

+ **AMERICAN LUNG ASSOCIATION®**
Research Awards Nationwide
2004-2005



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MISSION

The mission of the
American Lung Association is
**to prevent lung disease and
promote lung health.**

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 342,000 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 Clinical Research Centers Network consists of 20 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 20 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 over 4,000 Americans each year.

There is reason for optimism despite these bleak facts. Research on asthma offers a real chance for dramatic success, as it is to a great extent a reversible disease. The American Lung Association supports extensive research in asthma in a number of critical areas. Because asthma often runs in families, 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, and the role of obesity in making asthma worse.

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

ASTHMA

MEHRDAD ARJOMANDI, 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 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.

GUADALUPE X. AYALA, PHD

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

Helping Adolescents Get A Grip On Asthma

Tailored Asthma Communication To Improve Asthma Outcomes Among Preteens/Young Adolescents. Teaching young people with asthma how to manage their condition is critical to controlling the burgeoning asthma epidemic. Programs tailored to adolescents are sparse, and even fewer resources exist for minority adolescent populations. This study targets ethnically diverse preteens and adolescents with asthma, who are being studied to identify factors that facilitate successful asthma management. This information will be used to develop an asthma management program specially prepared for this hard-to-reach population, which will be available in both English and Spanish. The program will assess the results by examining whether participants more successfully managed their asthma. The goals are to engage adolescents in discussing asthma management issues, to understand the behavioral and social

factors that contribute to poor asthma management, and to discover effective ways to improve self-management knowledge and skills, and quality of life.

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

Investigating A Gene That May Contribute To Lung Disease

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

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

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.

ESTEBAN BURCHARD, MD

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

Genetic Background May Account For Differences In Asthma Susceptibility Among Latino Americans

Case-Control Association Studies Of Asthma And Genetic Confounding In Racially Admixed Populations. Latinos are the largest minority population in the United States, but all Latinos do not share a common genetic background. The largest Latino American groups, Mexicans and Puerto Ricans, are genetically complex and comprised of various proportions of Native American, African and European ancestry. Asthma prevalence, disease and death are highest among Puerto Ricans and lowest among Mexicans. One reason may be that genetic predisposition to asthma, or to more severe asthma, differs among Latino subgroups, which may have genetic variants of asthma candidate genes that explain such variations. This project is studying Mexican and Puerto Rican asthmatics and healthy controls to identify clinical and genetic risk factors for asthma in these ethnic groups. The goal is to ensure that ethnically or racially diverse populations are not excluded from the health benefits that are likely to result from current efforts to identify and characterize genes that contribute to the presence or severity of asthma. The findings may also provide a way to identify Latino Americans at high risk for severe asthma.

BLANCA CAMORETTI-MERCADO, PHD

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

Can Drugs Best Known For Lowering Cholesterol Offer More Effective Treatment For Asthma?

Modulation Of Lung Function By The Mevalonate Pathway. One of the hallmarks of asthma is airway inflammation and remodeling. Over time, tissue remodeling and structural changes decrease airway size. Although bronchodilator and anti-inflammatory medications can help control asthma symptoms, more effective treatment is needed. A class of drugs called statins, which have been highly successful in lowering cholesterol, have also shown unexpected benefits involving mechanisms that modify inflammatory responses both in the cardiovascular and renal systems, but the effect of statins on inflammation of the respiratory system has not been studied. Statins are known to be inhibitors of the mevalonate pathway, which is involved in a constellation of events that impact accumulation of smooth muscle mass as well as inflammation. This project is testing the hypothesis that airway smooth muscle function and airway inflammation can be modulated by inhibiting the mevalonate pathway. If this proves to be the case, statin drugs may offer a significant new approach to asthma treatment.

LAUREN E. COHN, MD

Yale University, New Haven, CT
Career Investigator • Co-funded with the American Lung Association and the American Lung Association of Connecticut

Replacing Allergy Injections With Inhaled Immunotherapy

Mechanisms Regulating Inhaled Tolerance Induction. Immunotherapy involves desensitizing the body to an allergen, or allergy-causing substance, by administering small amounts of it, usually in a series of injections. This traditional form of immunotherapy has not been highly successful in treating people who have allergies that trigger asthma episodes. These scientists hypothesize that inhaled immunotherapy may offer a more promising pathway for treating asthma and other chronic

diseases. They are assessing the effects of inhaled immunotherapy when the airways are inflamed, as they characteristically are in asthma. The results of their work will help to determine if it is possible to use inhaled immunotherapy as a mode of treatment for asthma.

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

How Does Estrogen Protect Against Asthma?

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).

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

Seeking New Ways to Treat Airway Inflammation

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 \$16 billion a year. It accounts for 11 million visits to health care providers, over 1.6 million emergency room visits, and over 450,000 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.

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 Alternations Due To Early Life Environmental Exposures, And The Development Of Childhood Asthma. Despite recent advances in treatment, over 6 million children have asthma. 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.

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 60 percent of asthma sufferers. The number of people who have allergic asthma continues to rise, while treatment remains less than per-

fect. 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.

HUSEIN HADEIBA, PHD

Stanford University Medical Center,
Stanford, CA

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

Harnessing Viruses To Defend Against Asthma

The Role Of Influenza: A Virus Infection In Asthma. The goal of this project is to understand the mechanisms that keep asthma from developing. Asthma is linked to exposure to allergens in the environment and to respiratory viral infections in early childhood, with the timing of virus infection appearing to play a critical role in either worsening or suppressing asthma. While concurrent viral infections such as influenza or respiratory syncytial virus tend to make asthma symptoms worse in children who already have asthma, other studies suggest that early childhood infections may guard against asthma. Clarifying how such protection occurs may suggest new approaches to a virus-based vaccine. These scientists are studying the immune response of laboratory animals exposed to the influenza A virus and then to an allergen associated with asthma, seeking to identify key cellular or molecular mediators that inhibit asthma. The knowledge they gain about how viral infections influence the course of asthma could make it possible to use viruses to prevent asthma.

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

Preventing Permanent Lung Damage From Childhood Asthma

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

Preventing Permanent Damage To The Airways In Asthma

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, PHD

Virginia Commonwealth University,
Richmond, VA

Research Grant • Funded by the American Lung Association of Virginia

Preventing Allergic Asthma Episodes

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.

HUICHUAN LAI, PHD, RD

University of Wisconsin, Madison, WI
Clinical Research Grant • Funded by the American Lung Association of Wisconsin

Can Staying Slim And Trim Help Keep Asthma At Bay?

Diet And Obesity As Environmental Risk Factors For Asthma. Genetic and environmental factors are both known to be involved in the origin of asthma, but their relative importance has yet to be established. Diet has been proposed as an environmental risk factor for asthma, based on the observation that the dramatic increase in numbers of asthmatics has coincided with a marked change in the American diet. Consuming a high-fat, high-calorie diet, combined with reduced physical activity and a more sedentary lifestyle, has produced a virtual epidemic of obesity in this country. It has also been found that people with asthma tend to weigh more than non-asthmatics, and overweight is associated with increased occurrence of wheezing. This study is examining the con-

tributions of diet and obesity to asthma during the period from birth to age seven. If its results support the hypothesis that diet and obesity increase the risk of developing asthma, then public health campaigns promoting healthy diet and weight loss may help to prevent the onset of asthma or modify its expression, thus reducing the health care burden for both asthma and obesity.

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.

LINYING LIU, MD

University of Wisconsin, Madison, WI
Research Grant • Funded by the American Lung Association

New Clues To Airway Inflammation In Asthma

Loss Of Membrane IL-5 Receptor On Eosinophils In Airway Inflammation: Functional Significance And Mechanisms.

A better understanding of the mechanisms that cause asthma is crucial to identifying new targets for treatment to alter its course and limit its ability to cause disease and death. Despite the alarming rise in frequency and severity of asthma, scientific understanding of many aspects of

this disease is still limited. These studies will provide new information on the role of interleukin (IL)-5, a substance known as a cytokine, that is a key player in the allergic airway inflammation characteristic of asthma. The researchers are also studying the role of IL-5's receptor on eosinophil function and delineating the mechanisms that regulate its expression. Eosinophils are white blood cells that are increased in allergic diseases and can damage the lung tissue in asthma. The data being developed will have important implications for treatment approaches in people with asthma.

MARGARITA MARTINEZ-MOCZYGEMBA, PHD
 Baylor College of Medicine, Houston, TX
Research Grant • Funded by the American Lung Association

Shutting Down Cell Signaling To Reduce The Damage Done By Asthma

Molecular Signals Regulating Interleukin-5 Receptor Down-Regulation. Chronic allergic inflammatory disorders such as asthma are due in large part to uncontrolled signalling of eosinophils. Eosinophils are a type of white blood cells that contain granules filled with a specific set of chemicals and enzymes that influence inflammatory reactions. They are increased in several classes of disease, including allergic disease. Knowing how to turn off eosinophil activation signals (IL-5) is critically important to discovering new treatments for these disorders. The aim of this research is to dissect the molecular signals that initiate and mediate the termination of IL-5 receptor signaling. Understanding how to accelerate or promote termination of IL-5 signaling would bring profound insight into allergic inflammatory lung disorders, and could lead to therapeutic agents that would reduce the respiratory damage caused by activated eosinophils in asthma and other diseases.

ADAM P. MATSON, MD
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 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 since 1980. 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.

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 Lifetime 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.

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.

RICHARD K. PLEMPER, PHD

Emory University, Atlanta, GA

Research Grant • Funded by the American Lung Association

Controlling The Spread Of Virus Infections In Youngsters Could Impact Asthma And COPD

Template-Based Design Of Paramyxovirus Entry Inhibitors. Members of the paramyxovirus family such as respiratory syncytial virus (RSV), human parainfluenza viruses (hPIV), and measles virus are the cause of major diseases including virus-induced pneumonia, bronchiolitis, and measles. In particular, RSV and hPIVs account for a significant number of hospitalizations and mortality mostly of infants and young children, since no vaccines are available that protect against these viruses. While early infection with RSV appears to be linked to the later development of asthma and chronic obstructive pulmonary disease (COPD), infection with hPIVs can result in the croup syndrome. These investigators are seeking new strategies to counter paramyxovirus infections. Their work is focused on inhibiting the viruses, which would minimize symptoms and reduce vital spread in settings of close contact of young children such as day care centers and pre-schools. Reducing the incidence and severity of RSV infection in infants could also have an impact on the incidence of asthma and COPD.

MARK F. SANDS, MD

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

Matrix Biology: A New Frontier For Studying Inflammation In Asthma

Molecular Mechanisms Of Lung Remodeling And Hyperresponsiveness In Asthma: Role Of Metalloproteinases And Inhibitors. Asthma appears to be a family of disorders rather than a single disease, leading to a syndrome that is the result of many gene variants interacting with complex environmental stimuli. This project is exploring the basic inflammatory mechanisms of asthma through studies of how cells interact with each other, migrating and communicating in their microenvironments. A specific component of matrix biology is being elucidated, an area of study on the cutting edge of asthma research. The data being developed will better define the nature of the inflammatory response, and will contribute to a clearer understanding of asthma, as well as to better treatment and even the ability to prevent asthma from developing. The lessons being learned about matrix biology may also be translated into other key areas of research such as acute lung injury.

REBECCA A. SHILLING, MD

University of Chicago, Chicago, IL
Research Training Fellowship • Funded by the American Lung Association of Metropolitan Chicago

Understanding How Genetic Interactions Add Up To Asthma And Allergy

Role Of ICOS Expressions Levels In Asthma And Allergy. The focus of this project is on the role of Inducible Costimulator (ICOS) gene expression levels, and the resulting influence on asthma and allergy. An individual's genetic predisposition to develop asthma depends upon the interaction of a number of genes with each other, and because of their genetic background people with certain combinations of genes are more susceptible to developing asthma than others. Identifying and studying genes associated with asthma will lead to the discovery of novel pathways involved in the origin of allergic diseases, and eventually to new means of treatment. Previous research on the role of ICOS has demonstrated that ICOS-mediated

signals may be important for the development of Th2 effector and memory cells that are important mediators of the inflammatory response that is characteristic of asthma. These studies are elucidating the effects of ICOS on the immune system mechanisms involved in the development of asthma, with the goal of defining the role of ICOS in the development and maintenance of asthma and allergy.

ELIZABETH K. TAM, MD

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

Trouble In Paradise: Molds May Be The Villains

Distribution And Characterization Of Airborne Molds In Hawaii. While some of the mechanisms responsible for the increase in asthma in Hawaii are shared with other regions of the United States, some environmental agents and genetic variations are unique to these islands. Preliminary findings on the respiratory health effects of volcanic air pollution, or "vog," suggest that more cases of asthma are diagnosed in the windward communities of the Big Island, where vog is actually lowest but where moisture may promote the growth of molds. The researchers are investigating the relative effects of molds and other environmental agents on the prevalence of asthma, in the context of the island's racial diversity. The lung health of nearly 2,000 school children is being studied, and a mold monitoring program is being conducted concurrently, along with studies of wind speed and direction, respirable particulate matter, acidity, and sulfur dioxide. The results will more clearly delineate the relative contribution of several environmental factors to the onset and course of asthma, allergy, and other respiratory disorders, information that is valuable in treating and managing these conditions.

DANIEL J. TSCHUMPERLIN, PHD

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

Seeking New Ways To Treat Airway Narrowing In Asthma

Mechanical And Structural Properties Of The Airway Epithelium: Implications For Airway Narrowing In Asthma. Recent studies have shown that structural alterations occur in the airways of people with asthma, especially in the epithelium or lining of the airways. Several structural alterations are being considered as targets for treatment with medication, but little is known about precisely how remodeling affects the airway mechanics and airway narrowing that characterize asthma. This project is helping to fill this knowledge gap by studying how the airway epithelium contributes to the process that determines airway narrowing. The scientists are elucidating how inflammatory and mechanical stimuli induce changes in the airway epithelium, and whether these changes contribute to or protect against excessive airway narrowing. Their findings will provide new insights into the link between epithelial remodeling and airway narrowing, and a rational basis for new treatment approaches to target harmful aspects of airway remodeling.

MICHELLE ZEIDLER, MD

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

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

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 air-

ways 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.

