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COPD, SMOKING, AND AIR POLLUTION

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THE IMMUNE SYSTEM, INFLAMMATION AND LUNG SCARRING

DISEASES OF INFANTS AND CHILDREN

BREATHING MECHANICS, CONTROL OF BREATHING, AND SLEEP DISORDERED BREATHING

Research Awards Nationwide 2008-09

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

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

INTRODUCTION

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 400,000 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 supports basic and clinical research through training and "seed" grants for beginning investigators, which play a critical role in attracting and retaining talented scientists focused on lung research. Research is the key that will unlock the door to a better tomorrow for all people with lung disease.

ASTHMA

Close to 22.9 million Americans have asthma, and 12.4 million of them have had an asthma attack in the past year. Asthma is the leading serious chronic illness in children. Although rates have stabilized recently, medical professionals continue to be concerned with the dramatic increase in the number of asthma sufferers over the past two decades, during which asthma prevalence 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 almost 4,000 Americans each year.

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

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

American Lung Association Scholar: Asthma

ZHUGONG LIU, MD, PhD
UMDNJ-New Jersey Medical School

Could tiny intestinal parasites common in the developing world actually protect against allergic asthma? American Lung Association Asthma Scholar Zhugong Liu, MD, PhD, hopes to find out. He says that if these parasites, called helminths, are shown to protect against asthma, scientists may be able to develop helminth-based medicines to treat the disease.

Asthma is commonly divided into two types: allergic asthma and non-allergic asthma. Allergic asthma is the most common form of asthma, and its prevalence has increased dramatically in recent decades, particularly in highly developed countries like the United States.

The reason for this increase is still not known, but it may be related to the "hygiene hypothesis," which proposes that a lack of exposure to infectious agents may result in a dysfunctional immune system, which predisposes a person towards the development of immune disorders including allergic inflammation.

Due to both improved hygiene and the widespread use of vaccines and antibiotics in recent decades, a lack of exposure to infectious agents, particularly helminths, may thus increase susceptibility to allergic diseases. One route of infection is through the skin penetration. In those cases, the helminth may get into the blood circulation and reach the lung, where it can produce an initial inflammatory response. "However, after a few days, a secondary mechanism kicks in and the helminth begins to control inflammation to benefit its own survival," he says.

With an American Lung Association Biomedical Research Grant, Dr. Liu will examine the mechanism through which helminth infection controls the development of asthma. He will focus on a type of white blood cell called Th17 cells, which have recently been implicated as major players in the development of tissue inflammation that may lead to asthma. Dr. Liu will investigate how Th17 cells are suppressed by helminth infection and the role of this effect on the development of allergic asthma. "This study will increase understanding about the fundamental questions of how asthma and allergy develop," he says. "The answers could help investigators to develop strategies including helminth products to prevent and control the allergic response."

To see a complete description of Dr. Liu's research project, please go to page 10.

LIN-FENG CHEN, PhD

University of Illinois at Urbana-Champaign, Champaign, IL

Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the Upper Midwest

Targeting Protein That Causes Inflammation In Asthma And COPD

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

JASON S. DEBLEY, MD, MPH

Children's Hospital and Regional Medical Center, Seattle, WA

Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the Northwest

Changes In Airway Wall Can Provide Insight Into Childhood Asthma

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

CHEN DONG, PhD

University of Texas MD Anderson Cancer Center, Houston, TX

John L. Kirkwood Career Investigator Award ● Funded by the American Lung Association

Better Understanding Of Lung Inflammation May Shed Light On Many Lung Diseases

Lung Inflammation Mediated By Inflammatory Helper T Cells. Chronic inflammation is the underlying mechanism for many lung diseases including asthma, COPD, sarcoidosis, and lung cancers. Development of lung inflammation is complex. The researchers are studying a type of cell that produces a substance called interleukin-17, or IL-17, which has been associated with asthma. They have found that mice that produce too much IL-17 in the lung developed lung inflammation, excess mucus, and changes in the airway. The researchers will study the regulation and function of white blood cells called T-cells that produce IL-17 during lung inflammation. The research will provide new explanations of the mechanisms in the development of lung disease and may suggest new treatment.

JERRY EU, MD

Duke University Medical Center, Durham, NC

Career Investigator Award ● Funded by the American Lung Association

Blocking Calcium Channel In Airway Cells May Relieve Asthma Symptoms

Neuroendocrine Isoform Of L-Type Calcium Channel In Bronchoconstriction. An increase in calcium concentration within airway smooth muscle cells triggers narrowing of the airways, which is a key feature in asthma and chronic obstructive pulmonary disease. Calcium enters cells through calcium channels that act as gatekeepers. The researchers have discovered that a certain calcium channel is produced in large amounts in airway smooth muscle. This channel, called D-LTCC, could play an important role in airway constriction seen in asthma or COPD. The researchers will test this possibility by comparing airway smooth muscle tissue taken from genetically engineered mice that do not have D-LTCC, and from normal mice. If D-LTCC plays an important role in airway constriction, then the genetically engineered mice may develop less airway constriction compared with the normal mice when they are exposed to agents that induce asthma. If D-LTCC plays a major role in airway constriction, the researchers will then work to develop drugs to block the channel to relieve symptoms caused by airway constriction.

MONICA FOOTE, PhD

Cornell University, Ithaca, NY

Senior Research Training Fellowship ● Funded by the American Lung Association

Understanding Immune Helper Cells May Lead To Better Treatment For Allergic Asthma

Epigenetic Regulation Of The Neonatal Th2 Bias. Allergic diseases, including asthma, are inflammatory disorders that result when the immune system mounts an irregular response to environmental allergens. It is estimated that half of Americans with asthma suffer from allergic asthma, a condition that is commonly believed to originate in neonatal or fetal life. Certain white blood cells, called T helper (Th) cells, help other immune cells to mount responses by producing and secreting immune growth factors called cytokines. The immune system produces Th1 and Th2 cells, and both are needed for an effective immune response. People susceptible to allergic asthma, however, often mount potent Th2 responses. The researchers will investigate the mechanisms governing the development and persistence of early-life Th2 function, which will provide information that will be valuable in developing targeted, safe, and effective treatments for allergic asthma in children.

PEISONG GAO, MD, PhD

Johns Hopkins University, Baltimore, MD

Biomedical Research Grant ● Funded by the American Lung Association of the Atlantic Coast

Searching For Asthma Genes In African Americans

Identification Of Asthma Susceptibility Genes On Chromosome 11q In An African-American Population. Asthma is a complex illness with a strong genetic component. Despite an extensive search for genes that make people susceptible to developing asthma, such genes in diverse populations have not yet been found. Relatively few genetic studies have focused on populations of African descent, a unique population with more severe asthma. The researchers have used a new technology that has provided evidence for asthma genes in five sub regions on chromosome 11 in the African-American population. The researchers hope to refine these five sub regions and search for genetic variants with the strongest evidence of association with asthma in 1,000 African-American subjects. The identification of genetic variants and genes associated with asthma will contribute to a better understanding of the molecular cause of asthma as well as facilitate the genetic analysis of asthma. This in turn will unlock possibilities for improved early diagnosis and novel therapies.

