancer Before It Spreads

***Anti-Tumor Peptide For the Treatment Of Lung Cancer.*** There is currently no effective treatment method for people with advanced lung cancer. Since this is the most lethal type of cancer in the United States, there is an urgent need for a strategy to interrupt the process by which cancer develops in the lungs. Almost all lung cancer patients die as a result of metastasis, i.e., spreading of the cancer from the lungs to other areas of the body. This project is studying the molecular mechanism by which tumors spread. The scientists are focusing on a particular protein called KAI1 that is known to suppress metastasis. By gaining a better understanding of how KAI1 interacts with a specific protein found in the blood vessels, they hope to develop a new treatment that will significantly reduce the growth of the primary lung tumor and also prevent it from metastasizing.

### **JUN ZHOU, MD**

Moffitt Cancer Center, University of South  
Florida, Tampa, FL

*Young Investigator Award* • Funded by the American Lung Association of Florida

#### Detecting Lung Cancer At Its Earliest Stage

***Changing The Expression Of Early Lung Cancer Detection Marker – Heterogeneous Nuclear Ribonuclear Protein (hnRNP) A2/B1: A Possible Mechanism Of Carcinogenesis.*** Early detection of lung cancer is the best means of improving long-term survival

## LUNG CANCER

rates. This study focuses on the role of proteins which signal the presence of cancer cells in the lining of the lungs (epithelium), early in the course of its development. These proteins, called hnRNPs, have been seen both in lung tumors and in epithelial cells from the sputum of individuals who develop lung cancer. The researchers are studying the precise function of these hnRNPs in the complex process that results in cancer. They may be valuable as an early marker for lung cancer detection, which could lead to earlier and thus more effective treatment.

# THE IMMUNE SYSTEM,

The 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 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. 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 and chemical mediators involved in inflammation and scarring are being studied, mainly with advanced techniques of molecular genetics. Other diseases on which these studies will have an impact include *Sarcoidosis* and *Farmers Lung*, a form of *hypersensitivity pneumonitis*, as well as Lymphangiomyomatosis, (LAM) a devastating lung disease of young women. Since some patients with advanced lung scarring are candidates for lung transplantation, American Lung Association researchers are studying the role of the immune system in rejecting transplanted lungs and causing fibrosis of the airways, as well as other significant issues related to quality of life for lung transplant patients.

# INFLAMMATION, AND LUNG SCARRING

## **CLAIR BRAMMER, PHD**

University of Connecticut Health Center,  
Farmington, CT

*Research Training Fellowship* • Funded by the  
American Lung Association of Connecticut

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### **Understanding The Sentinels Of The Immune System**

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***Antigen Presentation In The Pulmonary Immune System.*** Dendritic cells (DCs) are the sentinels of the immune system, bearing the responsibility for capturing antigens, or foreign substances perceived as invaders. DCs process antigen and display it to T cells, another key class of immune system cells, thus initiating primary immune responses. Given their central role in controlling immunity, DCs are logical targets for studies that involve T cells and their role in allergy, autoimmune diseases, tumors and vaccines. These studies are seeking to define the precise means by which DCs induce airway inflammation, and to identify whether a receptor on the surface of the DC signals to the T cell to behave in a particular way. Learning more about lung DCs will enhance understanding of the cause and development of respiratory tract disease. This knowledge will help in designing treatment strategies that reduce or abolish symptoms without weakening the pulmonary immune system.

## **WORAKIJ CHALERMSKULRAT, MD**

University of North Carolina at Chapel Hill,  
Chapel Hill, NC

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

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### **Seeking Better Ways To Prevent Rejection Of Lung Transplants**

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***Chronic Lung Rejection: The Contribution Of The Airway Epithelium In Alloantigen Recognition And Alloimmune Injury.*** Lung transplantation is the last option for treatment in a variety of end-stage lung diseases. Progress in surgical techniques and the development of drugs that suppress the immune system have significantly reduced the risk of early acute rejection of the transplanted organ. The major remaining barriers are the shortage of available organs, and chronic or long-term rejection. Chronic lung rejection is manifested as a condition called obliterative bronchiolitis (OB), which is the leading cause of illness and death among lung transplant recipients who

survive for more than one year. Treatment for OB is limited, partly because little is known about its cause. It is mediated by the immune system, but certain aspects of the cascade of immune-inflammatory events that take place during the rejection process remain to be clarified. This project is focusing on two such critical events: the pathways by which the transplanted organ is recognized by the immune system, and the tissues that are targeted for injury. Greater knowledge in these two areas will be valuable in designing better ways to prevent rejection, or to treat it successfully.

## **ANA M. CORBACHO, PHD**

University of California, Davis, Davis, CA

*Research Training Fellowship* • Funded by the  
American Lung Association and Supplemented  
by the American Lung Association of California

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### **How The Body Produces An Important Player In Lung Inflammation**

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***Prolactin In The Lung: Modulation Of Nitric Oxide (NO) Synthesis.*** Nitric Oxide (NO) is believed to be a significant factor in processes involving inflammation and immune reactions in the respiratory system. It is known to have both toxic and protective effects at the cellular level and is believed to contribute to causing a variety of pulmonary diseases, including acute respiratory distress syndrome (ARDS), cystic fibrosis, chronic lung disease in premature infants, chronic obstructive pulmonary disease (COPD) and asthma. The researchers hypothesize that regulating NO synthesis in the lungs offers a window to modulate processes that are related to overall respiratory tract health and disease. Their current studies are designed to define the contribution of the hormone prolactin (PRL) to the biology of NO in the airways. The goal is to characterize how PRL modulates NO production and its participation in the molecular mechanisms underlying lung inflammation.

## **SARAH E. DUNSMORE, PHD**

Harvard Medical School, Boston, MA

*Research Grant* • Co-Funded with the American  
Lung Association and the American Lung Association  
of Massachusetts

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### **How Does Lung Scarring Begin?**

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***Mechanisms Of Transforming Growth Factor Beta Activation By Neutrophil Elastase In***

# IMMUNE SYSTEM, INFLAMMATION, AND LUNG SCARRING

**Lung Disease.** Pulmonary fibrosis, or scarring of the lungs, may result from a variety of factors. For example, one well-documented cause is exposure to asbestos in the home or the workplace. The condition is often life-threatening, with limited treatment options and a poor prognosis for those who are afflicted. Pulmonary fibrosis is characterized by excess deposits in the lungs of collagen, the body's fibrous connective tissue. The chain of events that leads to overproduction of collagen remains to be clarified. This research is addressing the hypothesis that a substance called neutrophil elastase can initiate pulmonary fibrosis by activating another substance known as transforming growth factor b (TGF-b). Understanding the precise mechanisms by which this occurs could result in new treatments for lung fibrosis and also for other inflammatory lung diseases.