BAOHUA ZHOU, PHD

Virginia Mason Research Center, Seattle, WA
Research Training Fellowship • Funded by the American Lung Association of Washington

Pinpointing The White Blood Cells Responsible For Asthma Inflammation

Roles Of Thymic Stromal Lymphopietin In Bronchopulmonary Inflammation. Eosinophils are a type of white blood cell that influence inflammatory reactions. Eosinophilic inflammation is a characteristic feature in the airways of many people with asthma, and most treatment and prevention strategies for asthma focus on controlling this phenomenon. However, recent research has suggested that in fact another class of cells called neutrophils, known to be important in the immune process, may account for more than half of all asthma cases. This group is using laboratory animal models to study the basic disease processes underlying neutrophilic airway inflammation, to gain a better understanding of how the inflammatory cascade is initiated. They are studying the roles of several mediators in the development of neutrophilic airway inflammation, which should yield results that are relevant to other neutrophilic asthma as well as to other neutrophilic airway diseases. Understanding how neutrophils and mediators interact to cause inflammatory disease should lead to better strategies for treating neutrophilic asthma, chronic obstructive pulmonary disease, and cystic fibrosis.

MEIXIA ZHOU, PHD

Stanford University, Stanford, CA
Research Training Fellowship • Co-funded with the American Lung Association and the American Lung Association of Puerto Rico and Supplemented by the American Lung Association of California

Putting Together The Asthma Puzzle: What Does The Tim-4 Gene Do?

Functional Studies Of TIM-4 Protein In Th2-Mediated Asthma. Current treatment for asthma mainly reduces its symptoms but cannot cure or prevent a disease that affects 20 million people in the United States alone, and costs billions of dollars a year. Further understanding of the mechanisms that regulate allergy and asthma is needed before medical science can truly conquer asthma. This group is studying a newly cloned gene called TIM-4, which appears to play a critical role in asthma regulation. The results will provide more detailed information about TIM-4 and how it is involved in regulating substances called Th2 cytokines, which are associated with the development of asthma and allergy. Understanding these molecular mechanisms will add valuable pieces to the jigsaw puzzle scientists must put together before they can design better treatment for asthma and allergy.

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

Studying A Newly Identified Enzyme Involved In Asthma Inflammation

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

cal 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.

ASTHMA CLINICAL RESEARCH CENTERS: A UNIQUE NETWORK TO BENEFIT PATIENTS

The Asthma Clinical Research Centers (ACRC) network, sponsored by the American Lung Association, conducts large clinical trials that provide vital information about caring for people who have asthma. The network comprises 20 clinical centers and a data coordinating center, making it the largest of its kind. Its unique focus on large numbers of patients differentiates it from current federally funded and commercial research, and provides practical information about asthma care that has direct benefit for patients. The ACRC network is currently conducting the following studies:

FINDING AN ALTERNATIVE TO STEROID INHALERS

LOCCS: The Leukotriene Modifier or Corticosteroid or Corticosteroid-Salmeterol Trial • Funded by GlaxoSmithKline

Treatment guidelines currently recommend controlling persistent asthma symptoms with medication, and inhaled corticosteroids are generally recognized as the most effective medication for this purpose. However, inhaled corticosteroids can have significant side effects, and some people prefer not to take steroid drugs. To provide an alternative, this study is comparing the effectiveness of three treatments: a low-dose inhaled corticosteroid, a non-corticosteroid, and a combination treatment that uses one half the usual steroid dose. This study seeks to identify treatment that is

simpler and easier for the patient, which encourages adherence, and that reduces the risk of undesirable side effects.

MEASURING AIRWAY REACTIVITY

**Methacholine Challenge Sub-study
Funded by GlaxoSmithKline**

Methacholine challenge testing is used to confirm the diagnosis of asthma and to assess the degree that a person's airways are responsive to irritating stimuli. A subgroup of LOCCS participants will be enrolled in the Methacholine Challenge sub-study. These patients will have a methacholine challenge test at the beginning, middle and end of the randomized treatment period. The goal of study is to investigate if any of the study treatments in the main study has an effect on airways reactivity during the course of the trial.

GENETICS AND ASTHMA ANCILLARY STUDY

**Pharmacogenetics of Asthma Drugs
Funded by the National Institutes
of Health's National Heart, Lung and
Blood Institute**

The goal of this study is identify genetic variants that will predict which patients in the LOCCS study responded favorably to inhaled corticosteroids, montelukast or the combination of salmeterol and corticosteroid treatment and predict which patients experience side effects. The results of this study may enable researchers to select a priori which patients respond favorably to these various treatments.

THE PLACEBO EFFECT: IMPLICATIONS FOR ASTHMA TREATMENT

**TAPE: Trial of Asthma Patient Education
Funded by the National Institutes
of Health's National Heart, Lung and
Blood Institute**

This study is investigating the placebo response in a multi-center clinical trial involving 600 participants who have asthma. Among the questions to be answered are whether a true placebo response does exist in asthma, and

whether it can be augmented by creating conditions in which the patient's expectations of benefit are increased. The researchers are also seeking to determine whether increased expectation of benefit augments the effect of actual treatment, and whether the placebo effect adds to or interacts with the effect of treatment. A better understanding of the placebo response can lead to improvements in asthma treatment and research.

ARE PATIENTS COMPLIANT WITH MEDICATIONS?

**TAPE Adherence Sub-study
Funded by the National Institute
of Health's National, Heart, Lung and
Blood Institute**

This sub-study will be conducted to monitor adherence using the Medication Event Monitoring System (MEMS). Clinical centers will attach a MEMS cap to each participant's pill bottle. This battery-powered device records the date and time when it is removed from the bottle, thus giving an indication of pills consumed. This will provide data to evaluate compliance. Adherence assessed with the MEMS caps will be compared to pill counts conducted by the clinics and daily records completed by participants.

ASTHMA AND ACID REFLUX DISEASE: TREATING ONE CONDITION CAN RELIEVE THE OTHER

**SARA: Study of Acid Reflux and Asthma
Funded by the National Institute
of Health's National, Heart, Lung
and Blood Institute**

Acid reflux disease, also known as gastroesophageal reflux or GERD, is frequent among people with poorly controlled asthma. It often occurs with no symptoms and can induce constriction of the airways. Poorly controlled asthma patients are frequently treated for GERD with drugs that suppress gastric acid, but this approach is expensive and its benefit has not been established. This clinical trial is testing the hypothesis that treating GERD with a class of drugs called proton pump inhibitors will reduce the frequency of exacerbations (worsening of the problem) in people with

inadequately controlled asthma. Four hundred people between the ages of 18 and 60 who have asthma that is not well controlled with inhaled steroids are being studied, and are randomly assigned to treatment with either a proton pump inhibitor or a placebo. The results will point the way to more effective ways to control acid reflux and prevent it from contributing to asthma.

CAN SINUSITIS TREATMENT IMPROVE ASTHMA CONTROL (SINUSITIS PILOT STUDY)

To be Funded by Schering-Plough

The major goal of the study is to develop a set of simple clinical criteria to reliably diagnose upper airway disease in asthmatics. This clinical tool will then facilitate further research and clinical care in the asthmatic population.

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DISORDERS OF THE LUNG'S BLOOD VESSELS

Acute Lung Injury, also known as 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 it 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. 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

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IRINA V. BALYASNIKOVA, PHD

University of Illinois at Chicago, Chicago, IL
Research Grant • Funded by the Metropolitan Chicago

Gene Therapy For Diseases Of The Pulmonary Blood Vessels

Antibody-Mediated VEGF Gene Transfer For Pulmonary Hypertension. Diseases that affect the pulmonary blood vessels are costly and difficult to treat, in part because scientists have not yet devised a way to selectively deliver therapeutic molecules to the pulmonary circulation. Pulmonary hypertension, or high blood pressure affecting the pulmonary arteries, is usually fatal within a few years of diagnosis. Advanced pulmonary hypertension is characterized by abnormal function and structure of the pulmonary endothelium, the cells that make up the inside layer of the lung's blood vessels. These researchers hypothesize that targeting the pulmonary endothelium with gene encoding vascular endothelial growth factor (VEGF) could be a valuable treatment approach to pulmonary hypertension. To accomplish this, they are investigating methods of gene delivery to the pulmonary endothelium, and seeking to increase the selectivity and efficiency of this new treatment approach to what has been until now a virtually untreatable and deadly condition.

SCOTT BOITANO, PHD

Arizona Respiratory Center, Tucson, AZ
Career Investigator Award • Funded by the American Lung Association

How Do Cells In The Lungs Communicate And Respond To Injury?

Cell Communication In The Alveolus. Although more than 40 types of cells are present in the lungs of mammals, just two cell types make up the lining (epithelium) of the alveoli, the microscopic air sacs through which oxygen and carbon dioxide are exchanged when we breathe. This research is elucidating how these cells normally interact with each other and with a third cell type, alveolar macrophages, and how they respond to injury. Distinct signaling pathways define the interactions between the three cell types and the subtle differences in pathways help to shape a coordinated defense against injury. Understanding how these

processes work at the basic cellular level could expedite the formulation and testing of new medical treatments for dysfunctional conditions that occur in the airways following disease or lung injury.

KEITH C. DERUISSEAU, PHD

University of Florida, Gainesville, FL
Research Training Fellowship • Funded by the American Lung Association of Florida

Preventing Respiratory Muscle Weakness In People Who Need Mechanical Ventilation

Mechanical Ventilation And Diaphragmatic Oxidant Injury. Patients who require mechanical ventilation (MV) for assistance in breathing often develop respiratory muscle weakness. As a result, these patients have difficulty breathing on their own when attempts are made to wean them from the ventilator. All too often, the result is longer hospital stays and increased health care costs. These researchers and others have clearly demonstrated that MV leads to significant dysfunction of the diaphragm. This group is studying the mechanisms of cellular oxidant production induced by MV, since oxidant damage makes a key contribution to respiratory muscle dysfunction. Delineating the biochemical pathways involved in MV-induced oxidant production in the diaphragm is an essential first step toward developing an effective approach to controlling this damaging process. These studies will provide new and important information for developing strategies to retard MV-induced oxidant stress and the dysfunction that follows.

JERRY EU, MD

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

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

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 adap-

tation 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 signaling 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.

EVA N. GRAYCK, MD

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

Understanding How Blood Vessels In The Lungs Are Regulated Will Contribute To Better Treatment

Nitric Oxide And G Protein-Coupled Alpha-1-Adrenergic And 5-HT Receptor Function In The Pulmonary Vasculature.

Understanding the factors that regulate the function of blood vessels in the lungs will allow scientists to develop new therapies for lung diseases that affect these vessels, including adult respiratory distress syndrome (ARDS) and persistent pulmonary hypertension in newborn infants (PPHN). Both of these serious conditions are complicated by hypoxia or lack of adequate oxygen in body tissues, high blood pressure in the blood vessels of the lungs, and failure of the

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right ventricle of the heart. This investigation seeks to elucidate the function of G-protein receptors in the lung, and to provide new information on the biology of nitric oxide in lung blood vessels. The information being developed has broad relevance for all lung diseases that affect the pulmonary blood vessels.

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.

IRINA A. KOLOSOVA, PHD

Johns Hopkins University School of
Medicine, Baltimore, MD

Research Grant • Funded by the American Lung
Association of Maryland

The Role Of CPI-17 In The Regulation Of Endothelial Cytoskeleton And Permeability

Leaky Little Blood Vessels Cause Big Problems In The Lungs. Vascular endothelial cells line the internal surfaces of blood vessels and form a semi-selective barrier between blood and surrounding tissues. This project is focused on the mechanisms by which small blood vessels or capillaries in the lungs become "leaky", allowing fluid to escape from the blood vessel and penetrate the tissue. This leak-

iness is an early characteristic in the development of acute respiratory distress syndrome (ARDS). It results in lung swelling and dysfunction, which contribute to the high rate of serious illness and death in people who are afflicted with ARDS and acute lung injury. Understanding the cell biology of endothelial lung cells will be of significant importance in the scientific quest to discover the mechanisms that lead to lung swelling, and will also make an important contribution to identifying effective strategies for treatment and prevention.

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 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 (PGI₂), but little is known about how these agents achieve their beneficial clinical results. This project is investigating the effects of NO and PGI₂ 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.

STEPHEN H. LEE, MD

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

Learning More About Long-Term Survival Can Improve The Odds For Future Patients

Determinants Of Survival After Pulmonary Thromboendarterectomy For Chronic Thromboembolic Pulmonary Hypertension.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious condition characterized by long-standing obstruction of the large pulmonary arteries, leading to impairment of normal blood flow through the lungs. The basis of CTEPH is thought to stem from unresolved blood clots in the lung. CTEPH is associated with significant morbidity and risk for early death due to progressive heart failure. Fortunately, selected patients with CTEPH can experience dramatic improvement after undergoing a procedure called pulmonary thromboendarterectomy (PTE), which removes the chronic obstructive material from the pulmonary arteries. This project is evaluating a group of patients who underwent PTE surgery between 1990 and 2002, to identify and analyze the influence of a variety of variables on long-term survival. The information derived from this research will be valuable in characterizing longer-term prognosis and survival of patients with CTEPH who undergo PTE.

JEFFREY S. LESSAR, MD

University of Maryland, Baltimore, MD

Research Training Fellowship • Funded by the American Lung Association of Maryland

Fever Can Be A Deadly Foe In Lung Injury

Mechanisms Of Augmented Chemokine Expression In The Hyperthermic Hyperoxic Lung.

Fever is beneficial during most infections, but its benefit may be lost and fever may be associated with increased mortality in people who have more severe illnesses. These researchers have shown that the increase in temperature that occurs during fever changes the body's immune response, resulting in the increased expression of a family of genes that activate and attract white blood cells to the lungs. Once attracted, these cells stick in the interstitial lung tissue rather than passing

through to the airways, which may allow them to cause more lung injury. This project is elucidating the mechanisms by which lung injury occurs, especially in critically ill people and those who are being treated with high levels of supplemental oxygen. The information generated may lead to new methods for preventing Acute Respiratory Distress Syndrome (ARDS) by blocking fever, and provide new basic information about the pathways that lead to lung injury, and how they are modified by fever.

QING LU, PHD

Brown University, Providence, RI

Research Grant • Funded by the American Lung Association

Improving Treatment For Two Deadly Disorders

The Mechanism Of Transforming Growth Factor-beta1 Regulation Of Endothelial Monolayer Permeability.