ANTHONY GERBER, MD, PhD

University of California, San Francisco, San Francisco, CA

Biomedical Research Grant ● Funded by the American Lung Association of California

Understanding Steroids' Effect On Airway Smooth Muscle

Characterization Of Glucocorticoid Signaling In Airway Smooth Muscle As A Platform For Gene And Drug Discovery. Glucocorticoids, or steroids, are a commonly used asthma medication. Research indicates that steroids have an important effect on airway smooth muscle, the muscle-like cells that form an important portion of the airways in the lung. But the way in which airway smooth muscle responds to steroids is not fully understood. The researchers will study the effects of steroids on airway smooth muscle, and will try to identify new drugs that work with steroids. This can have important implications for asthma treatment, since steroids do not fully control asthma symptoms in some patients, and can have severe side effects.

ANGELA HACZKU, MD, PhD

University of Pennsylvania, Philadelphia, PA

Career Investigator Award ● Funded by the American Lung Association

Naturally Occurring Lung Protein May Protect Against Airway Inflammation

Mechanisms Of Protection By Pulmonary Surfactant Protein D In Ozone-Induced Lung Inflammation. Allergic asthma is one of the most common chronic, debilitating diseases and its prevalence is on the rise. Air pollution, particularly ozone, induces asthma flare-ups that substantially worsen illness and can lead to death. The way in which ozone worsens asthma remains unknown. The researchers will investigate whether a naturally occurring molecule in the lung, called surfactant protein D (SP-D), plays a protective role during ozone-induced flare-ups of asthmatic inflammation. The study will yield information on the potential therapeutic effects of SP-D in ozone-induced asthmatic inflammation.

TEAL HALLSTRAND, MD
University of Washington, Seattle, WA
Career Investigator Award ● Co-funded by the American Lung Association and the American Lung Association of the Northwest

Does Injury To Surface Airway Cells Lead To Exercise-Induced Bronchoconstriction?

Epithelial Basis Of Exercise-Induced Bronchoconstriction. Exercise-induced bronchoconstriction (EIB) is a disorder that causes wheezing and shortness of breath following a short period of exercise. This disorder commonly occurs in people with asthma, as well as athletes and people with nasal allergies who do not have other symptoms of asthma. The researchers hope to determine if injury to the cells that line the surface of the airways causes susceptibility to EIB. They will take small samples of the airway lining cells from asthmatics who have EIB, and compare them with samples from asthmatics who do not have EIB, as well as non-asthmatic individuals. The study will lead to a better understanding of the cause of EIB, which may lead to new therapies to treat this common disorder.

OCTAVIAN HENEGARIU, MD
Yale University, New Haven, CT
Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of New England

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

Changes In Th2 Responses And Lung Inflammation In Mice With Conditional PPARG Deletion In CD4 T Cells. Certain white blood cells, called T helper (Th) cells, help other immune cells to mount responses by producing and secreting immune growth factors called cytokines. The immune system produces Th1, Th2, Th17 and regulatory T- cells, and all are needed for an effective immune response. People susceptible to allergic asthma, however, often mount potent Th2 responses. The researchers are studying whether a commonly used class of anti-diabetes drugs called thiazolidinediones (TZD), may promote Th2 responses in the immune system. TZD drugs bind to a protein called PPARG that is present in many cells, including cells of the immune system. TZD agonist drugs promote PPARG function and lead to a better control of the number of harmful activated immune cells, as well as a reduction in the release of pro-inflammatory cytokines, thus decreasing inflammation. Several studies have shown that the anti-inflammatory action of TZD is beneficial in treating asthma. But the researchers think that in addition to inhibiting PPARG, TZD may also be activating asthma-promoting Th2 cells, and the effects are being obscured by the drug's anti-inflammatory effect. They will use a mouse in which PPARG is deleted from some T-cells to investigate the effect of TZD on asthma-promoting cells in the immune system. They hope to discover whether using TZD in asthma has a long-term harmful effect, due to its Th2 activation.

FERNANDO HOLGUIN, MD, MPH
Emory University, Atlanta, GA
Clinical Patient Care Research Grant ● Funded by the American Lung Association

Can Diabetes Drug Improve Breathing In Obese Asthmatics?

A Randomized Placebo-Controlled Study Of Pioglitazone For The Treatment Of Asthma In Poorly Controlled, Moderate To Severe Obese Asthmatics. Asthma and obesity are intimately related. Being significantly overweight or obese increases the risk for developing asthma. For people who already have asthma, obesity increases the risk that their asthma will worsen and be more difficult to control. Compared with leaner asthmatics, obese people with asthma have more frequent asthma flare-ups and are less likely to achieve control with inhaled steroids, which are the main treatment for asthma. Obesity affects levels of fat-related hormones, which are present in the airways and may influence asthma severity. Pioglitazone, an anti-diabetic drug, may be able to reverse the effect that obesity has on fat-related hormones. This study will test whether treatment with pioglitazone can improve asthma control, airway "twitchiness" and breathing symptoms in poorly controlled obese asthmatics. Study subjects will receive either pioglitazone or a placebo, and will be evaluated after three months for asthma control, asthma-related quality of life and lung function. The results will be critical in determining whether pioglitazone could be an alternative medication for obese asthmatics not fully controlled on standard asthma medications.

DANNY HSIA, MD
University of Washington, Seattle, WA
Junior Research Training Fellowship – Senior Research Training Fellowship ● Funded by the American Lung Association of the Northwest

Predicting Which Children With RSV Will Develop Asthma

Exhaled Nitric Oxide Output In Infants With Pulmonary Hyperinflation Following Respiratory Syncytial Virus Bronchiolitis. Most lower respiratory tract illnesses with wheezing that occur in the first three

years of life are associated with infection with respiratory syncytial virus (RSV). Many studies have shown an association between RSV, subsequent wheezing, and the development of asthma. Between 20-40% of young children who have RSV suffer from recurrent wheezing episodes that resolve on their own as the child gets older. A major challenge for doctors is predicting which infants are at increased risk for developing asthma after RSV and which will resolve on their own. The researchers will use two measurements to see how each alone and in combination predicts recurrent wheezing as the child grows. One measurement, called the thoracic index, measures persistent airway narrowing, while the nitric oxide index measures ongoing airway inflammation. If these measurements prove useful, they will allow doctors to identify which children who have had RSV might benefit from asthma therapy very early in life and thereby avoid complications of asthma in very young children.

JASON LANG, MD

Nemours Children's Clinic, Jacksonville, FL

Clinical Patient Care Research Grant ● Funded by the American Lung Association of the Southeast

Can Antioxidant Therapy Help Obese Asthmatics?