## **KENNETH C. FANG, MD**

University of California, San Francisco,  
San Francisco, CA

*Career Investigator Award* • Funded by the  
American Lung Association

### Targeting The Fundamental Mechanisms That Cause Lung Scarring

***Metalloproteinase-Dependent Regulation Of Mast Cell-Fibroblast Interactions In Lung Fibrosis.*** Idiopathic pulmonary fibrosis (IPF) is an insidious disease that involves irreversible scarring of the lungs, and can be fatal within a few years of diagnosis. This project is striving to define the pathways by which mast cells regulate other cells called fibroblasts that deposit collagen in the lungs, and promote fibrosis. The focus is on the molecular mechanisms of cell signaling at the cell surface. Defining these mechanisms will provide a foundation for studying how mast cells function in laboratory animals, and defining their precise role in tissue fibrosis. Ultimately, the knowledge that is developed from these studies will allow scientists to approach treatment in a new way by targeting the fundamental mechanisms that are responsible for fibrosis, which will improve quality of life for patients with IPF.

## **CAROL A. FEGHALI, PHD**

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

### Clarifying The Pathways And Factors That Lead To Lung Scarring

***Increased IGFBP-4 In Pulmonary Fibrosis And Its Effects On Lung Fibroblasts.*** A condition called idiopathic pulmonary fibrosis, which can lead to permanent scarring of the lungs, disability and death, is the result of an overresponse of the body's immune system. Similarly excessive inflammatory reactions occur in many other serious lung diseases. This project is seeking to better define the process that leads to pulmonary fibrosis by studying the role played by a substance called IGFBP-4. The knowledge acquired will allow the researchers to identify key pathways and factors that are involved in the development of pulmonary fibrosis, and thus focus on steps in the process that can be specifically targeted by new or modified treatment approaches. The ultimate goal is to find ways of preventing, curing, or limiting the progression of this devastating disease.

## **ELIZABETH A. FITZPATRICK, PHD**

University of Tennessee Health Science  
Center, Memphis, TN  
*Dalsemer Research Grant* • Funded by the  
American Lung Association

### Studying A Key Substance Involved In Lung Scarring

***Regulation Of IFN-gR Expression On Lung Fibroblasts During Hypersensitivity Pneumonitis.*** Hypersensitivity Pneumonitis (HP), or lung inflammation, can develop in individuals who are repeatedly exposed to various irritating or toxic substances, and may progress to fibrosis (lung scarring). One of the most common types of HP is Farmer's Lung disease, which is caused by an organism commonly found in moldy hay. It is characterized by the formation of granulomas – small clumps of inflammation that appear on the alveoli, the tiny air sacs at the end of the bronchial tubes that perform the essential function of exchanging oxygen and carbon dioxide. The severity of Farmer's Lung disease depends upon the effect of a substance called IFN-g, which induces the production of other substances in a chain of

events that this group of researchers is studying. The insight gained from their investigations will allow a clearer understanding of how IFN-g contributes to granuloma formation, and may lead to the development of better treatment strategies.

## **MARILYN K. GLASSBERG, MD**

University of Miami, School of Medicine,  
Miami, FL

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

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### **Saving Young Women From A Fatal Lung Disease**

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***Estrogen Regulation Of MMP-2 Activity: Implications For The Nature And Treatment Of Lymphangiomyomatosis.*** The goal of this study is to enhance understanding of an aggressive and deadly lung disease called lymphangiomyomatosis (LAM), which strikes mainly young women. LAM destroys lung tissue and causes large cysts to develop, resulting in loss of lung function. No currently available treatment can cure or even slow down the progression of the disease. These researchers are studying what they believe to be a key mechanism that promotes irreversible lung damage in women who have LAM. If their hypothesis proves to be correct, the information gained could lead to a significant breakthrough in treating this fatal condition.

## **JAMES S. HAGOOD, MD**

University of Alabama at Birmingham,  
Birmingham, AL

*Career Investigator Award* • Funded by the American Lung Association

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### **Why Do Normal Cells Become Destructive?**

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***Fibroblast Thy-1 Heterogeneity And Lung Fibrosis.*** A number of chronic lung diseases cause fibrosis, diffuse scarring that makes every breath a struggle and is life-shortening. In a condition called idiopathic pulmonary fibrosis (IPF), scarring occurs throughout the lungs and usually progresses relentlessly to death. Although few people are aware of IPF, it is a major cause of morbidity and mortality in this country. Many other lung diseases also feature fibrotic changes, including chronic asthma. Treatment for fibrosis is currently limited to medications that do little to halt its progres-

sion or relieve its symptoms. These researchers are studying the process of fibrosis at the cellular level, to determine why normal cells called fibroblasts go destructively awry and cause fibrosis. By defining the way in which specific groups of fibroblasts participate in the development of fibrosis, and by understanding the molecular pathways that control their responses, it is likely that new treatments can be developed for a number of debilitating disorders.

## **MAI-LAN N. HUYNH, MD**

University of Colorado Health Sciences  
Center, Denver, CO

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

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### **How Does The Body Control Inflammation, And Why Does This Process Sometimes Backfire And Lead To Scarring?**

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***Regulation Of Transforming Growth Factor Beta 1 And Apoptotic Cell Clearance.*** It is well known that inflammation and tissue damage are associated with fibrosis (scarring) that takes place during wound healing, as well as in pulmonary diseases that result in lung scarring. The precise way in which the body limits and eliminates inflammation, and the reasons why this process leads to fibrosis remain to be clarified. This group is examining in detail one potentially important mechanism that may be involved in the resolution of inflammation and the generation of fibrosis. Their novel concept has important implications for understanding how fibrosis occurs in people with severe asthma and other serious lung diseases.