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) have devastating consequences. About 30 percent of patients with these conditions die, despite the availability of modern intensive care. Changes in lung microvascular permeability are important early steps in the development of ALI and ARDS. These studies are elucidating the mechanisms by which lung microvascular permeability is regulated. The knowledge gained will contribute to establishing new treatment strategies that could prevent the development of ALI and ARDS, or provide more effective therapy.

TIMOTHY J. MCMAHON, MD, PHD

Duke University Medical Center, Durham, NC

Research Grant • Funded by the American Lung Association

Understanding The Function Of Red Blood Cells In The Lungs

Molecular Determinants Of Red Blood Cell-Derived Nitric Oxide Bioactivity In the Hypoxic Lung.

Red blood cells play important but poorly understood roles in the circulatory system of the lungs. This project's goal is to determine how S-nitrosothiols (SNOs), substances derived from red blood cells, modulate acute constriction of blood vessels in the lungs due to hypoxia, or lack of adequate oxygen. This condition is called hypoxic pulmonary

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vasoconstriction (HPV). The researchers hypothesize that the bioactivation and metabolism of red blood cell SNOs in the hypoxic lung are critically controlled by specific enzymes and are characterizing how this chain of events occurs. Understanding precisely how red blood cells modulate HPV to optimize the uptake of oxygen in the lungs should be valuable in designing treatment for a wide spectrum of lung diseases, including high blood pressure in the lungs due to chronic lung disease and obstructive sleep apnea, as well as other serious disorders.

TORU NYUNOYA, MD

University of Iowa, Iowa City, IA
Research Training Fellowship • Co-funded with the American Lung Association and the American Lung Association of Illinois-Iowa

Too Much Oxygen Can Affect Lung Health

Hyperoxia-Induced Integrin Signaling Mediates Cell Cycle Arrest In Macrophages.

Hyperoxia, or an excess of oxygen, can be as damaging as insufficient oxygen to the lungs. Previous studies have shown that hyperoxia recruits cells called macrophages, which are involved in inflammation, to the lungs. Hyperoxia also decreases the lungs' defense system against bacteria. These scientists have found that hyperoxia induces a series of complex events that affect lung health, such as cell cycle arrest, cell spreading, survival signals, and other interactions. Understanding the mechanisms of how hyperoxia affects macrophage responses such as cell cycle arrest and survival signals will be important in developing strategies for preventing and treating toxic conditions in the lungs as a result of hyperoxia.

DEBORAH A. QUINN, MD

Massachusetts General Hospital, Boston, MA
Research Grant • Funded by the American Lung Association

Assessing The Risk Of Pulmonary Embolism In Women

Women and Pulmonary Embolism.

Pulmonary embolism (PE), in which a blood clot or other piece of foreign matter plugs an artery in the lungs, kills about 150,000 people

a year in the United States. This is equal to the annual number of deaths from lung cancer, even though PE can be treated and prevented with blood-thinning agents that keep clots from forming. PE has been reported to be higher in women than in men, suggesting that some risk factors for PE are tied to gender. This project is identifying significant risk factors for PE that are unique to women, such as childbearing and taking estrogen, and examining how these risk factors interact with general risk factors such as a lengthy stay in bed due to illness, or prolonged inactivity. The data being developed will allow them to construct a clinical prediction model to help identify women at the highest risk of PE, and assess the most effective methods of preventing it.

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 an estimated 18 million people in the USA, and chronic obstructive pulmonary disease (COPD) affects between 11 and 24 million 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.

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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.

DAYA UPADHYAY, MD

Stanford University, Stanford, CA
Research Grant • Funded by the American Lung Association of California

Preventing Irreversible Lung Damage In Acute Respiratory Distress Syndrome And Pulmonary Fibrosis

Modulation Of Oxidant-Induced Cell Cycle Arrest By Fibroblast Growth Factor-10: Role Of G1 Cyclins. Exposure to oxidants triggers intense and diffuse inflammation of the lungs, and a series of events that includes the loss of certain types of lung cells, swelling of lung tissue due to a buildup of fluid, the proliferation of cells called fibroblasts and an accumulation of collagen similar to acute respiratory distress syndrome (ARDS) and lung scarring. This project is focused on investigating fibroblast growth factor-10 (FGF-10), a substance that is required for lung development and is known to prevent oxidant injury. The scientists are elucidating the role of FGF-10 in preventing ox-

idant-induced cell injury by studying cell cycle regulation in the lung. Their work is clarifying the molecular and biological basis of the origin of disease in ARDS and lung scarring. Understanding these mechanisms may make it possible to design treatments to prevent irreversible lung damage in these conditions.

NICHOLAS E. VLAHAKIS, MD

Mayo Clinic/Foundation, Rochester, MN
Research Grant • Funded in partnership between the American Lung Association and the LUNgevity Foundation

Understanding How Blood Vessels Form And Grow Could Lead To New Treatments For Lung Diseases

The Role Of The Integrin Alpha9 Beta1 In Modulating VEGF-A Dependent Pulmonary Angiogenesis. This project is focused on angiogenesis, the process by which new blood vessels are formed and differentiated. Angiogenesis involves orchestrated biological processes that require interaction among numerous substances in the body, including growth factors, integrins, proteases, and various types of cells. It is central to the progression of cancer, as cancer tumors stimulate blood vessel formation around and into themselves, sending out chemical signals to promote the growth of new blood cells that feed cancer cells with oxygen and nutrients. This allows the malignant cells to grow, invading nearby tissue and spreading or metastasizing to other parts of the body. Angiogenesis is also involved in inflammation and wound healing. These scientists are clarifying the molecular mechanisms that underlie angiogenesis in the pulmonary system, to point the way toward better treatment for lung diseases in which angiogenesis plays a major role, such as lung cancer and acute lung injury and repair.

XIAORU YANG, MD, PHD

Johns Hopkins University, Baltimore, MD
Research Training Fellowship • Funded by the American Lung Association of Maryland

Local Calcium Signaling In Pulmonary Artery Smooth Muscle Cells During Chronic Hypoxia

Oxygen Deficiency Can Cause High Blood Pressure In The Lungs, But How Does It

Develop? Pulmonary hypertension or high blood pressure in the lungs can be induced by hypoxia, a deficiency of oxygen that occurs in a variety of lung diseases including chronic obstructive pulmonary disease (COPD). This research is studying the molecular and cellular changes in calcium level stability in the smooth muscle cells of the pulmonary arteries during chronic hypoxia. The investigators are using a combination of molecular biology techniques and state-of-the-art calcium imaging techniques to obtain previously unavailable information at the subcellular level. These data will provide new insight into how high blood pressure develops in the lungs, and may help in the search for better treatment for lung diseases involving this condition.

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 ventilation, 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.

American Lung Association researchers are studying a wide variety of other lung infections in the quest for better ways to prevent and heal them. Among the infections being investigated are HIV infection as well as a number of common and less common viruses, and several organisms that can cause pneumonia. Pneumonia that is acquired during a hospital stay (nosocomial pneumonia), a major problem for critically ill patients, is also being studied.

INFECTIONS

TEMITAYO O. AJAYI, MD

University of California, San Francisco, CA
Research Training Fellowship • Co-funded with the American Lung Association and the American Lung Association of Puerto Rico and Supplemented by the American Lung Association of California

Diagnosing Pneumonia In Hospitalized Patients Before It Spirals Out Of Control

Development Of PCR-Based Approaches To The Genotyping And Detection Of Pseudomonas Aeruginosa Pneumonia.

Nosocomial infections occur in patients who have been hospitalized due to some other disease, and affect more than two million people annually in the United States. Nosocomial pneumonia alone is responsible for numerous deaths and billions of dollars of medical costs each year. Most cases develop in the ICU and are associated with mechanical ventilation (breathing with assistance from a machine). A type of pneumonia called *Pseudomonas aeruginosa* for the organism that causes it is one of the most common forms associated with patients on ventilators. The goal of these studies is to provide new tools for identifying *P. aeruginosa* pneumonia more rapidly and accurately, which would make it possible to better control both the severity of the illness and the mortality rate, which is now about 42 percent.

ARUNA K. BEHERA, PHD

Tufts New England Medical Center,
Boston, MA
Research Grant • Funded by the American Lung Association

Targeting Genes To Prevent RSV Infection

Role Of Matrix Metalloproteinases In Respiratory Syncytial Virus Infection.

Respiratory syncytial virus (RSV) is the single most important cause of lower respiratory tract infection among infants, and is also a risk factor for developing asthma. This virus is responsible for about 4 million cases of respiratory tract infection annually, resulting in 125,000 hospitalizations and 2,500 deaths. It is most likely to be life-threatening in premature infants less than 6 months old, infants with chronic diseases, the frail elderly and those with weakened immune systems. Despite these severe consequences, no effective treatment is currently available. Understanding how RSV

disease originates is the key to developing meaningful treatment. These studies are elucidating the molecular mechanisms of a process known as RSV fusion protein activation, which plays a key role in RSV-induced infection. The knowledge being developed will provide information about particular genes that are responsible for this process, making it possible to develop anti-RSV therapeutic agents to target these genes.

AZZAQ BELAAOUAJ, PHD

Washington University School of Medicine,
Saint Louis, MO

Career Investigator Award • Co-funded with the American Lung Association and the American Lung Association of Missouri

Neutrophils: Good Guys, Bad Guys, Or Both?

Neutrophil Antimicrobial Systems And Lung Host Defense Against Bacteria.

Neutrophils, a type of white blood cell, are known to be associated with such diseases as cystic fibrosis, emphysema and ARDS (Acute Respiratory Distress Syndrome). While scientific interest has focused on the pathologic effects of neutrophils, their normal functions as a component of the immune system's defense of the body against foreign invaders are not well understood. These studies aim to demonstrate that neutrophils do play a beneficial role in protecting against lung infections, and the inflammation associated with such infections. The investigators hope to identify molecules that are targeted by neutrophils as part of the immune defense, which could be important information in developing new agents to treat lung infections.

LINDA S. CAULEY, PHD

University of Connecticut Health Center,
Farmington, CT

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

Finding A Better Influenza Vaccine By Studying The Body's Own Defenses

T Cell Activation And Inflammation In The Lungs.

Influenza infections are a serious health problem, especially for those whose defenses against disease are the weakest, such as very young children, elderly people, those with

chronic respiratory or circulatory problems, and others with a weakened immune system. Infection with influenza virus can be prevented by vaccination, but currently available methods can be slow to control new outbreaks of the virus and are not always effective. Most vaccines only provide immunity for about a year before new strains of virus emerge. To develop better vaccination strategies, it is essential to understand how the immune system protects the respiratory tract against respiratory virus infections. Researchers have shown that memory T cells in the lungs play an important role in guarding against virus infections. The current studies are clarifying how activated CO8 T cells are maintained in the lungs in the presence of inflammation, and how this process contributes to protective cellular immunity.

SHAQJI CHENG, MD, PHD

University of Florida, Gainesville, FL
Young Investigator Award • Funded by the American Lung Association of Florida

Virulence Genes Turn A Benign Presence Into A Killer Infection

Identifying Genes Expressed By *Aspergillus Fumigatus* During Invasive Pulmonary Aspergillosis. *Aspergillus fumigatus* is a fungus that causes fatal infections in patients with compromised immune systems, especially those who have received a heart or lung transplant. The death rate from aspergillosis infection in transplant recipients approaches 70 percent. This fungus is ubiquitous in the environment and is often a benign presence in humans. The mechanisms by which it switches to a disease-causing organism are not well understood but may involve newly expressed genes that enhance its virulence and enable it to cause invasive infection. This project seeks to identify these virulence genes, which would enhance understanding of how aspergillosis infection arises and point to new directions for diagnosis and antifungal drug and vaccine development.

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.

LAKSHMI DURAIRAJ, MD

University of Iowa Hospitals and Clinics,
 Iowa City, IA
Clinical Research Grant • Co-funded with the American Lung Association and the American Lung Association of Illinois-Iowa

Preventing Pneumonia In Vulnerable Intensive Care Patients

Aerosolized Xylitol For Reduction Of Lower Respiratory Tract Colonization In Ventilated Patients. This project is investigating a new way to prevent pneumonia that develops in hospitalized patients, known as nosocomial pneumonia. More than 85 percent of all cases of nosocomial pneumonia occur in people in the intensive care unit (ICU) who must use a ventilator to breathe. These individuals typically experience prolonged hospital stays, higher health care costs, and a significant mortality

rate. The problem is increasing as more and more people are treated for serious conditions that require ICU care and breathing assistance. Colonization of the respiratory tract with bacteria is an important step in the development of nosocomial pneumonia, and a high rate of colonization is known to exist among ICU patients on ventilators. To prevent this, these researchers are testing the effectiveness of an agent called Xylitol that has the potential to decrease respiratory tract colonization and infection. Administering Xylitol as an aerosol spray may prove to be a simple, inexpensive and safe way to ward off nosocomial pneumonia.

CHERYLYN A. ELWELL, PHD

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

Preventing A Stealth Infection By Tinkering With The Genes It Exploits

Novel Screen To Study Chlamydia Pneumoniae Pathogenesis. *Chlamydia Pneumoniae* is a germ that causes acute and chronic respiratory diseases, and has also been associated with heart and lung conditions. Chlamydia infections are difficult to diagnose, and attempts to develop a chlamydia vaccine have been futile. People with chlamydia infections often have no symptoms, allowing the infection to progress to chronic disease, lung tissue scarring and irreversible damage. New options for detecting and treating this infection are badly needed. These studies are seeking a way to prevent the chlamydia germ from surviving in the body by exploiting and subverting the function of specific genes that it uses to promote itself and to spread. Interfering with such "host genes" could interrupt or prevent infection. Understanding the interactions between host genes and chlamydia may also produce insights into the association between the presence of chlamydia and the development of heart and lung disease.