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

QING-HUA LIU, MD, PhD

Albany Medical College, Albany, NY

Biomedical Research Grant ● Funded by the American Lung Association

Increased Calcium Levels In Cells May Hold Clue To Airway "Twitchiness" In Asthma

Increased Local Ca2+ Signaling In Asthmatic Airway Smooth Muscle. Cold air, exercise, and other stimuli can result in wheezing and breathlessness in people with asthma. This is because airways narrow too easily and too much in response to these stimuli, a reaction called airway hyperresponsiveness (AHR), or "twitchiness" of the airways. AHR results from airway muscle cell contraction. This contraction requires an increase in calcium in the cells, which is normally low. However, when the calcium concentration increases to a certain threshold, it will trigger cell contraction. The researchers will study the role of increased calcium in airway hyperresponsiveness. A better understanding of these underlying molecular mechanisms has the potential to improve treatment of asthma.

ZHUGONG LIU, MD, PhD

UMDNJ-New Jersey Medical School, Newark, NJ

Biomedical Research Grant ● Support of this grant comes from the Mary Fuller Russell Research Fund

"Hygiene Hypothesis" Investigated In Allergic Asthma's Rise

The Role of IL-17 In Parasite Induced Immune Modulation Of Asthma. Asthma is commonly divided into two types: allergic asthma and non-allergic asthma. Allergic asthma is the most common form of asthma, and its prevalence has increased dramatically in recent decades, particularly in highly developed countries like the United States. The reason for this increase is still not known, but it may be related to the "hygiene hypothesis," which proposes that a lack of exposure to infectious agents may result in a dysfunctional immune system, that predisposes a person towards the development of allergic inflammation. Due to both improved hygiene and the widespread use of vaccines and antibiotics in recent decades, a lack of exposure to infectious agents, particularly intestinal parasites called helminths, may increase susceptibility to allergic diseases. The researchers will examine the mechanism through which helminth infection controls the development of asthma. They will focus on a type of white blood cell called a TH17 cell, which has recently been implicated as a major player in the development of tissue inflammation that may lead to asthma. They will investigate how Th17 cells are suppressed by helminth infection and the

role of this effect on the development of allergic asthma. Results from these studies are expected to provide important insights into developing preventive/therapeutic methods to suppress the harmful immune response that initiates and sustains allergic asthma.

ANDREW C. MELTON, PhD
University of California, San Francisco, San Francisco, CA
Junior Research Training Fellowship-Senior Research Training Fellowship ● Funded by the American Lung Association of California

Analyzing Protein's Role In Allergic Asthma May Lead To New Treatments

Regulation Of Allergic Asthma By Integrin-Alpha(v) beta8. Transforming growth factor-beta (TGF-beta) is a protein that protects against excessive immune system responses, such as those seen in people with allergic asthma. However, the mechanisms that regulate the activity of this protein in allergic asthma are unclear. Previous studies have shown that another protein, integrin-alpha(v)beta8, plays an important role in regulating the activity of TGF-beta. To investigate the role of integrin-alpha(v)beta8 in allergic asthma, the researchers will study this disease in mice that lack integrin-alpha(v) beta8. Without the ability of integrin-alpha(v)beta8 to regulate TGF-beta in these mice, the researchers expect to find that the mice will develop exacerbated airway responses when challenged with agents that induce allergic asthma. The experiments in this proposal will provide insight into the regulation of TGF-beta in allergic asthma and could facilitate the development of new treatments for this and other diseases.

TIMOTHY ORISS, PhD
University of Pittsburgh, Pittsburgh, PA
Biomedical Research Grant ● Funded by the American Lung Association

Can A Drug That Combats Inflammation In Diabetes Help People With Allergic Asthma?

Effects Of PPAR-gamma On Lung Dendritic Cell Maturation And Migration. In people with allergic asthma, certain types of allergens can trigger asthma attacks and symptoms such as coughing, wheezing, and shortness of breath. Non-allergic individuals do not have an immune system reaction to things they encounter every day in their diet or the air they breathe, a state known as immunologic tolerance. Allergy occurs when tolerance breaks down and an inflammatory response occurs to these common substances. Many people tend to "grow out of" their allergies, suggesting that tolerance has been re-established, since these people presumably are still exposed to the environmental triggers that prompted the inflammatory response leading to allergic asthma in the first place. The researchers seek to understand how tolerance is established and maintained by the immune system, and explore ways to re-establish or initiate tolerance in people where it has failed. The researchers will study one of a class of compounds that has shown effectiveness as an anti-inflammatory agent in the treatment of diabetes, and shows initial promise in the treatment of asthma-like conditions. This research might lead to the future use of these drugs to re-establish immunologic tolerance and thus to effect a "cure" for certain types of asthma.

BEATRIZ QUINCHIA-RIOS, PhD, DDS
University of Wisconsin, Madison, WI
Senior Research Training Fellowship ● Funded by the American Lung Association of the Upper Midwest

Airway Remodeling Research May Benefit Patients With Asthma

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

A K M SHAMSUDDIN, PhD

University of California, San Diego, San Diego, CA

Senior Research Training Fellowship ● Funded by the American Lung Association of California

Learning About Small Airways Can Lead To Big Gains In Knowledge

Comparison Of Ion Transport Properties In Trachea And Small Airways. Although most significant lung diseases such as asthma, chronic obstruction pulmonary disease and cystic fibrosis are generally thought to start in the small airways, most knowledge of small airways has been inferred from previous studies of large airways. Direct knowledge of the small airway properties and function is difficult to obtain because they are tiny and almost inaccessible. The researchers have designed a novel technique that allows direct investigation of small airways. They will now be able to determine whether early notions mostly based on observations of properties and functions of large airways are in fact valid for small airways. They will focus on ion transport of airway surface fluid, a thin film of salty water that covers the airways of the lung. The thickness and composition of this fluid is crucial to protecting the lung from infection and contamination. A better understanding of the mechanism of ion transport will enable the development of new therapies for airway diseases associated with defects in these mechanisms.

MARION SILLS, MD

University of Colorado, Denver, CO

Social Behavioral Research Grant ● Funded by the American Lung Association

Helping Emergency Departments Give Children With Asthma Attacks Timely Care

The Association Between Emergency Department Resources And Pediatric Asthma-Related Quality Indicators. Children with asthma attacks recover more quickly if they get timely emergency department (ED) treatment. The researchers will examine the importance of timeliness of treatment for children with acute asthma attacks, both in terms of what factors may contribute to improved timeliness and how children benefit from improved timeliness. The factors that improve timeliness in other medical conditions, like heart attacks, are related to the resources available in the ED and the demands being placed on those resources. If the ED does not have enough nurses, doctors, beds or other resources to accommodate the patients arriving, the ED is said to be "overcrowded." Patients with heart attacks have to wait longer for treatment if they are in an overcrowded ED, and delaying the care of heart attacks lowers a patient's chances of a good recovery. By figuring out which components of ED resources are most important for timeliness of asthma care, the researchers can help ED administrators and providers better understand how to give children more timely care for asthma attacks.