## **WILLIAM E. LAWSON, MD**

Vanderbilt University Medical Center,  
Nashville, TN

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

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### **How Does A Protein Deficiency Lead To Scarring Of The Lungs?**

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***SP-C Deficiency And Pulmonary Fibrosis.*** Many lung diseases develop as a result of a combination of genetic factors and environmental exposures. A condition called idiopathic pulmonary fibrosis, meaning scarring of the lungs of unknown origin, has long been thought to be related to exposures to substances in the environment. Recent studies suggest that

## IMMUNE SYSTEM, INFLAMMATION, AND LUNG SCARRING

there may also be a genetic component that contributes to the development of the disease in some people. In families where lung scarring occurs, there seems to be an association between alterations in a substance in the body called surfactant protein C, and the development of lung disease involving fibrosis. These scientists are evaluating how surfactant protein C deficiency could predispose a person to lung scarring. The knowledge gained will provide background for future investigations of treatment options. It is also likely to be beneficial in developing a better understanding of how this disease develops which could lead to identifying risk factors and thus allow earlier treatment, or even prevention.

### DAVID R. PARK, MD

University of Washington, Seattle, WA  
*Research Grant* • Funded by the American Lung Association of Washington

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#### Research In The Laboratory Leads To Better Care At The Bedside

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***Mechanisms Of Fas-Induced Alveolar Macrophage Activation.*** This project involves basic laboratory research at the interface between two fundamental areas of biomedical science, inflammation and apoptosis (programmed cell death). The goal is to increase understanding of how these processes lead to the development of lung diseases, including potentially life-threatening conditions such as tuberculosis, pneumonia, and acute respiratory distress syndrome. This information will contribute to developing improved treatments for inflammatory and infectious lung diseases.

### PYONG WOO PARK, PHD

Baylor College of Medicine, Houston, TX  
*Career Investigator Award* • Co-funded with the American Lung Association and the Pulmonary Fibrosis Foundation

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#### Studying A Key Regulator Of Lung Inflammation And Scarring

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***Proteoglycans In Lung Inflammation And Fibrosis.*** The goal of this series of experiments is to identify new targets and provide information that can be used to design new ways to reduce, halt or reverse the processes of lung inflammation and scarring. Such treatments are important in several major lung diseases,

including asthma and cystic fibrosis, as well as in others that are associated with high mortality, such as interstitial lung disease and adult respiratory distress syndrome (ARDS). The prognosis is poor for those with lung scarring, with a 60 percent mortality rate at five years after diagnosis. The investigators are focusing on how substances called heparan sulfate proteoglycans (HSPGs) influence the development of lung inflammation and scarring. They are specifically studying the part played by an HSPG called syndecan-1, and clarifying how it functions as a key regulator of lung inflammation.

### DAVID M. PERLMAN, MD

University of Minnesota, Minneapolis, MN  
*Research Training Fellowship* • Funded by the American Lung Association

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#### Turning Off Connective Tissue Cells That Run Amok

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***The Role Of Internal Ribosomal Entry Site Mediated Translation In The Control Of Apoptosis.*** Idiopathic pulmonary fibrosis (IPF), or lung scarring of unknown origin, is a devastating disease, which is progressive, irreversible and almost invariably fatal. Respiratory function progressively declines until the person no longer has enough lung capacity to survive. IPF results from the abnormal growth of connective tissue cells called fibroblasts, which cause scarring of lung tissue and loss of airspaces in the alveoli, the tiny air sacs that provide for gas exchange in the lungs. The body normally activates fibroblasts as part of wound healing, and when healing is complete, fibroblasts undergo apoptosis or programmed cell death. In IPF, the fibroblast response turns on and then does not turn off, causing ongoing fibrosis. One mechanism that may lead to this abnormal fibroblast response is evasion of the normal apoptotic pathways. This project is examining the nature of a process called translational control in apoptosis, which could lead to new treatments for IPF that would target the fibroblasts' translational machinery, or develop a system to reveal proteins that are important in the apoptotic process.

## **JULIA SANGHA, PHD**

University of California, San Francisco,  
San Francisco, CA

*Research Grant* • Funded by the American Lung Association of California

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### **New Meaning For VIP**

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***T Helper Cell Phenotype Polarization By VIP.*** The overall objective of this research is to determine the way in which VIP, a specific factor that is released from nerves in the lungs and from certain immune cells, is able to control the nature and magnitude of immune reactions in lung tissues. VIP and its receptors alter the ratio of two distinct types of immune cells, each of which makes a different contribution to immunity and inflammation in the lungs. The change in ratio results in less protection against immunity, and more allergy and inflammation. The researchers are genetically manipulating VIP receptors to delineate the molecular and cellular mechanisms involved in this process. The long-term goal is the development of new drugs that target the VIP receptors, which will be valuable in treating such diseases as allergic asthma.

## **DAVID J. TOPHAM, PHD**

University of Rochester, Rochester, NY

*Research Grant* • Co-Funded with the American Lung Association and the American Lung Association of Finger Lakes Region

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### **Controlling The Allergic Response That Triggers Asthma**

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***Role Of Collagen-Binding Integrins On DC4+ T-Cells In The Lung.*** The lung is a major site of exposure to antigens in the environment, some of which are infectious agents such as bacteria and viruses. The immune system reacts to these antigens, but the outcome is not always desirable. A rapid immune response to an invading germ is beneficial, while a strong response to an environmental antigen such as pet dander or pollen can spark an asthma episode. Immune responses to specific antigens are controlled by specialized T-cells, many of which become memory cells located in the lungs, where they form the first line of defense against infection and are also likely to be important in responding to environmental antigens. These researchers are seeking the

molecular mechanism that causes memory T-cells to remain in the lungs for extended periods of time. They are examining the role of substances called integrins VLA-1 and VLA-2. If their studies show these integrins are important in retaining memory T-cells in the lungs, this suggests ways to improve vaccination to promote the expression of these integrins and place more T-cells at the site of exposure, where they can more rapidly respond to infections such as influenza. Conversely, inhibiting expression of allergen-specific T-cells in the lungs of asthmatics could reduce the response to antigens that set off an asthma episode.

## **GARY A. VISNER, D.O.**

J. Hillis Miller Health Center University of Florida, Gainesville, FL

*Career Investigator Award* • Funded by the American Lung Association of Florida

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### **Preventing A Deadly Complication of Lung Transplantation**

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#### ***Pirfenidone As A Therapeutic Agent For Transplant Obliterative Bronchiolitis.***

Although most lung transplant surgery is successful, the main obstacle to long-term survival is a condition called bronchiolitis obliterans (OB). In this disorder, scar tissue (fibrosis) develops and spreads in the large air passages of the lungs, eventually obliterating them and preventing airflow. The condition is believed to be a chronic form of rejection by the body's immune system of the transplanted lungs. Despite being treated with drugs to suppress the immune system and prevent rejection, the majority of people who undergo a lung transplant still develop OB. These scientists are evaluating a new approach to controlling OB with a medication that has been shown to block the development of a number of other disorders in which scar tissue proliferates. They hypothesize that treating OB with both immunosuppressive drugs and an anti-fibrotic agent could abolish or drastically reduce its development after lung transplantation, greatly improving survival rates and quality of life.