HUSEIN HADEIBA, PHD

Stanford University Medical Center,
Stanford, CA
Research Training Fellowship • Funded by the American Lung Association and Supplemented by the American Lung Association of California

Harnessing Viruses To Defend Against Asthma

The Role Of Influenza A Virus Infection In Asthma. The goal of this project is to understand the mechanisms that keep asthma from developing. Asthma is linked to exposure to allergens in the environment and to respiratory viral infections in early childhood, with the timing of virus infection appearing to play a critical role in either worsening or suppressing asthma. While concurrent viral infections such as influenza or respiratory syncytial virus tend to make asthma symptoms worse in children who already have asthma, other studies suggest that early childhood infections may guard against asthma. Clarifying how such protection occurs may suggest new approaches to a virus-based vaccine. These scientists are studying the immune response of laboratory animals exposed to the influenza A virus and then to an allergen associated with asthma, seeking to identify key cellular or molecular mediators that inhibit asthma. The knowledge they gain about how viral infections influence the course of asthma could make it possible to use viruses to prevent asthma.

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

Why Does Obesity Increase The Risk Of Pneumonia?

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.

JANAK KOIRALA, MD, MPH

Southern Illinois University School of Medicine, Springfield, IL
Research Grant • Funded by the American Lung Association of Illinois-Iowa

When The Body's Defenses Fail, Opportunistic Infections Take Over

Interferon-gamma Macrophage Functions Against Mycobacterium Avium Complex Infection Of HIV-Infected Patients.

Macrophages are specialized cells that engulf and destroy bacteria and foreign particles in the lungs and other organs. People with HIV infection experience a progressive decline in macrophage functions, which plays a significant role in their vulnerability to opportunistic infections, including a serious infection called Mycobacterium avium complex (MAC). These researchers hypothesize that a defect in the means by which the body produces a substance called interleukin-12 (IL-12) mediated interferon-gamma (IFN-gamma) has a significant impact on macrophage function in people with advanced HIV infection. Their goal is to make a comprehensive assessment of IFN-gamma production, to explore the mechanisms of its effect on cellular immunity, and to find ways to improve macrophage functions in HIV infected patients. This will help delineate more clearly the way HIV disease and opportunistic infections arise. Identifying individuals with a defect in IFN-gamma production and macrophage function will allow physicians to initiate appropriate measures earlier. Further exploration of measures to overcome such defects will be valuable in developing more effective treatment.

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

Preventing A Deadly Infection In People With Cystic Fibrosis

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) 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.

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 60,000 cases of invasive disease occurring annually 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.

RICHARD K. PLEMPER, PHD

Emory University, Atlanta, GA
Research Grant • Funded by the American Lung Association

Controlling The Spread Of Virus Infections In Youngsters Could Impact Asthma And COPD

Template-Based Design Of Paramyxovirus Entry Inhibitors. Members of the paramyxovirus family such as respiratory syncytial virus (RSV), human parainfluenza viruses (hPIV), and measles virus are the cause of major diseases including virus-induced pneumonia, bronchiolitis, and measles. In particular, RSV and hPIVs account for a significant number of hospitalizations and mortality mostly of infants and young children, since no vaccines are available that protect against these viruses. While early infection with RSV appears to be linked to the later development of asthma and chronic obstructive pulmonary disease (COPD), infection with hPIVs can result in the croup syndrome. These investigators are seeking new strategies to counter paramyxovirus infections. Their work is focused on inhibiting the viruses, which would minimize symptoms and reduce vital spread in settings of close contact of young children such as day care centers and pre-schools. Reducing the incidence and severity of RSV infection in infants could also have an impact on the incidence of asthma and COPD.

MATTEO POROTTO, PHD

Mount Sinai School of Medicine,
New York, NY
Research Grant • Funded by the American Lung Association

Understanding The Role Of Inflammation In Viruses That Attack Children

Immunopathogenesis Of Lung Disease Caused By Human Parainfluenza Virus 3. Human parainfluenza virus type 3 (HPIV3) is second only to respiratory syncytial virus (RSV) as a cause of serious lower respiratory tract infections in infants and children, including croup, pneumonia, bronchitis and bronchiolitis. Excessive inflammation appears to be involved in HPIV3, and the disease in the lungs is determined by the interplay between the virus and the immune system's response. The cell type and mechanism responsible for dis-

ease that occurs in minute tissue structures after HPIV3 infection is completely unknown. To clarify how this occurs, the scientists are studying the mechanisms that regulate the body's inflammatory response to the invading virus, information that will be valuable in designing more effective treatment and prevention.

LYNN M. SCHNAPP, MD

University of Washington, Seattle, WA
Career Investigator Award • Co-funded with the American Lung Association of Washington and the American Thoracic Society

How Does Hiv Infection Lead To Lung Injury?

HIV-Matrix Interactions In The Lung. Pulmonary manifestations of HIV infection are a major cause of disease and death among people with AIDS. The lungs are an important reservoir of HIV and a site of virus replication, which results in HIV-induced lung injury. The means by which HIV leads to direct lung injury, and how virus replication is sustained within the lung are not known. The researchers hypothesize that lung damage mediated by HIV contributes to dysfunction of the immune system, which increases susceptibility to the opportunistic infections that plague people who are infected with HIV. Their studies focus on the interactions of HIV and HIV-infected cells with the surrounding extracellular matrix, which is particularly relevant to lung disease. The information they obtain will provide insight into how HIV infection impairs lung function and increases susceptibility to infections such as tuberculosis, and may lead to innovative therapies to prevent HIV-mediated lung damage.

ALBERT P. SENFT, PHD

Children's Hospital Medical Center,
 Cincinnati, OH
Research Training Fellowship • Funded by the American Lung Association

Controlling The Consequences Of A Nasty Virus

Respiratory Syncytial Virus And Macrophage Oxidative Burst. Respiratory syncytial virus (RSV) is a significant cause of respiratory tract illness in children, the elderly, and those with weakened immune systems. There is no cure for RSV infection, no vaccine to prevent it, and reinfection with this virus is common; thus, developing better approaches to controlling its consequences is highly important. Macrophages, specialized cells that engulf and destroy bacteria and foreign particles, play an instrumental role in protecting the lungs from disease-causing agents. RSV, like other viruses, inhibits the ability of lung macrophages to kill bacterial germs, thereby predisposing the lungs to secondary bacterial infections. These scientists are unraveling the way RSV prevents lung macrophages from doing their job. Clarifying the mechanisms by which this occurs will contribute to developing better treatment for secondary bacterial infections, and may also point the way toward preventing them.

CHAD STEELE, PHD

Children's Hospital of Pittsburgh,
 Pittsburgh, PA
Research Grant • Co-funded with the American Lung Association and the American Lung Association of Pennsylvania

Fighting Off Pneumonia In People With HIV Disease

Alveolar Macrophage Host Defense Against Pneumocystis Carinii. *Pneumocystis Carinii* pneumonia often attacks people who are infected with HIV, whose weakened immune systems make them susceptible to infections that are not often seen in healthy individuals. Although better means of prevention and treatment have reduced its incidence, *P. Carinii* infection is apparently delayed rather than eliminated. CD4 T cells, a key immune system cell that is destroyed by HIV disease, are critical in protecting against infection and use the alveolar macrophage as a weapon to combat *P. Carinii*. Alveolar macrophages are specialized cells in the lungs that engulf and destroy bacte-

ria and foreign particles. B-cell mediated immunity, also critical for protection against infection, similarly relies on alveolar macrophages to induce killing of *P. Carinii*, making the elimination of *P. Carinii* the exclusive responsibility of alveolar macrophages. These studies are providing new insight into how the alveolar macrophages recognize and kill *P. Carinii*, and what substances they produce during this process. This knowledge should make it possible to identify treatment strategies to combat this devastating pulmonary infection.

NEAL J. THOMAS, MD

Pennsylvania State University, Hershey, PA
Clinical Research Grant • Co-funded with the American Lung Association and the American Lung Association of Pennsylvania

A Genetic Variation May Make Some Children More Vulnerable To Complications From A Common Virus

Surfactant Proteins Genetic Variants In Children With Respiratory Syncytial Virus Infection. Virtually all children acquire Respiratory Syncytial Virus (RSV) infection during the first two years of life, but only a small percentage require hospitalization, and only a few of those children become ill enough to require assistance in breathing. The researchers are seeking to determine whether these children have a genetic predisposition to develop serious RSV disease. If so, and if such children could be identified, it might be possible to target them for preventive measures. The investigators are examining whether genetic differences in surfactant protein variants may be a key factor in why some children develop severe disease from RSV infection, and why they seem to go on to long-term chronic lung disease such as asthma. Surfactant is essential for normal expansion of the lungs and is abnormal or lacking in premature infants with respiratory distress syndrome and other diseases, suggesting that surfactant protein genetic differences may be a logical indication of vulnerability to severe problems arising from RSV infection.

STEVEN M. VARGA, PHD

University of Iowa, Iowa City, IA
Research Training Fellowship • Funded by the American Lung Association of Illinois-Iowa

Building A Better Vaccine

Cellular And Genetic Dissection Of Virus-Induced Lung Injury. Respiratory syncytial virus (RSV) is the most common cause of pneumonia and bronchiolitis, a viral inflammation of the small airways, in young children worldwide. RSV infection occurs mainly during the first two years of life, accounting for some 125,000 hospitalizations annually in the United States alone. An experimental vaccine for RSV was developed in the 1960s, but it caused the disease to worsen and increased mortality. Recent studies suggest that a subset of cells called CD4 T cells combine with undefined genetic factors to contribute to vaccine-enhanced lung pathology in RSV infection. This group is defining the role of RSV-specific memory CD4 T cells in mediating the RSV vaccine-enhanced disease process. They are also identifying the genetic factors that contribute to RSV vaccine-enhanced lung injury. These analyses will aid in understanding the cellular and genetic factors that contribute to RSV vaccine-enhanced lung injury, and provide new and valuable information for developing a safe and effective RSV vaccine.

GARY R. WHITTAKER, PHD

Cornell University College of Veterinary Medicine, Ithaca, NY
Career Investigator Award • Funded by the American Lung Association of New York State, Inc.

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

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 related complications are responsible for 36,000 deaths annually in the United States. 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

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

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

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

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

OTHER LUNG INFECTIONS

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 American Lung Association of New York State, Inc.

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 while air pollution can make the condition worse. The work of the American Lung Association has been critical in achieving a significant decline in cigarette smoking in the past 30 years, from 37.4 percent in 1970 to 22.5 percent in 2002, 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 some 159 million Americans live in counties with unhealthy levels of either ozone or particle pollution.

The American Lung Association supports a broad-based program of research into many aspects of COPD. Laboratory studies and patient-oriented investigations continue to look for answers to the fundamental questions of how the lungs and airways are damaged in COPD and what can be done to treat and prevent this destruction. 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. Patient centered studies are addressing such problems as the best way to assess quality of care. Other investigations 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

ZSUZSANNA BEBOK, MD

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

How Does Chronic Inflammation Develop In The Respiratory Tract?

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.

MICHAEL A. CAMPOS, MD

University of Miami School of Medicine,
Miami, FL
Young Investigator Award • Funded by the American Lung Association of Florida

How Does Airway Disease Occur In People With A Protein Deficiency That Causes A Form Of Emphysema?

Role Of Alpha-1 Proteinase Inhibitor Synthesized In Human Airway Epithelial Cells. Alpha-1 antitrypsin deficiency (AIAD) is a genetic condition that results in an inherited form of emphysema, due to the lack of a protective protein called alpha-1-antitrypsin that is normally secreted by the liver in

large quantities. AATD occurs in approximately one half of one percent of all emphysema patients and is also associated with a high prevalence of airway diseases, including chronic bronchitis and asthma. The origin of airway disease in people with AATD is not well understood, but may be linked to the intense inflammation that is typically present in the airways and the alveoli of these individuals. The airway epithelium or lining of the airways also secretes this protein, and the researchers hypothesize that the epithelium may also be involved in this inflammatory process. A series of experiments designed to increase understanding of the role of airway epithelium in inflammation are being carried out. The resulting data will clarify how airway disease comes about in patients with AATD and provide baseline knowledge for future studies.

PAUL J. CHRISTENSEN, MD

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

How Does Cigarette Smoke Lead To Lung Damage?

The Role of Granulocyte-Macrophage Colony Stimulating Factor In The Development Of Smoke-Induced Lung Disease. Chronic obstructive lung disease (COPD) is characterized by obstruction of airflow due to chronic bronchitis or emphysema. The primary cause of COPD is exposure to tobacco smoke, which accounts for between 80 and 90 percent of the deaths due to this devastating disease. The mechanism by which tobacco smoke leads to COPD is not well defined, but inflammation of the airways and bronchial hyperreactivity are thought to play a key role in the process by which the disease begins. These studies are examining the involvement of a substance called granulocyte-macrophage colony stimulating factor (GM-CSF) in the development of airway hyperresponsiveness and smoke-induced lung disease. Understanding the basic mechanism of how cigarette smoke leads to lung damage, how to protect the lungs from this damage, and how to reverse the damage once it is established are important steps toward discovering new ways to treat COPD and improving the lives of the millions of people who suffer from it.

DAWN L. DEMEO, MD, MPH

Brigham & Women's Hospital, Harvard Medical School, Boston, MA
Research Grant • Funded by the American Lung Association of Massachusetts, the American Lung Association of Western Massachusetts, and the Alpha-1 Foundation

Why Are More Women Than Men Dying From COPD?

Genetic Investigation Of Sex Differences In Chronic Obstructive Pulmonary Disease.

The number of women who died in 2001 as a result of chronic obstructive pulmonary disease (COPD) was greater than the number of deaths among men. This ominous trend suggests that women may be more susceptible to the effects of cigarette smoking on the lungs than men are, but scientific data on the genetic basis of this phenomenon are lacking. Such information is essential to understanding how COPD develops, determining how best to treat it, and developing targeted educational efforts to help prevent it. These scientists are investigating genetic differences between men and women that may have a bearing on COPD, which like most chronic diseases involves multiple genes and the interaction of genetic susceptibility with environmental factors. Their findings may establish a biologic and genetic explanation for differences in COPD between women and men. With that knowledge, more aggressive and effective gender-specific public health messages about the risks of tobacco use and COPD in women may be designed, and better treatment may be offered.