OMAR TLIBA, DVM, PhD

University of Pennsylvania, Philadelphia, PA

Biomedical Research Grant ● Funded by the American Lung Association

Investigating Causes Of Steroid-Resistant Asthma May Lead To New Treatments

Mechanisms Of Steroid Resistance In Airway Smooth Muscle Cells. Although most people with asthma respond to treatment with corticosteroids, these drugs don't work in a substantial number of patients. Despite treatment with high doses of corticosteroids, these patients still have persistent lung inflammation and labored breathing, and are at increased risk of dying from asthma attacks. Advances in understanding the mechanisms that are involved in the diminished action of corticosteroids will lead to the development of a more effective therapy for patients who do not respond to steroids. The researchers will study airway smooth muscle, a lung tissue that plays a key role in airway inflammation and bronchial hyperresponsiveness (airway "twitchiness"), two main features of asthma. They hypothesize that chemical messengers called cytokines, which are released by immune cells in response to asthma triggers such as allergens and viruses, reduce the actions of corticosteroids in airway smooth muscle. The researchers will examine how these cytokines interfere with the responsiveness of airway smooth muscle cells to steroids. This research may offer insight into the design of new treatments for steroid-resistant asthma.

JIAN ZHANG, MD

University of Chicago, Chicago, IL

Career Investigator Award ● Funded by the American Lung Association of the Upper Midwest

Controlling IgE Production Key To Treating Allergic Asthma

Regulation Of IgE Production By E3 Ubiquitin Ligase Cbl-b. The body releases immunoglobulin E (IgE) antibodies when it comes in contact with an allergen such as dust, pollen or mold spores. For most allergy sufferers, the release of IgE produces symptoms such as a runny nose, sneezing, and itchy or watery eyes. However, for those with allergic asthma, the release of IgE can trigger a full-blown asthma attack. Therefore,

controlling IgE levels is crucial for treatment of allergic asthma. The researchers will study a specific protein, called Cbl-b, and determine whether and how it regulates factors that control IgE production. This research could provide information that will lead to better treatments for allergic asthma.

WENWU ZHANG, PhD
Indiana University, Indianapolis, IN
Senior Research Training Fellowship ● Funded by the American Lung Association

Investigating How Airway Smooth Muscle Contracts In Asthma

Cytoskeletal Mechanisms For The Regulation Of Airway Smooth Muscle Function. In people with asthma, airway smooth muscle is excessively sensitive to various stimuli and contracts, narrowing the airways and causing airflow obstruction. The molecular mechanisms by which airway smooth muscle responds to external forces and regulates its contractions are not known. The researchers will study the way in which mechanical forces on the lung, which are present during breathing, affect the responsiveness of the airway muscle. This research may provide a basis for the development of new therapeutic approaches for the treatment of 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 benefits for patients. The ACRC Network is currently conducting the following studies:

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

SARCA: Study of Acid Reflux and Childhood Asthma

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

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

Completed ACRC Studies

Study of Inactivated Influenza Vaccine in Asthmatics (SIIVA)
Results: The flu vaccine is safe for asthmatics and does not induce an asthma attack.

Effectiveness of Low-Dose Theophylline As Add-On Therapy In Treatment of Asthma (LODO)
Results: Neither montelukast nor low-dose theophylline improved clinical asthma control, although they both improved lung function equally. Inexpensive low-dose theophylline was more beneficial in those patients who had not been prescribe inhaled corticosteroids than montelukast.

The Leukotriene Modifier or Corticosteroid or Corticosteroid-Salmeterol (LOCCS)
Results: Once-daily fluticasone plus salmeterol was as effective as twice-daily fluticasone treatment, while oral montelukast taken once a day was not as effective. However, montelukast did provide control for most patients.

Trial of Asthma Patient Education (TAPE)
Results: Have not been released.

Sinusitis and Rhinitis in Asthma (SIRNA)
Results: Have not been released.

Study of Acid Reflux in Adults with Asthma (SARA)
Results: Have not been released.

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

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

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

American Lung Association researchers are attacking the problem of ARDS primarily on the cellular and molecular levels. Researchers are discovering new chemical pathways that mediate this devastating disease and are using this information to develop novel methods for treatment and prevention. The mechanisms of pulmonary hypertension are being studied from several perspectives as well. Here, too, the emphasis is upon understanding the basic mechanisms so that new therapeutic approaches can be tried. Novel ideas abound, such as using medications related to Viagra® to treat this condition.

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

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

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

JAMES HOTH, MD
Wake Forest University School of Medicine

As a trauma surgeon, James Hoth, MD, often sees the body responding to a traumatic injury to the lung by setting off an inflammatory response. "Some patients with trauma to the lung recover, while others die or develop pneumonia, and we need to know more about why that is," says Dr. Hoth, Assistant Professor of Surgery at Wake Forest University.

He has received an American Lung Association Biomedical Research Grant to investigate the body's response to a bruised lung, or pulmonary contusion, which can result from blunt injuries such as those that might occur in an automobile accident. There has been little meaningful improvement in treatment or outcome once a person sustains such a lung injury.

Dr. Hoth is studying a mouse model of pulmonary contusion, to examine the immune system's response to traumatic lung injury. He is investigating proteins on the cell membrane called toll-like receptors, which play a big role in activating the body's immune response to lung trauma. "They sound an alarm to the rest of the body," he says.

He has found that certain toll-like receptors signal to immune system cells called neutrophils, calling them to the site of injury in the lung. Neutrophils fight infection, but when too many of them gather in the lungs they release enzymes that can damage lung tissue and reduce lung function. "Instead of helping, they can worsen the injury," Dr. Hoth says.

This initial injury can be made worse by a so-called "second hit," or additional insult to the immune system, such as an infection, which sends even more neutrophils to the lung. Developing a drug to stop the initial action of toll-like receptors would be unlikely to help lung trauma patients, Dr. Hoth says, because the immune system acts immediately upon the injury to send neutrophils to the lung, leaving no time for intervention. What seems more promising is to develop treatments for lung injury that prevent this "second hit" reaction, he says. He is hopeful that his research will contribute to potential treatments that might help dampen the body's inflammatory response to lung injury.

To see a complete description of Dr. Hoth's research project, please go to page 22.

KAMRAN ATABAI, MD
University of California, San Francisco, San Francisco, CA
Biomedical Research Grant ● Funded by the American Lung Association of California

Lack Of Protein May Lead To More Severe Lung Scarring After Injury

The Role Of Mfge8 And Apoptotic Cell Clearance In Modulating Pulmonary Fibrosis After Lung Injury. Acute lung injury (ALI) is a common response of the lung to many different types of direct and indirect injury such as pneumonia, multiple bone fractures, and blood transfusions. ALI is characterized by an often escalating spiral of inflammation that can aggravate the lung injury. Despite the same initial degree of injury, some patients recover quickly while others have a progressive and worsening course. When the lung is injured, many cells are killed or undergo programmed cell death, a process called apoptosis in which cells essentially kill themselves when they are under extreme environmental stress. Recent evidence suggests that having too many apoptotic cells in the lung can lead to more severe lung injury and scarring. The researchers will study a protein called Mfge8 that is made in the lung and binds to apoptotic cells, facilitating their removal. They will evaluate whether mice that lack Mfge8 develop more lung scarring after injury. This research has the potential to identify new therapeutic targets for lung injury and scarring.