# IMMUNE SYSTEM, INFLAMMATION, AND LUNG SCARRING

## **ERIC S. WHITE, MD**

University of Michigan Medical School,  
Ann Arbor, MI

*Dalsemer Research Scholar Award* • Funded by  
the American Lung Association

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### **Understanding How The Body Produces Too Many Connective Tissue Cells Could Provide Insight Into Controlling This Process**

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**Role Of PTEN In Pulmonary Fibrosis.** Most people who develop pulmonary fibrosis, or lung scarring, experience a significant progression of their disease and ultimately die of respiratory failure. Current treatments for this condition are largely ineffective and often lead to additional problems due to side effects. New insights into how the disease develops are clearly needed to create more effective treatment. The researchers are studying the specific steps that occur to produce conglomerates of fibroblasts, the connective tissue cell thought to be responsible for the formation of scars. Their goal is to identify the mechanisms by which fibrotic-lung fibroblasts are regulated, compared to normal lung fibroblasts. This could permit the development of more targeted and specific treatments to prevent the overproduction of scarring characteristic of this disease.

## **JULIE A. WILDER, PHD**

Lovelace Respiratory Research Institute,  
Albuquerque, NM

*Research Grant* • Co-funded with the American Lung Association and the American Lung Association of Arizona/New Mexico

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### **How Do Our Genes Control The Immune Response In The Pulmonary System?**

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#### **Regulation Of The Pulmonary Immune Response To *Cryptococcus Neoformans* By The IL-12 And IL-12 Receptor Beta 2 Chain.**

A person's lungs inhale 10,000 liters of air a day, including a variety of tiny particulates, soluble substances, and microbes. Most of this unneeded and unwelcome material is cleared out by mechanisms in the respiratory system. Occasionally, however, the body mounts an immune response to an invasion of the lungs by a foreign substance. This response usually gets rid of infectious microorganisms such as bacteria and viruses, but in a few cases, the immune response is not effective and the result is chronic lung infection and inflammation. Partly because of their genetic makeup, some peo-

ple's immune systems respond inappropriately to non-infectious particles called allergens, and this allergic response can also cause chronic lung inflammation. This project is seeking to identify and understand the genes that regulate how pulmonary immune responses are initiated and manifested. If the researchers can pinpoint these genes and their products, it will be possible to design better and more targeted treatments for people with a variety of lung diseases.

## **KEVIN C. WILSON, MD**

Boston University School of Medicine,  
Boston, MA

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

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### **Too Many T-Cells Can Spell Trouble**

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#### **The Role Of Pro-Interleukin-16 In T-Lymphocyte Growth Regulation.**

T-lymphocytes are a class of white blood cells that play an essential part in the immune system, helping to defend the body against invading organisms that cause disease. However, when T-lymphocytes overgrow, or proliferate excessively, they contribute to the disease process instead of preventing it. This takes place in many respiratory diseases, including asthma, emphysema and a number of less well known but equally serious and even life-threatening conditions. These researchers are examining how a substance called pro-interleukin-16 (pro-IL-16) regulates T-cell growth. They have demonstrated that pro-IL-16 is a powerful suppressor of T-cell growth and are clarifying how this takes place and identifying the genes that are involved. A better understanding of the mechanism by which pro-IL-16 suppresses T-cell growth may identify other molecules that participate in the process, each of which could be a marker for diagnosing disease or assessing its prognosis, or become a target for treatment.



# DISEASES OF INFANTS

Research 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 thirty 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 the leading causes of death in infants up to one year of age. There is still no cure for cystic fibrosis, and the problems of treatment have increased as children 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 excess oxygen used to support life in these fragile infants. Nearly 100,000 children are hospitalized each year due to ***Respiratory Syncytial Virus (RSV)***, and an estimated 4,500 of them die of complications related to the disease.

Researchers supported by American Lung Association grants this year will attack the problems of RDS by studying the chemistry of the vital surfactant molecule. The process by which the immune system matures will be examined as well. The mechanism of the damage caused by life support oxygen is also being probed. The critical threats to life in CF patients are abnormally thick mucous in the airways and increased susceptibility to certain infections. American Lung Association investigators will continue to seek answers to why these occur. A variety of studies are directed to the basic mechanism of lung development, leading to a better understanding of congenital lung disease. SIDS is known to be related to maternal smoking, and the way in which nicotine may predispose to this disorder is under investigation.

# & CHILDREN

## **SAVERIO BELLUSCI, PHD, MS**

Children's Hospital of Los Angeles,  
Los Angeles, CA

*Career Investigator Award* • Funded by the American Lung Association

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### **Growing Better Lungs And Repairing Injured Lungs**

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***FGF10 Signaling In Embryonic Lung Development.*** This project is seeking to identify new ways to increase lung growth in babies born with immature lungs, and to improve the outcome of lung injury, particularly in chronic lung diseases such as emphysema and fibrosis (lung scarring). The investigators are studying FGF10, a growth factor that performs several important functions in the development of the epithelium, the cells that cover the internal and external surfaces of the body. They propose to clarify the means by which signals from FGF10 control and contribute to the development of healthy lungs in laboratory animals. This knowledge may then be extended to create a greater understanding of how the lungs develop in unborn babies. It may also help to pinpoint new targets for improving the coordinated development of the cells that line the lungs and other body cavities.

## **VRUSHANK G. DAVE, PHD**

Children's Hospital Medical Center,  
Cincinnati, OH

*Research Grant* • Funded by the American Lung Association

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### **Frog Embryos May Unlock The Secret Of How Human Lungs Develop**

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***Early Molecular Events In Lung Specification.*** The epithelium or lining of the lungs comes from endodermal cells, which are formed very early in the embryo. Nothing is known about how these cells give rise to lungs, but scientists believe there is a unique pathway that causes the endodermal cells to begin the process that results in the formation of lung bud cells. About 15 percent of all birth defects affect the lungs, and many congenital lung diseases are due to abnormal occurrences that involve endodermal cells before the lungs are formed. Although a number of critical steps take place at this very early stage of development, this area of research has remained largely unexplored because the process is so difficult to study in an unborn mammal. These

researchers are focusing on frogs, since frog embryos develop outside the body. Because frogs are also vertebrates, the findings will shed light on the processes that underlie the origin of the cells that lead to lung cells in humans. Eventually, this knowledge could make it possible to genetically modify these progenitor cells and correct hereditary lung diseases, and also to enhance the natural healing process after lung injury.