KEITH C. DERUISSEAU, PHD

University of Florida, Gainesville, FL
Research Training Fellowship • Funded by the American Lung Association of Florida

Preventing Respiratory Muscle Weakness In People Who Need Mechanical Ventilation

Mechanical Ventilation And Diaphragmatic Oxidant Injury. Patients who require mechanical ventilation (MV) for assistance in breathing often develop respiratory muscle weakness. As a result, these patients have difficulty breathing on their own when attempts are made to wean them from the ventilator. All too often, the result is longer hospital stays and increased health care costs. These researchers and others

have clearly demonstrated that MV leads to significant dysfunction of the diaphragm. This group is studying the mechanisms of cellular oxidant production induced by MV, since oxidant damage makes a key contribution to respiratory muscle dysfunction. Delineating the biochemical pathways involved in MV-induced oxidant production in the diaphragm is an essential first step toward developing an effective approach to controlling this damaging process. These studies will provide new and important information for developing strategies to retard MV-induced oxidant stress and the dysfunction that follows.

RAMZI KAFOURY, MPH

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

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

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.

PING-PING KUANG, MD

Boston University Medical Campus,
Boston, MA
Research Grant • Co-funded with the American Lung Association and the American Lung Association of Massachusetts

Seeking A Way To Prevent Emphysema

Regulation Of Fibulin-5 Gene Expression In Lung Fibroblasts. Emphysema is a major cause of death and disability in chronic obstructive pulmonary disease (COPD). This condition destroys the walls of air spaces in the lungs, creating abnormally large air spaces. The amount of lung surface available for oxygen uptake is thereby decreased, which makes it harder to breathe and leaves people with severe emphysema struggling for every breath. Fibulin-5 is a newly discovered molecule that is important in the processes related to repair after lung injury and to the development of emphysema. The molecular mechanisms by which fibulin-5 is expressed are unknown. This project is investigating, identifying and characterizing the mechanisms that underlie the regulation of fibulin-5 gene expression, which will elucidate how fibulin-5 is regulated and expressed during the development of emphysema and the lung injury repair process. This new knowledge may suggest ways to intervene in the development of emphysema.

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, Inc.

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 (hypercap-

nea). 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.

KOLAWOLE OKUYEMI, MD, MPH

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

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.

IRINA PETRACHE, MD

Johns Hopkins University, Baltimore, MD
Research Grant • Co-funded with the American Lung Association, the American Lung Association of Maryland, and the American Lung Association of Delaware

Why Do Some Lung Cells Commit Suicide That Leads To Emphysema?

The Role Of Oxidative Stress In Ceramide-Induced Pulmonary Cell Apoptosis And Emphysema. There are currently no effective treatments for reversing or even slowing down the lethal progression of emphysema. The programmed cell death, or apoptosis, of the alveolar cells that form the tiny saclike structures in the lungs where gas exchange takes place is a central occurrence in the development of this disorder. Apoptosis and inflammation combine

synergistically with oxidative stress to trigger the destruction of lung tissue. This project is elucidating the mechanisms by which apoptosis of lung cells takes place in emphysema. The investigation should add significantly to scientific knowledge about the relationship between apoptosis and oxidative stress as destructive pathways of emphysema. Armed with this knowledge, it should be possible to identify new targets for treatment.

JOSEPH M. PILEWSKI, MD

University of Pittsburgh, Pittsburgh, PA
Career Investigator Award • Funded by the American Lung Association of Pennsylvania

A Safe And Simple Way To Clear Mucus From The Airways

Effect Of Bicarbonate On Mucociliary Clearance. Airway obstruction by mucus contributes significantly to the development of progressive respiratory disease in people with chronic bronchitis and bronchiectasis, chronic inflammatory airway diseases. Mucus obstruction also plays a role in asthma episodes. This project is examining whether inhaled bicarbonate can increase the clearance of mucus in a laboratory model of lung cells, and in patients with these conditions; subsequent studies will assess whether pulmonary function improves when mucus clearance is increased. Although inhaled bicarbonate is not expected to cure chronic bronchitis, bronchiectasis or asthma, it may offer an inexpensive, safe means of treatment that is widely applicable and easy to administer, and it may prove to delay the progression of lung disease by improving airway clearance.

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. 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.

THOMAS H. SISSON, MD

University of Michigan, Ann Arbor, MI
Research Grant • Funded by the American Lung Association

Identifying A New Culprit In The Onset Of Emphysema

The Role Of The Plasminogen System In The Pathogenesis Of Emphysema. Mounting evidence suggests that emphysema results from an imbalance in the lungs of enzymes known as proteases and anti-proteases. Alpha-1 antitrypsin is known to be an important participant in the normal protease/anti-protease balance, and matrix metalloproteinases are also implicated in the development of emphysema, but sufficient information to direct new strategies for prevention is lacking. Other proteases and inhibitors belonging to the plasminogen activation system have previously received little attention as a potential culprit in emphysema. These investigators have demonstrated for the first time that imbalances in the plasminogen system can cause emphysema, and are seeking to broaden understanding of how emphysema originates by further exploring the role of the plasminogen system. They are also investigating how exposure to tobacco influences the protease/antiprotease balance in the lungs. This information should make it possible to better predict who is at risk for emphysema, and may also define new avenues of treatment.

AKSHAY SOOD, MD, MPH

Southern Illinois University School of Medicine, Springfield, IL
Clinical Research Grant • Co-funded with the American Lung Association and the American Lung Association of Illinois-Iowa

Evaluating The Effectiveness Of A Telephone Helpline For Smokers Who Want To Quit

Effectiveness Of A Reactive Anti-Smoking Telephone Help Line. The American Lung Association has launched a telephone line to help smokers quit. The project is based on a proposal originally developed by the American Lung Association of Illinois. These researchers are evaluating the effectiveness of this "reactive" telephone line, in which smokers 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. Establishing the program's effectiveness is critical to determining its value compared to other smoking cessation approaches.

VASANTHI R. SUNIL, PHD

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

Ozone-Battling Macrophages: Defenders Of The Lungs Sometimes Become Part Of The Problem

Role Of Heat Shock Protein 60 In Ozone-Induced Lung Toxicity. Ozone is the main component of the form of air pollution known as photochemical smog, readily combining and reacting chemically or oxidizing with biological substances such as cells and tissue. Inhaled ozone can be a powerful respiratory irritant, capable of causing pulmonary edema or swelling, airway hyperresponsiveness, and damage to the cells that line the lungs. The lungs are constantly exposed to inhaled com-

pounds, and macrophages are the primary cells involved in defending the lungs against these toxicants. Tissue damage caused by a number of toxins is due not only to the direct action of the compound on the tissue, but also to the actions of inflammatory mediators generated in large part by macrophages. The investigators are examining the role of HSP 60, an important mediator of inflammation and tissue injury. Understanding the mechanisms underlying ozone-induced lung injury at the molecular level will provide key insights into designing strategies for preventing lung injury.

PHILIP THAI, MD

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

Abnormal Mucus Production Can Have Lethal Effects In Lung Disease

Interaction Between IL-17 And IL-13 In The Expression Of Mucin And Related Genes In Airway Epithelial Cells. This project is researching the basic biology of how the body produces mucus. Abnormal mucus production plays an important role in such lung diseases as asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis, causing airway obstruction and often leading to significant disease and even death. Increased understanding of the mechanisms that bring it about will lead to improvements in treating and preventing these sometimes life-threatening diseases.

ROBERT VASSALLO, MD

Mayo Clinic, Rochester, MN
Research Grant • Funded by the American Lung Association

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

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

How Do Lung Cells Respond To Tobacco Smoke?

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

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

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.

JIANLIANG ZHANG, PHD

University of Florida, Gainesville, FL
Career Investigator Award • Funded by the American Lung Association of Florida

How Does Cigarette Smoke Lead To The Death Of Lung Cells?

Mitochondrial Cytochrome C Oxidase Mechanisms Of Smoke-Induced Lung Endothelial Cell Death. Cigarette smoking is firmly established as a major cause of chronic obstructive pulmonary disease (COPD), including emphysema. Programmed cell death or apoptosis of endothelial cells in the lungs is induced by cigarette smoke, and plays a critical role in emphysema. Nitric oxide (NO), a major gas component in cigarette smoke, is known to be involved in triggering apoptosis, but the molecular mechanisms that contribute to this complex process remain unclear. This

project is testing a hypothesis regarding the chain of events that leads to endothelial apoptosis. The findings will add to current knowledge of the mechanisms by which cigarette smoke impacts the lungs and leads to severe disease such as emphysema.

QUNWEI ZHANG, MD, PHD

University of Pennsylvania, Philadelphia, PA
Research Grant • Funded by the American Lung Association of Pennsylvania and the American Lung Association of Puerto Rico

Small And Sneaky Components Of Air Pollution Attack On Several Fronts.

Endothelial Generation Of Reactive Oxygen Species In Lung Exposure To Ultrafine Particles. Particulate matter (PM), a major outdoor air pollutant, is produced by the burning of fuels by industry and diesel vehicles, and by earth-moving activities such as construction and mining. PM affects the respiratory system and contributes to or worsens such lung disorders as asthma, lung cancer, chronic obstructive pulmonary disease (COPD) and lower respiratory tract infections. Ultrafine particles, a component of PM, also play a key role in inducing cardiovascular effects, which has significance for disorders of the blood vessels in the pulmonary system as well as for cardiovascular disease such as heart attack, angina, heart failure, and heart rhythm disorders. Ultrafine particles may pass from the lungs into the bloodstream because of their very small size. This project is studying the direct effects of ultrafine particles on specific types of cells, to develop information about how PM induces both lung and cardiovascular diseases.

Tuberculosis remains an important disease in the United States and a worldwide epidemic that kills some 2 million people each year. Since it is transmittable 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.

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

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 million 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.

ALAN G. CZAPLICKI, MA

Northwestern University, Evanston IL
Lung Health Dissertation Grant • Co-funded with the American Lung Association and the American Lung Association of Metropolitan Chicago

Managing The Spread Of Tuberculosis: What Works, What Doesn't?

The Risk Of Treatment: Tuberculosis, Public Health Practice And The State. This project explores governmental efforts to reduce the spread of tuberculosis in the United States and Canada. Both countries face continuing problems regarding the spread of tuberculosis among disadvantaged minority populations and recent immigrants from countries where tuberculosis is widespread. Reaching out to these groups is central to any effective strategy for eliminating tuberculosis. This study seeks to understand how local and state public health systems, prison systems, advocacy groups for poor and immigrant populations and the American Lung Association can best collaborate to achieve their goals. Comparing how the United States and Canada are handling this

issue will highlight the advantages and disadvantages of the decentralized American public health and medical system, versus the Canadian system of a national health service that serves as a central medical authority. It will provide valuable insight into how organizations can work together more effectively to contain a serious and growing public health problem.

JENNIFER FURIN, MD, PHD

Brigham & Women's Hospital, Boston, MA
Clinical Research Grant • Co-funded with the American Lung Association, the American Lung Association of Massachusetts, and the American Lung Association of Middlesex County

Why Do Some Tuberculosis Patients Stick With A Complicated Treatment Program While Others Abandon It?

Compliance With Therapy For Multidrug-Resistant Tuberculosis. Tuberculosis is one of the leading lethal infections of adults in the world today. Drug-resistant strains of the disease are becoming more common, and treating them is increasingly difficult. People with multiple drug-resistant tuberculosis (MDRTB) are more likely than other tuberculosis patients to be noncompliant and fail to take their medication, yet little is known about why this is so. Noncompliance is likely to be related to having to take as many as eight different drugs for as long as two years. Sticking with this complex treatment program is particularly important in MDRTB, because not taking the medication can generate new strains of tuberculosis that are incurable in that they will not respond to any drugs. This project is studying two groups of MDRTB patients, one in which compliance is high and one in which individuals have abandoned or not complied with therapy. The goal is to identify factors associated with compliance and to develop means of improving it among those who fall by the wayside.

TARA L. HERRMANN, BS

University of Iowa, Coralville, IA
Lung Health Dissertation Grant • Funded by the
 American Lung Association of Illinois-Iowa

**The Adaptive Immune System's Role In
 Containing And Controlling Tuberculosis**

**Possible Regulation Of Signal Transduction
 Events By Mycobacterium Tuberculosis.**

Tuberculosis continues to be a global health issue, with an estimated 2 billion people in the world infected with *Mycobacterium tuberculosis*, and more than 2 million people dying of the disease in a year. Although treatment has greatly improved, considerable therapeutic limitations still exist. Coupled with the worldwide spread of AIDS, with its increased susceptibility to tuberculosis, and the emergence of multi-drug resistant *M. tuberculosis*, the need for new and innovative care and treatment has become paramount. These researchers are studying the molecular mechanisms by which dendritic cells regulate the adaptive immune system in its efforts to contain and control invading *M. tuberculosis*. The results of this investigation will provide a foundation for developing new therapies and vaccines for tuberculosis.

RUSSELL K. KARLS, PHD

University of Georgia College of Veterinary
 Medicine, Athens, GA
Research Grant • Funded by the American Lung
 Association of Georgia

**Understanding How Tuberculosis Infection
 Hides Within The Body**

**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.

PAYAM NAHID, MD

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

Tracking The Spread Of Tuberculosis

**Impact Of The Number Of Contacts On The
 Transmission Of Tuberculosis – A Molecular
 Epidemiologic Study.** The Centers for Disease Control and Prevention estimate that of the nearly 10-15 million people in the U.S. who are infected with tuberculosis, 10 percent will develop active disease if they are not identified and treated. Contact investigations are conducted by health departments around the country to find, screen, and treat anyone who has had contact with a person with active tuberculosis, but a certain number of cases yield no contact information. This study is using cutting-edge molecular genotyping technology to examine the transmission of tuberculosis in zero-contact providers, versus people with tuberculosis who do provide contacts. Describing this group's unique characteristics and the spread of disease associated with them will provide valuable information to tuberculosis control groups and help improve procedures for tracking this subset of high-risk patients.

GERARD J. NAU, MD, PHD

University of Pittsburgh Medical Center,
 Pittsburgh, PA
Research Grant • Co-funded with the American
 Lung Association and the American Lung
 Association of Pennsylvania

**Manipulating The Immune System To Wipe
 Out Lurking Tuberculosis Germs**

**Immunotherapy Of Mycobacterium
 Tuberculosis Infection.** The goal of this project is to develop a fresh approach to treating tuberculosis, a major cause of lung disease and death worldwide. The World Health Organization has estimated that 1 billion people will become infected with tuberculosis between 2002 and 2020; of these, 150 million will become ill, and 36 million will die. Current tuberculosis treatments are cumbersome and take months to complete. Those who have active infections and fail to complete treatment often develop drug-resistant strains of tuberculosis, which are even more difficult and expensive to treat. These investigators are

seeking ways to manipulate the immune system to provide more effective treatment for latent tuberculosis infection that lurks within the body, and can become active at any time and infect others. Immunotherapy could eliminate these reservoirs of bacteria, prevent reactivation, and interrupt the spread of tuberculosis. It would complement existing tuberculosis treatment and could be applicable to a variety of infections.