KONSTANTIN BIRUKOV, MD, PhD
University of Chicago, Chicago, IL
Career Investigator Award ● Co-funded by the American Lung Association and the American Lung Association of the Upper Midwest

Can A Drug Used To Protect Against Radiation Damage Also Treat Lung Injury?

Novel Strategies For Treatment Of Acute Lung Injury Using Radiation Protector Amifostine. Acute lung injury (ALI) and the more severe acute respiratory distress syndrome (ARDS) are types of severe, acute lung dysfunction affecting all or most of both lungs that occur as a result of illness or injury. ARDS has a case fatality rate of 25-40%. Despite recent progress in treatment of ALI, there is still no satisfactory strategy to reduce lung damage and tissue injury in this condition. The researchers will study the compound amifostine, a drug used to control some side effects of chemotherapy and radiation therapy, to see whether it can significantly reduce ALI induced by infectious agents. Amifostine belongs to a group of agents called cytoprotectants, which protect normal tissue from some of the side effects caused by treatments for cancer. The researchers believe that studying amifostine's protective effects may bring a promising direction in drug discovery aimed at the development of new drugs for prevention of pulmonary edema (fluid in the lungs) as a result of acute lung inflammation and trauma.

ANNA BIRUKOVA, MD
University of Chicago, Chicago, IL
Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the Upper Midwest

Growth Factor May Play Role In Treating Acute Lung Injury

Cell Adhesions In Hepatocyte Growth Factor-Induced Lung Endothelial Barrier Protection. Acute respiratory distress syndrome (ARDS) remains a major cause of illness and death. During the acute phase of lung injury, protein-rich fluid can flow into the spaces between the air sacs in the lung, causing pulmonary edema, or fluid in the lungs. A protein called hepatocyte growth factor (HGF) is one substance that appears in the lung after acute lung injury, and regulates a wide variety of events. Recent studies have suggested an important role of HGF in protecting against this fluid leak in the lungs. The researchers will study whether HGF can play a key part in significantly reducing the acute phase of ARDS associated with increased fluid leak in the lungs. If so, the findings would suggest a potential role for HGF in treating acute lung injury.

YUANNING CAO, PhD
Johns Hopkins University, Baltimore, MD
Research Training Fellowship ● Funded by the American Lung Association of the Atlantic Coast

Insights Into Protein Family Involved In Pulmonary Hypertension May Lead To Treatments

Calcineurin/NFAT-Dependent Regulation Of TRPC Channels In Pulmonary Hypertensive Rats. Pulmonary arterial hypertension (PAH), or abnormally high blood pressure in the arteries of the lungs, can progress to heart failure and death. Current therapies for PAH are limited. Recent research has shown that PAH is associated with changes in smooth muscle cells of pulmonary arteries. Increasing calcium inside these cells leads to pulmonary artery contraction and promotes overgrowth of these cells, which narrows the inside of the arteries, leaving less room for blood to flow through. The researchers will study how certain genes are "turned on" during the process of PAH development. They will focus on the interactions between two families of pro-

teins called TRPC and NFAT, which have been shown to play important roles in regulating various functions of smooth muscle cells in blood vessels. The research will provide important information on mechanisms that contribute to the development of PAH. This information may lead to the development of novel therapeutic treatment for this deadly disease.

NAVDEEP CHANDEL, PhD

Northwestern University, Chicago, IL

Career Investigator Award ● Funded by the American Lung Association of the Upper Midwest

Evaluating Immune System Protein's Role In Acute Respiratory Distress Syndrome

Mitochondrial ROS Regulation of TGF-Beta 1 Induced Gene Expression. There is no effective treatment for patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). These disorders are associated with an unacceptably high death rate. Transforming growth factor-beta 1 (TGF-B1) has been identified as a critical immune system protein regulating tissue repair in animal models of lung injury and scarring. Too little TGF-B1 activity may prevent resolution of inflammation and impair tissue repair while too much activity may lead to fibrosis, or scarring in the lungs. The researchers will study the relevance to lung disease of a chemical signaling pathway in TGF-B1. The results may provide the rationale for developing and testing novel therapeutic strategies for ARDS and ALI.

SERGEI DANILOV, MD, MPH

University of Illinois, Chicago, Chicago, IL

Career Investigator Award ● Co-funded by the American Lung Association and the American Lung Association of the Upper Midwest

Uncovering Enzyme's Role In Pulmonary Hypertension

Role Of Caveolin-1 In Lung Endothelial ACE Expression. Pulmonary hypertension, or high blood pressure affecting the pulmonary blood vessels, is difficult to treat and is usually fatal within a few years of diagnosis. The cells that make up the inside layer of the lung blood vessels, called dysfunctional pulmonary endothelium, have a central role in the initiation and progression of severe pulmonary hypertension. The researchers previously have shown that an enzyme called angiotensin-1-converting enzyme (ACE), which is involved in the regulation of blood pressure, plays a role in the development of pulmonary hypertension. They will study abnormalities in structures called caveolae that are found in endothelial cells, to see if they affect ACE production and function in lung blood vessels. The researchers believe that better understanding the mechanisms that govern production of ACE in the lung will greatly enhance the understanding of the development of pulmonary hypertension and facilitate the development of new, effective treatments of this severe lung disease.

VINICIO DE JESUS PEREZ, MD

Stanford University, Palo Alto, CA

Senior Research Training Fellowship ● Funded by the American Lung Association

Chemical Pathways May Hold Key To Pulmonary Arterial Hypertension

Cross-Talk Between The Wingless And Bone Morphogenetic Protein Signaling Pathways In Pulmonary Artery Endothelial Cells. Pulmonary arterial hypertension (PAH) is a rare but devastating disorder characterized by elevated pressures in lung blood vessels. Without treatment, PAH can progress to heart failure and death. While the cause of PAH is not known, it is thought that the disease may start when pulmonary blood vessels are injured, and in response cells multiply out of control, leading to blocking of small blood vessels. Mutations in a chemical signaling pathway called bone morphogenetic protein (BMP) are known to contribute to the disease's development, but other factors may also play critical roles in disease development and progression. The researchers will study how BMP interacts with another chemical pathway called the wingless (Wnt) pathway, which plays a crucial role in regulating key cellular processes. They will see how BMP and Wnt impact growth, survival, and migration of cells, critical processes that are abnormal in PAH. Understanding how these two pathways interact may increase the knowledge of how PAH develops and also may reveal potential targets for future therapies to help improve the care of patients with this devastating disease.