## **ANDRE A. S. DICK, MD**

The Milton S. Hershey Medical Center,  
Pennsylvania State University, Hershey, PA  
*Research Training Fellowship* • Funded by the American Lung Association of Pennsylvania

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### **Preventing High Blood Pressure In Newborn Infants' Lungs**

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***Abnormal Angiogenesis: Implication In Pulmonary Hypoplasia.*** High blood pressure in the lungs of newborn infants, known as primary (?) pulmonary hypertension (PPH), is a significant cause of disease and mortality. The condition is fatal in more than half of all newborns who develop it. These scientists are studying the mechanisms involved in abnormal lung development, with the ultimate goal of finding ways to reverse it and promote growth of healthy lungs. They are seeking to unravel the processes by which the blood vessels (vasculature) of the lungs develop, and the mechanisms that promote normal lung development. Since little is known about the role of vasculature in normal lung development, the information acquired will provide a new basis for developing better treatments for babies with PPH, or for preventing the disease altogether by treating it before birth.

## **WEI DING, MD, PHD**

Children's Hospital Los Angeles Research  
Institute, Los Angeles, CA

*Research Training Fellowship* • Funded by the American Lung Association and Supplemented by the American Lung Association of California

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### **Improving The Outlook for Infants With Immature Lungs**

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***Functional Characterization Of The Human Sprouty2 Gene Promoter.*** Lung diseases and other breathing problems are the number one killer of babies younger than a year old, partic-

ularly those who are born prematurely. Develop-mental immaturity of the lungs, resulting in failure to breathe normally, is a major reason for this sad statistic. This study is concerned with the molecular mechanisms that govern how the respiratory system is formed, especially the mechanism by which a gene called *Sprouty2* is regulated. This gene is important in the process of lung formation; studying it may lead to the discovery of how developmental abnormalities of the lungs occur. The findings could provide a basis for developing new strategies for preventing congenital malformation of the lungs, as well as novel ways to treat lung injury and enhance lung repair.

#### MELINDA R. DWINELL, PHD

Medical College of Wisconsin,  
Milwaukee, WI

*Research Grant* • Funded by the American Lung Association

#### Protecting Against The Negative Effects Of A Lifesaving Treatment

**Development And Plasticity In Respiratory Control.** The goal of this project is to develop a clearer understanding of the short-term and long-term effects of oxygen therapy on breathing in infants who are placed on a mechanical ventilator, or breathing machine. While mechanical ventilation saves the lives of newborns with immature lungs, one common side effect is bronchopulmonary dysplasia (BPD), a chronic lung disease in premature babies with a low birth weight. Relatively little is known about the effects of oxygen therapy on an infant's ventilatory control system, and the subsequent impact on overall health. Although the causes of Sudden Infant Death Syndrome (SIDS) remain unclear, there may be a greater risk of developing SIDS due to changes in the ventilatory control system following oxygen therapy. These studies are elucidating how ventilatory responses change during the early months of life, especially following oxygen therapy from birth. This knowledge may eventually make it possible to create new treatment strategies to defend against the negative effects of oxygen therapy.

#### LUC E. GOSSELIN, PHD

State University of New York at Buffalo,  
Buffalo, NY

*Career Investigator Award* • Co-Funded with the American Lung Association and the American Lung Association of Western New York

#### Preventing Respiratory Failure In Duchenne Muscular Dystrophy

**Muscular Dystrophy: Inflammation, Dysfunction And Fibrosis.** Duchenne muscular dystrophy (DMD) is a genetic disorder that affects skeletal muscle, first appearing early in life and creating a vicious cycle of injury and repair. The result is profound muscle wasting and weakness, and increased muscle stiffness due to an excessive accumulation of connective tissue. The diaphragm, the major muscle used in breathing, is particularly susceptible to the disease process. Consequently, the majority of people with DMD die of respiratory failure by their early twenties. The mechanisms leading to diaphragm muscle dysfunction are not well understood, and there is presently no cure for DMD. This project is studying the impact of an inflammatory mediator called TGF- $\beta$ 1 in promoting diaphragm muscle stiffness, and is also testing anti-inflammatory drugs that may prevent diaphragm muscle stiffness and dysfunction. Results from these studies may lead to clinical trials in people with DMD, with the long-term goal of preventing respiratory failure and alleviating the suffering associated with this lethal disease.

#### NAZEEH N. HANNA, MD

UMDNJ-Robert Wood Johnson Medical  
School, New Brunswick, NJ

*Research Grant* • Funded by the American Lung Association of New Jersey

#### Neutrophil Overload Can Create Problems For Premies

**Mechanisms Of Altered Neutrophil Apoptosis In Bronchopulmonary Dysplasia.** Bronchopulmonary dysplasia (BPD), a chronic lung disease, is a major cause of disease and death in premature infants. Inflammation plays an important role in BPD, and these studies are concerned with understanding the multiple factors that regulate inflammation in a newborn baby's lungs. The scientists are investigating how neutrophils, a type of white blood cell, are involved in lung injury, because large numbers

of neutrophils are present in the airways of newborns that develop BPD. Neutrophils are programmed to undergo apoptosis (cell death), but this process appears to go awry in BPD. The investigators hypothesize that the resulting reduced clearance of neutrophils from the lungs accounts for the severity of inflammatory injury. Understanding the mechanisms that regulate the prolonged survival of neutrophils in newborns will suggest strategies for better treatment or even prevention of BPD.

## **KEVIN S. HARROD, PHD**

Lovelace Respiratory Research Institute,  
Albuquerque, NM  
*Career Investigator Award* • Funded by the  
American Lung Association

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### **Understanding Lung Disease By Clarifying How Lung Genes Are Expressed**

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#### ***Lung Specific Transcriptional Regulation During The Host Response To Infection.***

Respiratory infections are a major cause of lung disease, especially in children. Their impact on children is especially important because lung infections can lead to chronic diseases such as asthma. These investigators are studying the genetic factors involved in diminished lung function during the course of acute lung infection. They hypothesize that substances produced by the body to react against infection also decrease the expression of certain genes, leading to diminished lung function and the development of lung disease as the body tries to protect itself against the invading infection. Elucidating the molecular mechanisms that regulate the expression of lung genes is crucial to understanding the process by which this destructive cycle is set in motion.