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

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

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.

HOMAYOUN SHAMS, DVM, PHD

University of Texas Health Center, Tyler, TX
Research Grant • Funded by the American Lung Association

Studying A Peptide That May Be The Key To An Effective Tuberculosis Vaccine

Characterization Of Mycobacterial Peptides That Are Recognized By CD4+ And CD8+ T-Cells. Tuberculosis is the oldest pulmonary infectious disease known to affect humans. In view of the HIV epidemic that has generated a population that is highly susceptible to tuberculosis and the dramatic emergence of multidrug-resistant tuberculosis, tuberculosis will remain a major health problem in the years to come. Development of an effective vaccine against tuberculosis would have a major impact on public health throughout the world. To develop a vaccine, it is essential to identify molecules that can elicit protective immunity against *Mycobacterium tuberculosis*, the germ that causes tuberculosis. Such molecules include peptides, which are composed of amino acids. We have identified a peptide that elicits strong responses from persons infected with *M. tuberculosis*, and it appears to be a promising candidate for inclusion in a new anti-tuberculosis vaccine. The results of these studies may also be useful for designing vaccines against other organisms that infect the lungs, such as viruses and fungi.

RAMAKRISHNA VANKAYALAPATI, PHD

University of Texas Health Center, Tyler, TX
Research Grant • Co-funded with the American Lung Association and the American Lung Association of Texas

Natural Killer Cells Help Prevent Tuberculosis Germ From Causing Disease

The Contribution Of Natural Killer (NK) Cells To Innate Defense Against Tuberculosis. Most people who become infected with the germ that causes tuberculosis remain healthy and do not develop active tuberculosis disease. Understanding how the body's normal immune response controls tuberculosis infection offers important insights into the mechanisms of protective immunity against tuberculosis, information that is essential to developing an effective vaccine. These studies are providing data on the role of natural killer (NK) cells in the

immune system's defenses against tuberculosis, which will facilitate the development of antituberculosis vaccines as well as immunotherapy for people with weakened immune responses. The investigators are also laying the foundation for additional studies regarding the role of NK cells in the immune system's response to other organisms that attack the lungs, such as viruses and fungi.

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, some with a goal of developing novel methods of prevention of this, the major cancer killer in the United States. 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. Others 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. Finally, novel diagnostic techniques are being explored as early detection remains the key to cure.

LUNG CANCER

CAROLYN J. BAGLOLE, PHD

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

Blocking Lung Inflammation Caused By Smoking May Help Prevent Lung Cancer

Cigarette Smoke-Induced Human Lung Fibroblast Activation: Implications For Inflammation And Cancer. This research entails basic studies at the cellular level of the early events in lung disease that involve inflammation. Lung cells called fibroblasts are known to be linked to the chronic inflammation that is associated with progression to lung cancer. These studies seek to clarify the role fibroblasts play in the process of inflammation and cancer that is induced by smoking cigarettes. While quitting smoking reduces the likelihood of developing lung cancer and other serious medical conditions, it does not offer a guarantee that the chronic inflammation associated with extended tobacco use will not turn into cancer. A better understanding of the molecular mechanism of smoke-induced inflammation may make it possible to selectively block the pathway by which it occurs, thereby reducing lung disease. This would be a significant step in preventing lung cancer among the 90 million current and former smokers in the country today.

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 160,000 Americans annually. Even with the best currently available treatment, it can only be cured at its earliest stage, and the 5-year survival rate is a low 15 percent. 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.

WEIGUO HAN, MD, PHD

Health Research, Inc./New York State Department of Health, Albany, NY
Research Training Fellowship • Funded by the American Lung Association of New York State, Inc.

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.

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.

HASMEENA KATHURIA, MD

Boston University School of Medicine,
Boston, MA

Research Training Fellowship • Funded by the American Lung Association

Blocking A Protein To Keep Lung Cancer Under Control

Regulation Of Caveolin-1 In Lung Tumors And Cell Lines. Lung cancer is the leading

cause of cancer death among both men and women in the United States, with a 5-year survival rate of only 15 percent. Little is known about how lung cancer arises at the molecular level. These researchers hypothesize that a structural protein called caveolin-1 may be involved both in the origin of lung tumors and in their spread, or metastasis. They are characterizing how caveolin-1 is expressed in lung cancer cells, how such expression is regulated, the cell type in which it occurs, and when it takes place. If caveolin-1 is required for advanced tumor stage, understanding how it is regulated has important implications for treatment. If it is reexpressed in cancer cells that have metastasized to other locations in the body, blocking reexpression could offer a way to keep lung cancer from spreading.

VENKATESHWAR G. KESHAMOUNI, PHD

University of Michigan, Ann Arbor, MI

Research Grant • Funded in partnership between the American Lung Association and the LUNGeity 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 5-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-gamma, 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.

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 • Funded in partnership between
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 anti-cancer 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.

JULIANA J. OH, PHD

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

Identifying A Gatekeeper Gene That May Prevent Lung Cancer From Developing

Characterization Of H37, A Lung Cancer Tumor Suppressor Gene At Chromosome 3p21.3.

Despite the fact that smoking is the primary cause of lung cancer, only 10-15 percent

of lifetime smokers eventually develop it. This suggests that genetic factors may predispose certain people to lung cancer, whereas the genetic makeup of other smokers may ward it off. The researchers have cloned and are studying a gene called H37 that is located at the chromosomal region known as 3p21.3, the most frequently altered chromosomal region in lung cancer. They have demonstrated that H37 possesses tumor suppressor gene characteristics and are currently investigating the mechanism by which it suppresses tumors, and its role in lung development and the development of cancer. This gene may eventually serve as a new treatment for lung cancer, as well as a biomarker that could identify individuals at high risk for developing lung cancer. It can also be a valuable tool for diagnosing lung cancer in its early stages, assessing the effectiveness of treatment, and evaluating prevention efforts.

ANGEL R. PINEDA, PHD

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

Image Guidance Aids In Diagnosing Lung Cancer

Task-Based Reconstruction Of Ultrafast Tomosynthesis For Guidance Of Lung-Nodule Biopsy. Diagnosing lung cancer earlier in the course of the disease could improve the currently bleak prognosis for this terrible disease, which is presently the most common cause of cancer death in the United States. Detecting lung cancer early enough to treat it effectively requires the ability to biopsy small lung nodules, which is difficult to accomplish by means of the conventional techniques for removing suspicious tissue and examining it for the presence of cancer. The researchers are developing an image guidance procedure for transbronchial needle aspiration, in which a hollow needle is used to collect small lung nodules for examination. The new procedure will allow the simultaneous visualization of the needle being used to aspirate tissue for biopsy, and the lung nodule being aspirated. This will greatly improve the effectiveness of minimally invasive biopsy procedures, with the least possible X-ray exposure to the patient.

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.

MOHAMAD O. SHAMMA, MD

Southern Illinois University School of Medicine, Springfield, IL
Junior Research Training Fellowship • Funded by the American Lung Association of Illinois-Iowa

Evaluating The Role Of Pet Scanning In A Common Form Of Lung Cancer

Evaluation Of FDG-PET For Mediastinal Staging Of Non-Small Cell Lung Cancer In A Histoplasmosis Endemic Region. Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for about eighty percent of new cases. Surgery is the standard treatment for NSCLC that has not metastasized or spread extensively or to distant lymph nodes. Staging this cancer, or diagnosing its level of malignancy, is vitally important in determining the prognosis and selecting the most effective treatment. Individuals with

NSCLC that has spread to the mediastinal lymph nodes have an average 5-year survival rate of approximately 10 percent, compared to a survival rate of 50 percent when there are no mediastinal metastases. PET scanning is frequently used to identify mediastinal metastases of NSCLC, but its accuracy has not been determined in areas that have high rates of histoplasmosis, a fungal infection that occurs mostly in the south central United States. This research is evaluating the accuracy and cost-effectiveness of PET scanning in a region that does have a high rate of histoplasmosis, compared to regions that do not.

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 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. 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. Researchers are also seeking new ways to prevent the lung scarring that follows certain types of lung inflammation.

INFLAMMATION, AND LUNG SCARRING

IMMUNE SYSTEM, INFLAMMATION, AND LUNG SCARRING

AZZAQ BELAAOUAJ, PHD

Washington University School of Medicine,
Saint Louis, MO
Career Investigator Award • Co-funded with the
American Lung Association and the American
Lung Association of Missouri

Neutrophils: Good Guys, Bad Guys, Or Both?

Neutrophil Antimicrobial Systems And Lung Host Defense Against Bacteria. Neutrophils, a type of white blood cell, are known to be associated with such diseases as cystic fibrosis, emphysema and ARDS (Acute Respiratory Distress Syndrome). While scientific interest has focused on the pathologic effects of neutrophils, their normal functions as a component of the immune system's defense of the body against foreign invaders are not well understood. These studies aim to demonstrate that neutrophils do play a beneficial role in protecting against lung infections, and the inflammation associated with such infections. The investigators hope to identify molecules that are targeted by neutrophils as part of the immune defense, which could be important information in developing new agents to treat lung infections.

MICHAEL R. BLACKBURN, PHD

University of Texas Health Science Center,
Houston, TX
Career Investigator Award • Co-funded with the
American Lung Association and the American
Lung Association of Texas

Controlling An Enzyme That Turns On Inflammation

Role Of Ecto-5's-Nucleotidase In Chronic Lung Disease. These investigators are identifying signaling pathways that represent new treatment targets for chronic lung diseases such as asthma and COPD. They are studying adenosine, a signaling nucleoside that is thought to be involved in regulating chronic lung disease. They have demonstrated that increasing adenosine levels in laboratory animals can lead to lung inflammation and damage similar to what is found in people with asthma and COPD. Current studies are focused on CD73, an enzyme that plays a key part in producing adenosine. This enzyme is elevated in inflamed lungs, suggesting that activating the adenosine signaling pathway is paramount in regulating chronic lung disease. A greater

understanding of CD73 could lead to new treatment that inhibits CD73 activity in the lungs of people with chronic lung disease. This would prevent adenosine from accumulating in the lungs, where it promotes inflammation and tissue damage.

SCOTT BOITANO, PHD

Arizona Respiratory Center, Tucson, AZ
Career Investigator Award • Funded by the
American Lung Association

How Do Cells In The Lungs Communicate And Respond To Injury?

Cell Communication In The Alveolus.

Although more than 40 types of cells are present in the lungs of mammals, just two cell types make up the lining (epithelium) of the alveoli, the microscopic air sacs through which oxygen and carbon dioxide are exchanged when we breathe. This research is elucidating how these cells normally interact with each other and with a third cell type, alveolar macrophages, and how they respond to injury. Distinct signaling pathways define the interactions between the three cell types and the subtle differences in pathways help to shape a coordinated defense against injury. Understanding how these processes work at the basic cellular level could expedite the formulation and testing of new medical treatments for dysfunctional conditions that occur in the airways following disease or lung injury.

CLAIR BRAMMER, PHD

University of Connecticut Health Center,
Farmington, CT
Research Training Fellowship • Funded by the
American Lung Association of Connecticut

Understanding The Sentinels Of The Immune System

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.

MONICA G. CHIARAMONTE, PHD

Children's Hospital Medical Center,
Cincinnati, OH

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

Controlling A Lethal Lung Disease

Role Of Complement Component C5 In The Modulation Of Bleomycin Induced Pulmonary Fibrosis. Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive disorder that affects about 5 million people worldwide and 200,000 in the U.S. alone. One of a group of disorders called interstitial lung diseases, its cause is unknown, it is generally lethal, and there are no effective means of preventing or treating it. A better understanding of the disease-causing mechanisms by which IPF develops is clearly needed to improve the quality of life and extend the lives of those who are afflicted with this deadly condition. These scientists are studying the role of a substance known as complement component C5 in protecting against pulmonary fibrosis. Their research will provide valuable insights into the basic mechanisms underlying the development of pulmonary fibrosis in IPF and other interstitial lung diseases, and may lead to new ways of either preventing it or reversing its course.

THOMAS G. DIACOVO, MD

Washington University School of Medicine,
St. Louis, MO

Career Investigator Award • Funded by the American Lung Association

Keeping Carpet-Bagger Cells In Their Place To Control Inflammation In The Lungs

Mechanisms And Implications Of PI3Kdelta In Neutrophil Migration And Activation. Inflammatory diseases that affect the lungs

respect no age boundaries, killing and incapacitating infants and children as readily as adults and the elderly. Neutrophils are a type of white blood cell that play a prominent role in inflammation; the ability to inhibit the accumulation of neutrophils in lung tissue would be a valuable tool for treating a variety of lung diseases. This project is focused on identifying precisely how neutrophils are summoned by other substances in the body to participate in the inflammatory process, and how it might be possible to blockade the molecular pathway through which they migrate. This information will make a significant contribution to the development of a new family of anti-inflammatory drugs designed to limit the progression of such devastating diseases as acute respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD).

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.

MARILYN K. GLASSBERG, MD

University of Miami, School of Medicine,
Miami, FL

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

Saving Young Women From A Fatal Lung Disease

Estrogen Regulation Of MMP-2 Activity: Implications For The Nature And Treatment Of Lymphangioleiomyomatosis. The goal of this study is to enhance understanding of an aggressive and deadly lung disease called lymphangioleiomyomatosis (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

Why Do Normal Cells Become Destructive?

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 progression 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.