HUI DONG, MD, PhD

University of California, San Diego, San Diego, CA

Biomedical Research Grant ● Funded by the American Lung Association of California

Searching For Answers To Mystery Of Idiopathic Pulmonary Arterial Hypertension

Role Of Na/Ca Exchange In The Pathogenesis Of Idiopathic Pulmonary Arterial Hypertension. In pulmonary arterial hypertension (PAH), the muscles within the walls of pulmonary arteries tighten up and the walls of the arteries thicken as the amount of muscle

increases (overgrows) in some arteries. This narrows the inside of the arteries, leaving less room for blood to flow through. The result is that the right side of the heart works harder to pump blood through the lungs. Over time, the heart muscle weakens and loses its ability to pump enough blood. This is called right heart failure, which is the most common cause of death in people with PAH. One type of PAH is called idiopathic pulmonary hypertension (IPAH), in which PAH is inherited or occurs for unknown reasons. Recently, researchers discovered that pulmonary arterial smooth muscle cells within the walls of the pulmonary arteries of patients with IPAH show elevated levels of free calcium ion (Ca2+), indicating that high levels of Ca2+ may be critical stimuli for overgrowth of the smooth muscle cells. Ca2+ is controlled by several cellular mechanisms, one of which is the exchange of sodium and calcium on the cell membrane. The researchers will evaluate whether sodium/calcium exchange contributes to IPAH and if so, how. The information obtained from this research could be used to design drugs targeting specific molecules to treat IPAH.

MATTHEW EXLINE, MD

The Ohio State University, Columbus, OH

Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the Midland States

Protein May Help Protect Against Death From Sepsis

Apoptosis In Sepsis: The Role Of Humanin, A Novel Anti-Apoptotic Peptide. Sepsis is a potentially deadly condition in which the body's immune system responds to a severe infection. However, it does not appear that patients with sepsis die from their infection directly. Recently, it has been suggested that septic patients die due to a weakening of the body's immune system through a process of cell suicide, called apoptosis. It has been shown in animal studies of sepsis that if apoptosis is halted then death from sepsis is reduced. Humanin is a protein that has been shown to block apoptosis. The researchers plan to verify that humanin is present in immune cells, and to study whether humanin is reduced in the blood of septic patients. They will evaluate whether the concentration of humanin in the blood helps predict the outcome of a septic patient, and will investigate whether giving septic mice synthetic humanin will protect them against death, and if so, whether this is due to a reduction in apoptosis. This work will significantly improve the understanding of apoptosis in the immune system during sepsis and may lead to new therapies for septic patients.

FABEHA FAZAL, PhD

University of Rochester, Rochester, NY

Biomedical Research Grant ● Funded by the American Lung Association

Blocking Excess Production Of A Protein May Lead To New Treatments For Lung Injury

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

LAURA FREDENBURGH, MD

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Biomedical Research Grant ● Funded by the American Lung Association

COX-2 Enzyme May Play Key Role In Pulmonary Hypertension

Role Of Cyclooxygenase-2 In Hypoxia-Induced Pulmonary Hypertension And Vascular Remodeling. Pulmonary hypertension is a disease of the blood vessels of the lung in which the pressure in the pulmonary arteries rises above normal levels and can become life-threatening. Pulmonary hypertension is incurable. Current treatment allows many patients with pulmonary hypertension to live for several years after their diagnosis. However, the disease usually leads to progressive right-sided heart failure as the blood vessels in the lung undergo changes known as vascular remodeling and the pressure in the pulmonary arteries continues to rise. New therapies that target the vascular remodeling process are desperately needed to halt progression of this incurable disease. Recently a class of medications called COX-2 inhibitors, which interfere with the COX-2 enzyme, has been found to increase the risk of heart attacks and stroke. The COX-2 enzyme may play

a central role in the development of pulmonary vascular remodeling. The researchers hope to determine how the COX-2 enzyme affects the development of pulmonary hypertension and the progressive vascular remodeling that leads to worsening symptoms and death. This research eventually may lead to new therapies for this devastating disease process.

JAMES HOTH, MD

Wake Forest University, Winston-Salem, NC

Biomedical Research Grant ● Funded by the American Lung Association

Seeking Better Understanding Of Body's Response To Lung Injuries

Regulation Of Lung Injury By Toll-like Receptors After Pulmonary Contusion. A bruised lung, or pulmonary contusion, can result from blunt injuries such as those that might occur in an automobile accident. The effect of this injury can range from shortness of breath to death in up to 25% of afflicted patients. There has been little meaningful improvement in treatment or outcome once a person sustains such a lung injury. This is due to a number of factors, including a lack of animal models where the biological responses to severe lung injury can be studied. The researchers will study a mouse model of pulmonary contusion to examine the immune system's response to traumatic lung injury. This research will contribute to the understanding of lung trauma and enhance the ability to meet the current challenge of developing new and effective treatments for trauma patients.

ERIN KROSS, MD

University of Washington, Seattle, WA

Senior Research Training Fellowship ● Co-funded by the American Lung Association and the American Lung Association of the Northwest

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

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

MARK LOONEY, MD

University of California, San Francisco, San Francisco, CA

Biomedical Research Grant ● Funded by the American Lung Association of California

Discovering Ways To Prevent And Treat Transfusion-Related Acute Lung Injury

Neutrophil Immunobiology In Transfusion-Related Acute Lung Injury (TRALI). Acute lung injury is an often devastating syndrome caused by excessive inflammation leading to leakage of plasma and protein into the normally air-filled lung. A variety of different causes leads to acute lung injury, such as pneumonia, sepsis, and aspiration of stomach contents. Acute lung injury affects approximately 190,000 people in the United States every year and the death rate is approximately 40%. One of the causes of acute lung injury is the transfusion of blood products. This syndrome is called transfusion-related acute lung injury, or TRALI. TRALI is the number-one cause of deaths related to blood product transfusions reported to the U.S. Food and Drug Administration, and it has been increasing in incidence. To help better understand TRALI and to discover ways to prevent or treat it, the researchers have developed a mouse model that closely mimics the human condition. This is the first model of TRALI in a living animal and provides an opportunity to discover and manipulate how lung injury develops. They will focus their research on neutrophils, which are sentinel immune cells that have been identified as the major cellular source of injury in TRALI. Using genetically manipulated mice, the researchers will explore the mechanisms by which lungs are primed for injury, how neutrophils contribute to this injury, and ways to decrease lung damage in experimental TRALI.

DOUGLAS MINIATI, MD
University of California, San Francisco, San Francisco, CA
Biomedical Research Grant ● Funded by the American Lung Association of California

Probing Role Gene Plays In Tangle Of Abnormal Blood Vessels In The Lung

Role Of Notch4 In The Development Of Lung Arteriovenous Malformations. Lung arteriovenous malformations (AVMs) are masses of abnormal blood vessels that grow in the lungs. They are a significant problem for which there is no effective medical treatment. Examples of patients who are prone to develop lung AVMs include people with liver cirrhosis, some children with congenital heart disease, and patients with a genetic disorder of blood vessels called hemorrhagic teleangiectasia. The researchers will study a gene called Notch4. Initial research indicates that overproduction of this gene in the cells lining the vessels can cause AVM formation. If the researchers find that Notch4 causes lung AVM development, it could lead to development of therapeutic agents to preemptively treat patients at risk for AVM formation in the lungs.