## **BROOKS M. HYBERTSON, PHD**

Webb-Waring Institute for Cancer, Aging and  
Antioxidant Research, Denver, CO  
*Research Grant* • Funded by the American Lung  
Association

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### **How Do Lung Cells Transport Surfactant And Use It For Protection?**

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#### ***Regulation Of A-Tocopherol Secretion Into The Lung Lining Fluid.***

Surfactant is a mixture of lipids and proteins that lines the tiny air sacs in the lungs called alveoli. This project seeks to determine the cellular mechanism by

which the lung cells that produce surfactant incorporate into it an antioxidant called a-tocopherol. This substance is the major component of the lipid antioxidant vitamin E, and may play a primary role in protecting surfactant lipids in the lungs against oxidative stress. It is known that a-tocopherol is secreted by alveolar type II cells, and the researchers are now elucidating how these cells transport it. The lungs undergo increased oxidative stress in many diseases, including cystic fibrosis, acute respiratory distress syndrome (ARDS) and bronchopulmonary dysplasia. Knowing how the alveolar cells process a-tocopherol may be valuable in designing new treatments for patients with these conditions that would help prevent the damage caused by oxidative stress.

## **HASAN S. JAFRI, MD**

University of Texas Southwestern Medical  
Center, Dallas, TX  
*Research Grant* • Funded by the American Lung  
Association

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### **Targeting A Ubiquitous Virus That Has Been Linked To Asthma**

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#### ***Role Of Chemokines In RSV-Induced Airway Hyperresponsiveness.***

Respiratory syncytial virus (RSV) is the leading respiratory disease-producing microorganism in children worldwide. Virtually, all children are infected by RSV at least once by the time they reach the age of three. As many as forty percent of infected children develop lower respiratory tract RSV disease, which is known to be strongly associated with recurrent wheezing and asthma later in life. Since there are no effective drugs for viral diseases, current treatment is aimed at relieving the symptoms. These researchers are characterizing the mechanisms by which RSV infection induces airway hyperresponsiveness, and evaluating the role of molecules called chemokines in this process. They are seeking to determine whether new treatment strategies that target certain chemokines could affect the severity of the disease and thus prevent its long-term consequences.

**VICTOR E. LAUBACH, PHD**

University of Virginia Medical Center,  
Charlottesville, VA

*Career Investigator Award* • Funded by the  
American Lung Association of Virginia

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**Stimulating Damaged Lungs To Repair  
Themselves**


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***Mechanisms Of Unequal Lobar Growth In  
Post-Pneumonectomy Lung Growth.***

Although lung transplantation success rates have improved, the shortage of donor lungs remains a major obstacle. Newborns, infants and children are especially likely to die while waiting for lungs to become available. These investigators are studying certain mechanisms involved in compensatory lung growth, a process by which new lung tissue is generated after surgery to remove a lung. Their aim is to identify and understand the stimuli and the molecular mediators within the body that regulate compensatory lung growth. The knowledge gained will form a basis for potential new treatments for many types of lung disease and lung injury. Eventually, an injured or diseased lung could be stimulated to repair itself through mechanisms similar to those seen in compensatory lung growth, rather than removing part or all of it.

**TIMOTHY D. LE CRAS, PHD**

Children's Hospital Medical Center,  
Cincinnati, OH

*Career Investigator Award* • Funded by the  
American Lung Association

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**Preventing Lung Disease In Premature Infants  
On Breathing Machines**


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***Role Of Vascular Endothelial Growth Factor  
In Hyperoxic Lung Disease In Newborns.***

Many premature babies who must be placed on respirators in order to survive develop a chronic illness called Bronchopulmonary Dysplasia (BPD), which is caused by the excess oxygen used to support life in these fragile infants. Scientists believe this life-threatening problem is due to lung injury and the arrest of lung development, which normally continues after a baby is born. The mechanisms by which excess oxygen, or hyperoxia, interrupt normal lung development is not well understood. Recent studies have suggested that vascular endothelial growth factor (VEGF) may play a central role in the development of BPD. This project

aims to determine how VEGF contributes to the development of lung injury and disease in newborns. The findings may serve as a basis for new treatment strategies to prevent lung disease due to excess oxygen in newborns.

**CHANGGONG LI, PHD**

University of Southern California,  
Los Angeles, CA

*Research Grant* • Funded by the American Lung  
Association and Supplemented by the American  
Lung Association of California

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**Studying How The Lungs Develop Before Birth  
To Glean New Insights Into Preventing Lung  
Disease In Infants**


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***The Role Of Wnt5a In Lung Development.***

Premature infants often develop a condition called bronchopulmonary dysplasia (BPD) that involves scarring of lung tissue and is accompanied by obstruction of the airways and heightened susceptibility to infection. It has recently been recognized that the specific defect in the lungs of premature babies with BPD is alveolar hypoplasia, a reduction in the density of the alveoli, the tiny air sacs in the bronchial tubes that exchange oxygen for carbon dioxide. This group is studying the mechanisms of how an unborn baby's lungs develop during the later stages of pregnancy. They are presently investigating the role of a signaling molecule called Wnt5a that performs a critical function in the process of lung development. Understanding the impact of Wnt5a may help to decipher the way in which alveolar hypoplasia and BPD develop, and could make a significant contribution to combating this problem.

**ERIK P. LILLEHOJ, PHD**

University of Maryland, Baltimore, MD

*Research Grant* • Funded by the American Lung  
Association

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**Identifying How A Key Molecule Goes Wrong  
In Cystic Fibrosis**


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***Muc1 Mucin Receptor Proteolysis In Airway  
Clearance Of Pseudomonas Aeruginosa.*** The major cause of death in cystic fibrosis is airway obstruction due to the presence of thick mucus that becomes heavily infected with a bacterium called *Pseudomonas aeruginosa*. This microbe is also associated with other major lung diseases and is almost always present in the air-

ways of healthy people as well. Such selective infection with *P. aeruginosa* may be due to a mechanism in the lungs of patients with disease that is not present in normal airways. These researchers hypothesize that a molecule called Muc1 mucin, which is found on the surface of airway cells and is a specific binding site for *P. aeruginosa*, plays a part in the latter stages of the infection. The results of their investigations will allow them to better identify possible aberrations of Muc1 mucin in cystic fibrosis, which would contribute to developing new medications for treating both the lung infection and the overproduction of mucus.