TARA L. HERRMANN, BS

University of Iowa, Coralville, IA

Lung Health Dissertation Grant • Funded by the American Lung Association of Illinois-Iowa

The Adaptive Immune System's Role In Containing And Controlling Tuberculosis

Possible Regulation Of Signal Transduction Events By Mycobacterium Tuberculosis. Tuberculosis continues to be a global health issue, with an estimated 2 billion people in the world infected with *Mycobacterium tuberculosis*, and more than 2 million people dying of the disease in a year. Although treatment has greatly improved, considerable therapeutic limitations still exist. Coupled with the worldwide spread of AIDS, with its increased susceptibility to tuberculosis, and the emergence of multi-drug resistant *M. tuberculosis*, the need for new and innovative care and treatment has become paramount. These researchers are studying the molecular mechanisms by which dendritic cells regulate the adaptive immune system in its efforts to contain and control invading *M. tuberculosis*. The results of this investigation will provide a foundation for developing new therapies and vaccines for tuberculosis.

JANAK KOIRALA, MD, MPH

Southern Illinois University School of
Medicine, Springfield, IL

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

When The Body's Defenses Fail, Opportunistic Infections Take Over

Interferon-Gamma Macrophage Functions Against Mycobacterium Avium Complex Infection Of HIV-Infected Patients. Macrophages are specialized cells that engulf and destroy bacteria and foreign particles in the lungs and other organs. People with HIV infection experience a progressive decline in macrophage functions, which plays a significant role in their vulnerability to opportunistic infections, including a serious infection called *Mycobacterium avium* complex (MAC). These researchers hypothesize that a defect in the

means by which the body produces a substance called interleukin-12 (IL-12) mediated interferon-gamma (IFN-gamma) has a significant impact on macrophage function in people with advanced HIV infection. Their goal is to make a comprehensive assessment of IFN-gamma production, to explore the mechanisms of its effect on cellular immunity, and to find ways to improve macrophage functions in HIV infected patients. This will help delineate more clearly the way HIV disease and opportunistic infections arise. Identifying individuals with a defect in IFN-gamma production and macrophage function will allow physicians to initiate appropriate measures earlier. Further exploration of measures to overcome such defects will be valuable in developing more effective treatment.

VIBHA N. LAMA, MD

University of Michigan, Ann Arbor, MI
Research Grant • Funded by the American Lung Association

Preventing Lethal Lung Scarring After Transplantation

Role Of Pro-Fibrotic Milieu In The Development Of Bronchiolitis Obliterans Syndrome. Lung transplantation is the only hope of survival for many people with end stage lung disease. The 1-year survival rate after transplantation is approximately 80 percent, but long-term outcome is limited by the development of bronchiolitis obliterans syndrome (BOS). BOS is a universally progressive disease that inexorably leads to scarring of the airways and death. This group is studying the mechanisms by which BOS originates, particularly the role of cells and mediators linked to the development of scarring or fibrosis. Knowing the biology of the fibroblasts, the primary cell that is responsible for fibrosis, and the role of various mediators in the development of fibrosis in BOS, offers the possibility of designing treatment to prevent it. This project also lays the foundation for studying fibroblasts and mediators after transplantation, which will increase understanding of the stage at which fibrotic changes occur and provide clues about how and when to intervene.

ANN MARIE LEVINE, MD

Children's Hospital Medical Center,
Cincinnati, OH
Career Investigator Award • Funded by the American Lung Association

Using A Substance In The Body To Prevent Lung Inflammation

Modulation Of Pulmonary Inflammation By Surfactant Protein-D. Inflammation of the lungs is a serious and sometimes life threatening condition that has a variety of causes. Effective treatment remains elusive, and improving it requires a better understanding of the molecular and cellular pathways involved in regulating the inflammatory process. The aim of these studies is to determine the role of surfactant protein D (SP-D) in preventing lung inflammation. Decreased levels of SP-D are associated with inflammation in people who have cystic fibrosis, and in acute respiratory distress syndrome (ARDS), but the mechanisms by which SP-D regulates lung inflammation are poorly understood. Clarifying SP-D's role and elucidating the way in which SP-D regulates receptors that mediate SP-D's protective effect may provide the basis for new ways to treat or prevent lung infections caused by a variety of organisms.

LINYING LIU, MD

University of Wisconsin, Madison, WI
Research Grant • Funded by the American Lung Association

New Clues To Airway Inflammation In Asthma

Loss Of Membrane IL-5 Receptor On Eosinophils In Airway Inflammation: Functional Significance And Mechanisms.

A better understanding of the mechanisms that cause asthma is crucial to identifying new targets for treatment to alter its course and limit its ability to cause disease and death. Despite the alarming rise in frequency and severity of asthma over the past 20 years, scientific understanding of many aspects of this disease is still limited. These studies will provide new information on the role of interleukin (IL)-5, a substance known as a cytokine that is a key player in the allergic airway inflammation characteristic of asthma. The researchers are also studying the role of IL-5's receptor on eosinophil function and delineating the mechanisms that

regulate its expression. Eosinophils are white blood cells that are increased in allergic diseases and can damage the lung tissue in asthma. The data being developed will have important implications for treatment approaches in people with asthma.

RUI-MING LIU, MD, PHD

University of Alabama, Birmingham, AL
Career Investigator Award • Funded by the American Lung Association

Unraveling The Complexities Of How Lung Scarring Develops

Glutathione, Transforming Growth Factor-Beta, And Lung Fibrosis. Lung fibrosis or scarring is the final stage of many lung diseases. Concentrations of glutathione (GSH), an important antioxidant, are decreased in the lung lining fluid of people with lung diseases that involve scarring, such as cystic fibrosis and idiopathic pulmonary fibrosis. Administering GSH or its precursor, N-acetyl cysteine, has been shown to improve pulmonary function. This suggests that GSH depletion may play a role in the development of lung scarring. The researchers are testing the hypothesis that GSH depletion promotes lung scarring by mediating the effects of a substance called transforming growth factor beta (TGF- β) that is involved in scarring and is known to decrease GSH content in various types of cells. This study will provide important information on how lung fibrosis originates, and may also yield new strategies for prevention and treatment.

ANNE M. MANICONE, MD

Fred Hutchinson Cancer Research Center, Seattle, WA
Research Training Fellowship • Co-funded with the American Lung Association and the American Lung Association of Washington

Studying Cells That May Promote Lung Inflammation

The Role Of CXCR3-Expressing Myeloid Cells In Th1-Mediated Lung Injury. Knowing how cells are selectively recruited to the lungs and to sites of injury from other locations in the body is essential in furthering scientific understanding of the

mechanisms by which the immune system functions, both normally and in disease states. This work is elucidating the role of a newly described population of myeloid cells in lung injury, and exploring whether these cells help promote inflammation. The cells are called CXCR3-expressing myeloid cells and have been associated with inflammatory conditions affecting the lungs. The information acquired in this research will enhance understanding of the mechanisms of lung inflammation, which is critical in developing better treatments for devastating and life-threatening lung diseases such as sarcoidosis, emphysema, and rejection of transplanted lungs.

DAVID G. MORRIS, MD

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

Identifying Genetic Pathways That Set The Stage For Lung Scarring

Genetic Variation In Murine Lung Collagen Metabolism. Lung diseases that involve fibrosis or scarring are deadly, poorly understood, and difficult to treat. These researchers are investigating the process of lung fibrosis in laboratory animals, using new protein labeling technology to measure collagen metabolism in the lungs. Collagen is a fibrous element of supporting tissue that provides strength to many organs. But when collagen metabolism goes awry and too much collagen builds up, fibrosis may develop. This work aims to identify genetic pathways that either facilitate or impede the process of fibrosis. The ability to classify tissue as over-producing or not over-producing collagen holds great promise as a disease marker and as an indicator of the prognosis for patients with fibrotic lung diseases. Uncovering genetic pathways that lead to progressive fibrosis can guide the development of rational therapy for these intractable disorders, and pave the way for a potentially very important application of a novel technology that has substantial implications for treatment.

IMMUNE SYSTEM, INFLAMMATION, AND LUNG SCARRING

GERARD J. NAU, MD, PHD

University of Pittsburgh Medical Center,
Pittsburgh, PA

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

Manipulating The Immune System To Wipe Out Lurking Tuberculosis Germs

Immunotherapy Of Mycobacterium Tuberculosis Infection. The goal of this project is to develop a fresh approach to treating tuberculosis, a major cause of lung disease and death worldwide. The World Health Organization has estimated that 1 billion people will become infected with tuberculosis between 2002 and 2020; of these, 150 million will become ill, and 36 million will die. Current tuberculosis treatments are cumbersome and take months to complete. Those who have active infections and fail to complete treatment often develop drug-resistant strains of tuberculosis, which are even more difficult and expensive to treat. These investigators are seeking ways to manipulate the immune system to provide more effective treatment for latent tuberculosis infection that lurks within the body, and can become active at any time and infect others. Immunotherapy could eliminate these reservoirs of bacteria, prevent reactivation, and interrupt the spread of tuberculosis. It would complement existing tuberculosis treatment and could be applicable to a variety of infections.

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

Studying A Key Regulator Of Lung Inflammation And Scarring

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 5 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.

MARK F. SANDS, MD

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

Matrix Biology: A New Frontier For Studying Inflammation In Asthma

Molecular Mechanisms Of Lung Remodeling And Hyperresponsiveness In Asthma: Role Of Metalloproteinases And Inhibitors. Asthma appears to be a family of disorders rather than a single disease, leading to a syndrome that is the result of many gene variants interacting with complex environmental stimuli. This project is exploring the basic inflammatory mechanisms of asthma through studies of how cells interact with each other, migrating and communicating in their microenvironments. A specific component of matrix biology is being elucidated, an area of study on the cutting edge of asthma research. The data being developed will better define the nature of the inflammatory response, and will contribute to a clearer understanding of asthma, as well as to better treatment and even the ability to prevent asthma from developing. The lessons being learned about matrix biology may also be translated into other key areas of research such as acute lung injury.

ALBERT P. SENFT, PHD

Children's Hospital Medical Center,
Cincinnati, OH

Research Training Fellowship • Funded by the American Lung Association

Controlling The Consequences Of A Nasty Virus

Respiratory Syncytial Virus And Macrophage Oxidative Burst. Respiratory syncytial virus (RSV) is a significant cause of respiratory tract illness in children, the elderly, and those with weakened immune systems. There is no cure for

RSV infection, no vaccine to prevent it, and re-infection with this virus is common; thus, developing better approaches to controlling its consequences is highly important. Macrophages, specialized cells that engulf and destroy bacteria and foreign particles, play an instrumental role in protecting the lungs from disease-causing agents. RSV, like other viruses, inhibits the ability of lung macrophages to kill bacterial germs, thereby predisposing the lungs to secondary bacterial infections. These scientists are unraveling the way RSV prevents lung macrophages from doing their job. Clarifying the mechanisms by which this occurs will contribute to developing better treatment for secondary bacterial infections, and may also point the way toward preventing them.

VASANTHI R. SUNIL, PHD

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

Ozone-Battling Macrophages: Defenders Of The Lungs Sometimes Become Part Of The Problem

Role Of Heat Shock Protein 60 In Ozone-Induced Lung Toxicity. Ozone is the main component of the form of air pollution known as photochemical smog, readily combining and reacting chemically or oxidizing with biological substances such as cells and tissue. Inhaled ozone can be a powerful respiratory irritant, capable of causing pulmonary edema or swelling, airway hyperresponsiveness, and damage to the cells that line the lungs. The lungs are constantly exposed to inhaled compounds, and macrophages are the primary cells involved in defending the lungs against these toxicants. Tissue damage caused by a number of toxins is due not only to the direct action of the compound on the tissue, but also to the actions of inflammatory mediators generated in large part by macrophages. The investigators are examining the role of HSP 60, an important mediator of inflammation and tissue injury. Understanding the mechanisms underlying ozone-induced lung injury at the molecular level will provide key insights into designing strategies for preventing lung injury.

ANDREW M. TAGER, MD

Massachusetts General Hospital,
Charlestown, MA
Dalsemer Research Grant • Funded by the American Lung Association

Hunting Down A New Way To Stop Lung Scarring

Mechanisms Of Fibroblast Migration And Recruitment In Pulmonary Fibrosis.

The cause of Idiopathic Pulmonary Fibrosis (IPF), which is characterized by lung scarring and kills more than half of its victims within five years of diagnosis, remains enigmatic. Once thought to be driven by chronic inflammation, scientists have recently theorized that it results from chronic lung injury, and repair processes within the body that go awry. Treatment strategies for suppressing chronic inflammation have been largely ineffective, and increasing research attention is being directed at fibrogenesis, the process by which lung scarring originates. These studies are concerned with a component of fibrogenesis, the recruitment of cells called fibroblasts into the lungs. The researchers hypothesize that interrupting this migration of fibroblasts could halt the progression of IPF. Designing treatment based on this strategy first requires an understanding of the mechanisms of fibroblast migration. The current studies are identifying the molecular mediators of fibroblast migration in the development of lung scarring, with the goal of opening the door to an exciting new strategy for treating a hitherto intractable disorder.

PHILIP THAI, MD

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

Abnormal Mucus Production Can Have Lethal Effects In Lung Disease

Interaction Between IL-17 And IL-13 In The Expression Of Mucin And Related Genes In Airway Epithelial Cells.

This project is researching the basic biology of how the body produces mucus. Abnormal mucus production plays an important role in such lung diseases as asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis, causing airway obstruction and often leading to significant disease and even death. Increased understanding

IMMUNE SYSTEM, INFLAMMATION, AND LUNG SCARRING

of the mechanisms that bring it about will lead to improvements in treating and preventing these sometimes life-threatening diseases.

DAYA UPADHYAY, MD

Stanford University, Stanford, CA
Research Grant • Funded by the American Lung Association of California

Preventing Irreversible Lung Damage In Acute Respiratory Distress Syndrome And Pulmonary Fibrosis

Modulation Of Oxidant-Induced Cell Cycle Arrest By Fibroblast Growth Factor-10: Role Of G1 Cyclins. Exposure to oxidants triggers intense and diffuse inflammation of the lungs, and a series of events that includes the loss of certain types of lung cells, swelling of lung tissue due to a buildup of fluid, the proliferation of cells called fibroblasts and an accumulation of collagen similar to acute respiratory distress syndrome (ARDS) and lung scarring. This project is focused on investigating fibroblast growth factor-10 (FGF-10), a substance that is required for lung development and is known to prevent oxidant injury. The scientists are elucidating the role of FGF-10 in preventing oxidant-induced cell injury by studying cell cycle regulation in the lung. Their work is clarifying the molecular and biological basis of the origin of disease in ARDS and lung scarring. Understanding these mechanisms may make it possible to design treatments to prevent irreversible lung damage in these conditions.