ANA MORAN, MD
Baylor College of Medicine, Houston, TX
Research Training Fellowship ● Funded by the American Lung Association of the Central States

Learning How To Prevent Lung Damage From Severe Traumatic Injury

Prevention Of Lung Apoptosis Following Shock/Trauma By Activation Of Stat3. Acute lung injury (ALI) occurs in up to 37% of patients suffering severe traumatic injuries and bleeding, and causes 74,500 deaths in the United States each year. Damage and death of cells within the lung are key features of ALI; a better understanding of how lung cells are injured by severe traumatic injuries and bleeding is needed in order to develop effective treatments. The researchers will study how the important genes that keep lung cells alive are "turned on" following severe injury and bleeding and determine whether these genes can be stimulated by substances such as the protein interleukin-6. The long-term goals of this study are to gain an improved understanding of the mechanisms involved in lung damage during severe traumatic injury and bleeding, and to identify genes within the lung cells that are critical for lung damage prevention. Identification of these genes may lead to development of treatments that will result in prevention of ALI in patients following severe traumatic injuries and bleeding.

SERGEI RYBALKIN, PhD
University of Washington, Seattle, WA
Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the Northwest

"Viagra" For The Lungs: Understanding How It Works May Improve Effectiveness

Characterization Of cGMP Phosphodiesterase (PDE5) Isoforms Expressed In Lung. Phosphodiesterase 5 (PDE5) is an enzyme (protein) produced in the lungs and other parts of the body that breaks down a substance called cyclic GMP. Cyclic GMP causes the blood vessels to widen. Sildenafil, well known as the drug Viagra, inhibits PDE5, leading to accumulation of cyclic GMP and widening of the blood vessels. Recently the U.S. Food and Drug Administration approved sildenafil under the brand name Revatio to treat pulmonary arterial hypertension, a life-threatening disease. The researchers will study the mechanisms of sildenafil's action on the lung. The research could lead to improved effectiveness and new applications for PDE5 inhibitors in the treatment of lung disorders.

PATRICK A. SINGLETON, PhD
University of Chicago, Chicago, IL
Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the Upper Midwest

Knowing Why Cell Barrier Is Disrupted May Lead To ARDS Treatment

HABP2/C1INH Regulation Of Acute Lung Injury. Acute lung injury (ALI) and the more severe acute respiratory distress syndrome (ARDS) are types of severe, acute lung dysfunction affecting all or most of both lungs that occur as a result of illness or injury. ALI/ARDS afflicts over 190,000 people a year in the U.S., resulting in 74,500 deaths. Despite recent progress in treatment of ALI, there is still no satisfactory strategy to reduce lung damage and tissue injury in this condition. The hallmark of ALI is inflammation-induced disruption of the cells called endothelial cells that line the pulmonary blood vessels, linking to one another with cell-cell junctions to form a physical barrier between the airways and the blood vessels of the lung. This disruption results in leakage of fluid, protein, and cells into the airspaces of the lung. The researchers seek to understand the mechanisms of the endothelial cell barrier disruption in an attempt to develop novel strategies to treat ALI/ARDS.

JIAN WANG, MD, PhD
Johns Hopkins University School of Medicine, Baltimore, MD
Biomedical Research Grant ● Funded by the American Lung Association of the Atlantic Coast

Investigating Mechanisms Of Pulmonary Hypertension Caused By Lack Of Oxygen

Role Of Bone Morphogenetic Protein 4 In Hypoxia-Induced Pulmonary Hypertension. In patients with diseases such as chronic obstructive pulmonary disease and interstitial pulmonary fibrosis, the lack of oxygen, known as hypoxia, can result in pulmonary hypertension (high blood pressure in the pulmonary artery). Pulmonary hypertension can lead to right-sided heart failure, which in turn may lead to severe fluid retention, life-threatening shortness of breath, shock, and death. The way in which hypoxia-induced pulmonary hypertension develops is not well understood. The researchers will study the cellular mechanisms underlying hypoxia-induced pulmonary hypertension. The information provided by this research could suggest new drug treatments to prevent and treat pulmonary hypertension, leading to a reduction in illness and death in a wide variety of lung diseases.

JIANLIANG ZHANG, PhD
University of Florida, Gainesville, FL
Career Investigator Award ● Funded by the American Lung Association of the Southeast

Pulmonary Arterial Hypertension In Patients With Smoking-Associated COPD

ERK1 / 2-VEZF1 Signaling Regulation Of Lung Endothelial ET-1 Expression. Elevation of pressure in the pulmonary artery, which carries blood from the heart to the lungs, is often seen in a subset of patients with moderate to severe chronic obstructive pulmonary disease (COPD). Tobacco smoking is the leading cause of COPD, responsible for 80-90% of all COPD deaths in the United States. Studies suggest a direct effect of tobacco smoke on lung endothelium, a layer of cells covering the inside of blood vessels. Smoking-induced endothelial dysfunction leads to overproduction of a substance, endothelin-1 (ET-1). ET-1 can tighten the vessel and may thicken the walls of pulmonary arteries. This makes the inside of vessels narrower. Experimental results indicate that smoking stimulates ET-1 gene expression in cultured lung endothelial cells. A protein in the nucleus modulates the synthesis of ET-1 through chemical communication within the cell, known as a cell signaling event. The long-term goal of this project is to investigate the process that leads to ET-1 overproduction, elevating lung arterial pressure. This research may lead to additional targets to be tested to reduce the incidence of pulmonary arterial hypertension in COPD patients.

COPD, SMOKING, AND AIR POLLUTION

Smoking is the major cause of chronic obstructive pulmonary disease (COPD), while air pollution can both cause the condition and make it worse. The work of the American Lung Association has been critical in achieving a significant decline in cigarette smoking in the past 30 years, from 37.4 percent in 1970 to 20.8 percent in 2006, and in accomplishing important reductions in air pollution during the same time frame. Nevertheless, over 45 million adults still smoke; until recently, teenage smoking has been on the rise; and the American Lung Association estimates that almost 125 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. Patient-centered studies are addressing such problems as the best way to assess and ensure quality of care. Other investigations are exploring genetic susceptibility to lung damage by cigarette smoke at the molecular level. In order to address the inordinately high level of smoking among American Indians and Native Alaskans, one group is testing the efficacy of an Internet site for smoking cessation that is designed to be culturally appropriate.

The American Lung Association continues to support research on smoking prevention and smoking cessation with an emphasis on motivation and education that is culturally specific.

American Lung Association Scholar: COPD, Smoking, and Air Pollution

JANET THOMAS, PhD
University of Minnesota

A safe home for children includes having clean air to breathe. But more than one-third of American children in the U.S. live in a home where people regularly smoke cigarettes. Janet Thomas, PhD is using an American Lung Association Social Behavioral Research Grant to test a novel approach to helping parents quit smoking, so that children are not exposed to secondhand smoke at home.