## **LIN L. MANTELL, MD, PHD**

North Shore-Long Island Jewish Health System, Manhasset, NY

*Career Investigator Award* • Funded by the American Lung Association of New York State and the American Lung Association of Nassau-Suffolk

### **Better Care For The Smallest Patients**

***Strategies Using Antioxidant Enzymes And Mitogen Activated Protein Kinase To Mitigate Hyperoxic Lung Epithelial Cell Injury.*** As medical care for newborns has become more sophisticated, more and more critically ill premature and full-term infants are surviving. However, a significant number develop problems such as BPD, or bronchopulmonary dysplasia. This chronic lung disease occurs in premature babies who had respiratory distress syndrome (RDS) the first few days after they were born. BPD is believed to result from damage to the lungs caused by oxidants that are generated during prolonged oxygen treatment with a respirator, which these infants need in order to survive RDS. This group is studying the signaling transduction pathways in the body that are involved in cell injury and death due to oxygen treatment. This information will help in developing treatment strategies to reduce oxidative lung damage in newborns, and prevent BPD.

## **BHAGAVATULA MOORTHY, PHD**

Baylor College of Medicine, Houston, TX  
*Career Investigator Award* • Co-Funded with the American Lung Association and the American Lung Association of Texas

### **Oxygen: A Life-Saver That Can Also Be Fatal**

***Molecular Mechanisms Of Lung Damage By Hyperoxia.*** Adults with lung abnormalities and premature infants with breathing difficulty due to underdeveloped lungs are often treated with supplemental oxygen. However, when premature babies experience a high concentration of oxygen (hyperoxia), they may develop a condition called bronchopulmonary dysplasia (BPD), a major cause of illness and death. One mechanism by which oxygen causes injury is through the formation of highly reactive substances called oxygen species that cause damage to tissues and organs. These studies are examining the role of certain enzymes in the formation or destruction of reactive oxygen species, to determine how they contribute to lung injuries related to hyperoxia. The information that is generated will provide a foundation for future research, which may lead to the development of treatment and prevention strategies for lung diseases associated with hyperoxia.

## **BRIAN M. MORRISSEY, MD**

University of California, Davis, School of Medicine, Sacramento, CA  
*Clinical Research Grant* • Funded by the American Lung Association

### **Can Vitamins E And C Help Control Cystic Fibrosis?**

***Nitric Oxide (NO) Metabolism And Oxidants Bronchiectasis.*** Cystic fibrosis (CF), a life-shortening genetic disease, is characterized by chronic infection, inflammation and progressive destruction of the lungs, a vicious cycle that is also seen in other chronic lung diseases. Despite advances in the development of antibiotics and other means of treatment, these diseases still result in overproduction of sputum, breathlessness and ultimately respiratory failure. As the body's own immune system fights against infection, it damages the lungs and the airways by producing destructive substances called oxygen radicals and proteolytic enzymes, which lead to oxidative stress. This project is examining the role nitric oxide plays

in oxidative stress, and the effect of systemic anti-oxidants (Vitamin E and Vitamin C) in mitigating it. A better understanding of these factors may help prevent the progression of lung disease in patients with CF and related conditions.

**MICHAEL L. MUCENSKI, PHD**

Children's Hospital Medical Center,  
Cincinnati, OH

*Research Grant* • Co-funded with the American Lung Association and the American Lung Association of Ohio

**Can Gene Therapy Correct Lung Defects Before Birth?**

***Proximal/Distal Lung Defects In Beta Catenin Compound Mutant Mice.*** These researchers are studying a particular pathway in the lungs, using genetically altered laboratory animals. Their experiments are addressing a fundamental question: which genes are critical to the normal development of the lungs? In addition to providing important insight into how normal lungs develop, these studies may also result in a unique animal model for studying gene therapies. Such therapies might eventually be used to correct lung defects in babies before they are born. They are also developing a second genetically altered animal model to provide a system for studying how human lung cancer develops.

**SURAFEL MULUGETA, PHD**

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

**When The Good Guy Turns Bad: Surfactant Saves Babies' Lives, But Its Mutations Also Contribute To Lung Diseases**

***Mutations In Surfactant Protein C Gene And Their Association To Interstitial Lung Diseases.*** A critical molecule called surfactant plays an important role in treating babies with immature lungs by stabilizing them, reducing the work of breathing, and lowering mortality. But recent findings have provided evidence that mutations in the Surfactant Protein-C (SP-C) gene are also associated with various lung diseases. The underlying mechanisms by which these mutations cause these disorders are unknown. This group is currently testing a

hypothesis as to why such mutations become the body's enemy. This will lay the groundwork for understanding how lung injuries are caused by mutant forms of SP-C. By examining the effects of the expression of the mutant genes in lung cells grown in the laboratory, the investigators hope to unravel the mysteries that still surround the process by which some lung diseases develop.

**STEPHEN PHAGOO, PHD**

Children's Hospital Los Angeles,  
Los Angeles, CA

*Research Grant* • Funded by the American Lung Association of California

**Can Certain Antibiotics Prevent Lethal Lung Inflammation in Cystic Fibrosis?**

***Macrolides in Burkholderia cepacia-mediated Cystic Fibrosis Lung Inflammation: Anti-inflammatory Molecular Signaling.*** Relentless inflammation is the major cause of lung destruction in cystic fibrosis (CF). The hallmark of this sometimes terminal disease is the over-expression of pro-inflammatory substances known as cytokines and chemoattractants, including one called IL-8. People with CF who are infected with a germ called *Burkholderia cepacia* produce an excessive amount of IL-8. The overall goal of this project is to determine whether macrolides, a class of antibiotics, may interfere with the production of IL-8. These studies could lead to novel treatment strategies for preventing the chronic inflammation that wreaks havoc in the lungs of CF patients infected with *B. cepacia*.

**MAHBOOB H. QURESHI, MD, PHD**

University of Kentucky, Lexington, KY  
*Research Training Fellowship* • Co-Funded with the American Lung Association and the American Lung Association of Kentucky

**Understanding The Immune System In The Very Young Could Lead To Better Protection Against Lung Infections**

***Role Of Dendritic Cells In Host Defense Against Pneumocystis Carinii In Neonates.*** Newborns and infants are highly susceptible to viral, fungal and bacterial infections, due to defects in their immune system that are not completely understood. Infants whose immune

systems have been further weakened by AIDS, cancer chemotherapy or organ transplantation are at particularly high risk of developing opportunistic infections such as *Pneumocystis carinii* and cytomegalovirus. A better understanding of the neonatal immune system is essential to the development of more effective treatment for these conditions, using immunotherapy in addition to currently available medications. This group is seeking to define the role of dendritic cells, a class of cells known to be involved in the host immune response. Their studies will clarify how dendritic cells participate in activating the protective immune response against invading organisms in the neonatal lungs. The findings will have important implications for finding new ways to protect highly susceptible newborns from often-fatal respiratory infections.