GARY A. VISNER, DO

J. Hillis Miller Health Center University of Florida, Gainesville, FL
Career Investigator Award • Funded by the American Lung Association of Florida

Preventing A Deadly Complication Of Lung Transplantation

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.

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

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

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 people'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.

BAOHUA ZHOU, PHD

Virginia Mason Research Center, Seattle, WA
Research Training Fellowship • Funded by the
American Lung Association of Washington

Pinpointing The White Blood Cells Responsible For Asthma Inflammation

Roles Of Thymic Stromal Lymphopietin In Bronchopulmonary Inflammation.

Eosinophils are a type of white blood cell that influence inflammatory reactions. Eosinophilic inflammation is a characteristic feature in the airways of many people with asthma, and most treatment and prevention strategies for asthma focus on controlling this phenomenon. However, recent research has suggested that in fact another class of cells called neutrophils, known to be important in the immune process, may account for more than half of all asthma cases. This group is using laboratory animal models to study the basic disease processes underlying neutrophilic airway inflammation, to gain a better understanding of how the inflammatory cascade is initiated. They are studying the roles of several mediators in the development of neutrophilic airway inflammation, which should yield results that are relevant to other neutrophilic asthma as well as to other neutrophilic airway diseases. Understanding how neutrophils and mediators interact to cause inflammatory disease should lead to better strategies for treating neutrophilic asthma, chronic obstructive pulmonary disease, and cystic fibrosis.

DISEASES OF

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 30 years, thanks to more sophisticated care and modern medicine's ability to replace a critical molecule called surfactant that is absent in premature lungs. Improved care techniques can now prolong life in children with *Cystic Fibrosis (CF)*. A clearer understanding of infant breathing has led to practical measures that have reduced deaths from *Sudden Infant Death Syndrome (SIDS or crib death)*.

Despite these advances, lung diseases and breathing disorders remain the leading causes of death in infants up to 1 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. Over 100,000 children are hospitalized each year due to *Respiratory Syncytial Virus (RSV)*, and an estimated 2,500 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 respiratory 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.

INFANTS & CHILDREN

SHANJANA AWASTHI, PHD

University of Texas Health Science Center,
San Antonio, TX
Research Grant • Funded by the American Lung Association

Can Immunotherapy Improve Treatment For Infants With Lung Disease?

Role Of Dendritic Cells And Pathogen-Pattern Recognition Receptors In The Premature Baboon Lung. Despite major advances in treatment, bronchopulmonary dysplasia (BPD) is still one of the most common and serious lung diseases in babies born prematurely. The condition is thought to be caused by prolonged oxygen treatment with a ventilator in extremely immature babies who are born and have respiratory distress syndrome. As many as 10,000 new cases occur each year in the U.S., accounting for treatment costs of more than 2 billion dollars. The investigators are seeking better treatment for BPD through a clearer understanding of how the immune system functions in the lungs of premature infants. Insights into abnormalities or deficiencies of the immune response could lead to effective immunotherapy that would complement existing treatment for BPD.

GUADALUPE X. AYALA, PHD

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

Helping Adolescents Get A Grip On Asthma

Tailored Asthma Communication To Improve Asthma Outcomes Among Preteens/Young Adolescents. Teaching young people with asthma how to manage their condition is critical to controlling the burgeoning asthma epidemic. Programs tailored to adolescents are sparse, and even fewer resources exist for minority adolescent populations. This study targets ethnically diverse preteens and adolescents with asthma, who are being studied to identify factors that facilitate successful asthma management. This information will be used to develop an asthma management program specially prepared for this hard-to-reach population, which will be available in both English and Spanish. The program will assess the results by examining whether participants more successfully managed their asthma. The goals are to engage

adolescents in discussing asthma management issues, to understand the behavioral and social factors that contribute to poor asthma management, and to discover effective ways to improve self-management knowledge and skills, and quality of life.

HUBERT O. BALLARD, MD

University of Kentucky, Lexington, KY
Joseph H. Humpert Pulmonary Research Award
Funded by the American Lung Association of Kentucky

A Safer Drug To Ward Off Lung Disease In Premature Infants

Lung Protection With Azithromycin In The Preterm Infant And The Role Of Ureaplasma And Mycoplasma In The Development Of Bronchopulmonary Dysplasia. Bronchopulmonary dysplasia (BPD) is an inflammatory disease of premature infants who need breathing assistance from a mechanical ventilator. It results in abnormal lung development and chronic lung disease that can affect lung function and health for a lifetime. Anti-inflammatory medications have the potential to lessen the incidence and severity of BPD, but currently available agents also have serious and sometimes deadly side effects. These studies are investigating the possible role of a macrolide antibiotic called azithromycin, which has anti-inflammatory properties, in reducing the incidence and severity of BPD without damaging side effects. If macrolide antibiotics are found to have a clear anti-inflammatory effect in BPD, they may also prove useful in certain other chronic inflammatory lung diseases. The researchers are also defining the role of lung infections such as mycoplasma and ureaplasma in the origin of BPD in very premature infants.

SAVERIO BELLUSCI, PHD, MS

Children's Hospital of Los Angeles,
Los Angeles, CA
Career Investigator Award • Funded by the American Lung Association

Growing Better Lungs And Repairing Injured Lungs

FGF10 Signaling In Embryonic Lung Development. This project is seeking to identi-

fy 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

Frog Embryos May Unlock The Secret Of How Human Lungs Develop

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.

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.

KEVIN S. HARROD, PHD

Lovelace Respiratory Research Institute,
Albuquerque, NM

Career Investigator Award • Funded by the American Lung Association

Understanding Lung Disease By Clarifying How Lung Genes Are Expressed

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 cer-

tain 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.

HASAN S. JAFRI, MD

University of Texas Southwestern Medical Center, Dallas, TX

Research Grant • Funded by the American Lung Association

Targeting An Ubiquitous Virus That Has Been Linked To Asthma

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 3. As many as 40 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

Stimulating Damaged Lungs To Repair Themselves

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

Preventing Lung Disease In Premature Infants On Breathing Machines

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.

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, Inc.

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.

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.

VICTOR NIZET, MD

University of California, San Diego, CA
Career Investigator Award • Funded by the American Lung Association

Helping The Tiniest Patients To Survive Pneumonia

Lung Injury And Inflammation In Neonatal Pneumonia: Basic Pathogenesis And Benefits Of Surfactant Phospholipid Therapy.

Lung diseases and breathing disorders are the leading cause of death in infants up to 1-year-old. Babies born prematurely and/or in minority or low socioeconomic populations are at the highest risk. These researchers are studying Group B *Streptococcus* (GBS), the number one cause of bacterial pneumonia in newborns. Despite advances in treatment, mortality remains unacceptably high and significant numbers of infants who do survive GBS are left with long-term medical complications. The investigators are examining whether a substance called surfactant phospholipid DPPC can block harmful GBS toxins and offer more effective treatment

for these babies. Surfactant is a mixture of lipids and proteins that normally lines the tiny air sacs in the lungs called alveoli, but is absent in premature lungs. These studies will provide fundamental new insights into the way pneumonia develops in newborns, how the lining of the infant's lung acts as a barrier against infection, and the potential value of treating such infections with DPPC.

MICHAEL OLDHAM, PHD

University of California, Irvine, CA
Clinical Research Grant • Funded by the American Lung Association of California

Quantifying The Protective Effect Of The Upper Airways In Children And Adolescents

Deposition Of Inhaled Carcinogens In ETS In Children And Adolescents. Since the upper airways from the nostrils through the larynx are the portal of entry to the lungs, it is critical to understand their protective effect, especially as these anatomical structures develop from childhood into adulthood. This project is quantifying the effect that growth and development of the upper airways has on the deposition of particulate matter, a major outdoor air pollutant, in the airways and lungs of children and adolescents. It is urgent to understand the role of the upper airways in the deposition of particulate matter in the lungs. The findings of this research may be applicable to a variety of particulates and to treatment programs that use inhaled medications.

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*.

RICHARD K. PLEMPER, PHD

Emory University, Atlanta, GA
Research Grant • Funded by the American Lung Association

Controlling The Spread Of Virus Infections In Youngsters Could Impact Asthma And COPD

Template-Based Design Of Paramyxovirus Entry Inhibitors. Members of the paramyxovirus family such as respiratory syncytial virus (RSV), human parainfluenza-viruses (hPIV), and measles virus are the cause of major diseases including virus induced pneumonia, bronchiolitis, and measles. In particular, RSV and hPIVs account for a significant number of hospitalizations and mortality mostly of infants and young children, since no vaccines are available that protect against these viruses. While early infection with RSV appears to be linked to the later development of asthma and chronic obstructive pulmonary disease (COPD), infection with hPIVs can result in the croup syndrome. These investigators are seeking new strategies to counter paramyxovirus infections. Their work is focused on inhibiting the viruses, which would minimize symptoms and reduce viral spread in settings of close contact of young children such as day care centers and pre-schools. Reducing the incidence and severity of RSV infection in infants could also have an impact on the incidence of asthma and COPD.

MATTEO POROTTO, PHD

Mount Sinai School of Medicine,
New York, NY
Research Grant • Funded by the American Lung Association

Understanding The Role Of Inflammation In Viruses That Attack Children

Immunopathogenesis Of Lung Disease Caused By Human Parainfluenza Virus 3.

Human parainfluenza virus type 3 (HPIV3) is second only to respiratory syncytial virus (RSV) as a cause of serious lower respiratory tract infections in infants and children, including croup, pneumonia, bronchitis and bronchiolitis. Excessive inflammation appears to be involved in HPIV3, and the disease in the lungs is determined by the interplay between the virus and the immune system's response. The cell type and mechanism responsible for disease that occurs in minute tissue structures after HPIV3 infection is completely unknown. To clarify how this occurs, the scientists are studying the mechanisms that regulate the body's inflammatory response to the invading virus, information that will be valuable in designing more effective treatment and prevention.

NARONG SIMAKAJORNBOON, MD

Tulane University School of Medicine,
New Orleans, LA
Research Grant • Co-funded with the American Lung Association and the American Lung Association of Louisiana

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

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 activa-

tion 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.

NEAL J. THOMAS, MD

Pennsylvania State University, Hershey, PA
Clinical Research Grant • Co-funded with the American Lung Association and the American Lung Association of Pennsylvania

A Genetic Variation May Make Some Children More Vulnerable To Complications From A Common Virus

Surfactant Proteins Genetic Variants In Children With Respiratory Syncytial Virus Infection.

Virtually all children acquire Respiratory Syncytial Virus (RSV) infection during the first two years of life, but only a small percentage require hospitalization, and only a few of those children become ill enough to require assistance in breathing. The researchers are seeking to determine whether these children have a genetic predisposition to develop serious RSV disease. If so, and if such children could be identified, it might be possible to target them for preventive measures. The investigators are examining whether genetic differences in surfactant protein variants may be a key factor in why some children develop severe disease from RSV infection, and why they seem to go on to long-term chronic lung disease such as asthma. Surfactant is essential for normal expansion of the lungs and is abnormal or lacking in premature infants with respiratory distress syndrome and other diseases, suggesting that surfactant protein genetic differences may be a logical indication of vulnerability to severe problems arising from RSV infection.

STEVEN M. VARGA, PHD

University of Iowa, Iowa City, IA
Research Training Fellowship • Funded by the
American Lung Association of Illinois-Iowa

Building A Better Vaccine

Cellular And Genetic Dissection Of Virus-Induced Lung Injury. Respiratory syncytial virus (RSV) is the most common cause of pneumonia and bronchiolitis, a viral inflammation of the small airways, in young children worldwide. RSV infection mainly occurs during their first two years of life, accounting for some 125,000 hospitalizations annually in the United States alone. An experimental vaccine for RSV was developed in the 1960s, but it caused the disease to worsen and increased mortality. Recent studies suggest that a subset of cells called CD4 T cells combine with undefined genetic factors to contribute to vaccine-enhanced lung pathology in RSV infection. This group is defining the role of RSV-specific memory CD4 T cells in mediating the RSV vaccine-enhanced disease process. They are also identifying the genetic factors that contribute to RSV vaccine-enhanced lung injury. These analyses will aid in understanding the cellular and genetic factors that contribute to RSV vaccine-enhanced lung injury, and provide new and valuable information for developing a safe and effective RSV vaccine.

DANIEL J. WEISS, MD, PHD

University of Vermont, Burlington, VT
Career Investigator Award • Funded by the
American Lung Association

Replacing Defective Cells: A New Treatment Possibility For Cystic Fibrosis

Repopulation Of CFTR KO Mouse Lungs With Bone Marrow Derived Cells. Cystic fibrosis (CF) is one of the most common genetic diseases, and most of its victims die in their late teens or early twenties. These studies are exploring a new treatment possibility, based on recent findings suggesting that cells taken from adult bone marrow in laboratory animals can go to the lungs and transform into new epithelial cells. Epithelial cells form the lining of the lungs and are defective in CF. This raises the prospect that cells from normal human bone marrow donors might be used to repopulate the defective lining of the lungs in

people with CF. It might also be possible to remove bone marrow cells from CF patients, correct their defect, and then return them to the patient. Before either of these approaches can be applied, much more information is needed to understand how adult bone marrow cells make their way to the lungs and transform into lung epithelial cells. These studies will help to delineate how this takes place in laboratory animals, and will serve as a basis for investigations in patients with CF.

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 Immunodeficiency Virus (HIV). HIV destroys a specific white blood cell, the helper T-lymphocyte or T-cell. Without this T-cell, the cellular immune system cannot function properly. AIDS is diagnosed in a patient with HIV infection who has a major complication, such as *pneumocystis carinii* pneumonia.

airway

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

amoeba

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

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 to 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 pre-mature 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 air-spaces 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.

GLOSSARY

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, 1 month to 1 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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Celebrating its 100th anniversary, the American Lung Association works to prevent lung disease and promote lung health. Lung diseases and breathing problems are the leading causes of infant deaths in the United States today, and asthma is the leading serious chronic childhood illness. Smoking remains the nation's leading preventable cause of death. Lung disease death rates continue to increase while other leading causes of death have declined.

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.