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### **How Do Normal Lungs Develop, And What Happens When The Process Goes Awry?**

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***Microfibril-Associated Glycoprotein-2 In Elastogenesis.*** Elastic fibers composed of substances called elastin and microfibrillar proteins are formed as part of the normal process of lung development. These fibers are essential structural elements of the alveoli, the microscopic air sacs in the lungs through which oxygen and carbon dioxide are exchanged. Bronchopulmonary dysplasia (BPD), a life-threatening problem in premature infants, involves incomplete formation of alveoli. Emphysema, which afflicts close to 3 million Americans, is characterized by the destruction of lung elastin. Pulmonary hypertension, another severe problem, involves abnormal formation of elastic fibers. To gain insight into how normal lungs develop and what takes place when this process goes awry, the researchers are examining the molecular interactions among microfibrillar proteins. These studies will pave the way for greater insight into the mechanisms of diseases such as BPD and emphysema.

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### **What Is the Connection Between Smoking During Pregnancy And Crib Death?**

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#### ***Effect Of Prenatal Nicotine Exposure On PDGF-Mediated Anti-Apoptotic Pathway During Hypoxic Ventilatory Roll-Off In Caudal Brainstem Of Developing Rats.***

Cigarette smoking during pregnancy is a leading cause of illness and death in newborns and infants. Sudden Infant Death Syndrome (SIDS, or crib death) is the third leading cause of death in babies during the first year of life, and cigarette smoking is the major risk factor for SIDS. The underlying mechanism that links a baby's exposure to cigarette smoke before birth and SIDS is unknown, but several findings suggest that the nicotine in cigarette smoke is the key culprit. This group is studying how nicotine exposure during pregnancy affects the activation of certain pathways in the developing fetus that trigger a series of complex events. Understanding these events may explain the relationship between prenatal smoke exposure and SIDS. Such knowledge could make it possible to develop more effective strategies for prevention, and better ways to intervene in this major health problem.

# GLOSSARY

## A

### **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 Immuno Deficiency Syndrome) A disease in which the cellular immune system is disabled. It is caused by infection by the Human Immuno Deficiency 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 lung.

### **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.

### **ameba**

A genus of naked, lobose, pseudopod-forming protozoa of the class Sarcodina that are abundant soil-dwellers, especially in rich organic debris and are also commonly found as parasites.

### **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 lung, 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 that is 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, 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 including many common molds such as Clavatus, Flavus, Aspergillus Fumigatus, Nidulans, Niger, Tereus.

### **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 mucous production characterized by cough, wheezing and shortness of breath.

### **autoimmune disease**

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

## B

### **bacteremia**

The usually transient presence of bacteria in the blood.

### **bacterium**

(Bacteria) A single-celled, microscopic organism existing in many forms, some of which are disease causing.

### **beta-Adrenergic Agonists**

Any of various drugs that combine with and activate receptors which exist on cell surfaces of some effector organs and tissues explain 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.

## bronchiectasis

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

## bronchitis

Inflammation of the bronchial tubes.

## bronchoconstriction

Reduction in the caliber of a bronchus or bronchi.

## BPD

(Bronchopulmonary Dysplasia) A condition of the lungs in infants and children which may follow treatment of the Respiratory Distress Syndrome in infants. It is characterized by distortion of the airways and scar formation.

## burkholderia cepacia

Is a bacterium found in approximately 5% of those with Cystic Fibrosis. Cepacia Syndrome is when someone infected with *B. cepacia* experiences rapid decline in health.

## C

## cancer

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

## caudal brainstem

The section of the brain stem that includes the basic neural networks for control of functions such as regulation of circulation and breathing.

## caveolar kinases

Enzymes that catalyzes 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.

## 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) A generic term that usually includes chronic bronchitis and emphysema, but may include asthma as well.

## 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 man.

## 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 lung, 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 cytoplasm that controls cell shape, maintains intracellular organization, and is involved in cell movement.

## cytotoxic

Toxic to cells

## D

## dedifferentiation

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

## dendrites

Any of the usually branching protoplasmic processes that conduct impulses toward the body of a nerve cell.

## desensitizing

To make (a sensitized or hypersensitive individual) insensitive or nonreactive to a sensitizing agent.

## differentiation

The development of a discriminating conditioned response with a positive response to one stimu-

lus and absence of the response on the application of similar but discriminably different stimuli. The maturation of cells from premature forms 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.

**E**

**edema**

Accumulation of excessive fluid in tissues.

**elastin**

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

**emphysema**

A condition characterized by the destruction of the walls of airspaces which results in permanently abnormal 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 lung.

**F**

**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 lung is called "pulmonary fibrosis."

**G**

**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.

**H**

**HIV**

(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.

**I**

**immunization**

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

**Immunodulation**

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

**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.

**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.

## L

## 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.

## M

## macrophage

Specialized cells that engulf and destroy bacteria and foreign particles in the lungs and other organs. These cells in the lungs are called *alveolar macrophages*.

## malignant

Usually refers to the behavior of a tumor which 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.

## 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.

## N

## neutrophil

A white blood cell important in the immune process.

## O

## 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 lung.

## P

## 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 lung that prevents alveoli from collapsing.

## physiology

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

## pneumonia

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

## pneumocystis carinii

A microorganism now considered to be a fungus which is an important cause of pneumonia in AIDS and other immune-suppressed patients.

## prostaglandin

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

## proteins

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

## pulmonary arteries

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

## pulmonary fibrosis

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

## R

## 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.

## S

## 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.

**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 the 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.

**T****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 micro-organism called *Mycobacterium tuberculosis*. The disease usually begins in the lung, 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.

**V****vaccine**

An inactivated (noninfectious) preparation of a microorganism that can be injected into a patient to stimulate the production of antibody 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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*The American Lung Association has long funded vital research on the causes of and treatments for lung disease. It is the foremost defender of the Clean Air Act and laws that protect citizens from secondhand smoke. The Lung Association teaches children the dangers of tobacco use and helps teenage and adult smokers overcome addiction. It educates children and adults living with lung diseases on managing their condition. With the generous support of the public, the American Lung Association is "Improving life, one breath at a time."*

*For more information about the American Lung Association or to support the work it does, call **1-800-LUNG-USA** (1-800-586-4872) or log on to **[www.lungusa.org](http://www.lungusa.org)**.*