Secondhand smoke contributes to about 50,000 deaths in the U.S. each year and is linked to asthma in children. The goals of her project are to eliminate smoking in the home to protect the health of everyone living there, and to promote smoking cessation in the smoker. Researchers will evaluate two methods to motivate families to restrict home smoking. One group will receive a home visit by a counselor who will provide a brochure documenting the health impact of home exposure to secondhand smoke. The second group will receive the same brochure and will be taught skills to limit smoking in the home. They will also receive the results of a lab test conducted on the urine of a child in the home that will document cotinine (a byproduct of nicotine use) and NNAL, a known cancer-causing agent found only in tobacco. Three months later, the researchers will return to see if the method the smokers received changed their home smoking policies and if the treatment had any effect on their smoking behaviors.

“If we can teach people that the chemicals in tobacco smoke can be detected in the urine of their children, this may not only create change in the family but may create a network effect in that participants will educate others in their communities and neighborhoods to limit smoking in their homes,” she says.

To see a complete description of Dr. Thomas’ research project, please go to page 30.

DAVID AU, MD

University of Washington, Seattle, WA

Career Investigator Award ● Co-funded by the American Lung Association and the American Lung Association of the Northwest

Importance Of Getting COPD Patients To Adhere To Therapy

Effect Of Medication Adherence On Outcomes And Costs Among Patients With Chronic Obstructive Pulmonary Disease. Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States. Drug therapy has become the mainstay of treatment for COPD, but there is little data about the effects of adhering to pharmaceutical therapy on the risk of death or COPD flare-ups. There is also no data about the effects of adhering to drug therapies on utilization of resources or cost of care. The researchers, by studying veterans receiving care in the Pacific Northwest, will address this gap by examining the effects of adhering to drug therapy on important patient-related outcomes including COPD flare-ups, death, and costs to the health care payer. The researchers hope to inform payers of medical care, health care systems, individual providers, and patients about the importance of adhering to medical therapy and identify those patients who may benefit from interventions that improve adherence to medical therapies.

RUSSELL P. BOWLER, MD, PhD

National Jewish Medical and Research Center, Denver, CO

Career Investigator Award ● Co-funded by the American Lung Association, the American Lung Association of the Southwest and the Alpha-1 Foundation

Understanding How Cigarette Smoke Causes Lung Disease

Investigating The Role of EC-SOD Heparin Binding Domain In COPD. Cigarette smoke is the number-one preventable cause of lung disease and is the major cause of chronic obstructive pulmonary disease (COPD). However, most smokers do not get lung disease and the factors that determine a person's susceptibility to cigarette smoke remain unknown. The researchers have found that an antioxidant enzyme in the lung is protective against cigarette-smoke induced inflammation and that a gene alteration in this antioxidant enzyme reduces the likelihood that a smoker gets COPD. The way in which this occurs is unknown, but learning how these mechanisms work will be important in understanding how cigarette smoke causes lung disease. The researchers will use animal models and cell models to investigate these mechanisms. Their work could lead to better design of new therapies to treat COPD.

CYNTHIA D. BROWN, MD

University of Virginia, Charlottesville, VA

Clinical Patient Care Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the Atlantic Coast

New Device Could Improve Sleep In COPD Patients

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

LIN-FENG CHEN, PhD

University of Illinois at Urbana-Champaign, Champaign, IL

Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the Upper Midwest

Targeting Protein That Causes Inflammation In Asthma And COPD

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

CHRISTINE DALEY, PhD
University of Kansas, Kansas City, KS
Social Behavioral Research Grant ● Funded by the American Lung Association

Internet Site On Smoking And Lung Health For American Indians And Alaska Natives

Educating American Indians And Alaska Natives About Smoking And Lung Health Using The Internet. Approximately 32% of American Indians and Alaska Natives (AI/AN) smoke cigarettes, compared with 22% of whites and 23% of African Americans, and have proportionately more lung health problems. In addition, tobacco has spiritual and cultural significance to many, though not all, AI/AN people. It is therefore necessary to provide AI/AN people with culturally appropriate education about tobacco and its health consequences. Currently, little such information is available and there are no Internet sites for these communities dedicated to tobacco and lung health. The researchers will develop such a site in three steps. Through focus groups, researchers will ask AI/AN community members about their Internet use to get health information and types of information they would like to see about tobacco and lung health. They will develop the site and assess it for scientific accuracy, readability, cultural appropriateness, and ease of navigation. They will then conduct a second series of focus groups to show AI/AN community members the site, and to ask for recommended changes. When changes are incorporated, the researchers will then go live with the site.

JERRY EU, MD
Duke University Medical Center, Durham, NC
Career Investigator Award ● Funded by the American Lung Association

Blocking Calcium Channel In Airway Cells May Relieve Asthma Symptoms

Neuroendocrine Isoform Of L-Type Calcium Channel In Bronchoconstriction. An increase in calcium concentration within airway smooth muscle cells triggers narrowing of the airways, which is a key feature in asthma and chronic obstructive pulmonary disease (COPD). Calcium enters cells through calcium channels that act as gatekeepers. The researchers have discovered that a certain calcium channel is produced in large amounts in airway smooth muscle. This channel, called D-LTCC, could play an important role in airway constriction seen in asthma or COPD. The researchers will test this possibility by comparing airway smooth muscle tissue taken from genetically engineered mice that do not have D-LTCC, and from normal mice. If D-LTCC plays an important role in airway constriction, then the genetically engineered mice may develop less airway constriction compared with the normal mice when they are exposed to agents that induce asthma. If D-LTCC plays a major role in airway constriction, the researchers will then work to develop drugs to block the channel to relieve symptoms caused by airway constriction.

ANGELA HACZKU, MD, PhD
University of Pennsylvania, Philadelphia, PA
Career Investigator Award ● Funded by the American Lung Association

Naturally Occurring Lung Protein May Protect Against Airway Inflammation

Mechanisms Of Protection By Pulmonary Surfactant Protein D In Ozone-Induced Lung Inflammation. Allergic asthma is one of the most common chronic, debilitating diseases and its prevalence is on the rise. Air pollution, particularly ozone, induces asthma flare-ups that substantially worsen illness and can lead to death. The way in which ozone worsens asthma remains unknown. The researchers will investigate whether a naturally occurring molecule in the lung, called surfactant protein D (SP-D), plays a protective role during ozone-induced flare-ups of asthmatic inflammation. The study will yield information on the potential therapeutic effects of SP-D in ozone-induced asthmatic inflammation.

RUI JIANG, MD, PhD
Columbia University Medical Center, New York, NY
Research Grant-Clinical Grant ● Funded by the American Lung Association of the City of New York

Are Cured Meats Associated With COPD?

Cured Meat Intake, 3-Nitrotyrosine Levels, And Lung Function/Density. Although smoking is the principal cause of chronic obstructive pulmonary disease (COPD), only a minority of smokers develop symptomatic COPD. Diet may play an important role in the rate of lung function decline and the development of COPD. Cured meats such as bacon, sausage and processed meats are high in nitrites, which cause emphysema in animal models. High cured meat intake was associated with lower lung function in one human study and with an increased risk of newly physician-diagnosed COPD in two other studies. So far, however, no published studies have evaluated the associations of cured meat intake with computed tomography (CT) lung density, a measure of emphysema, and longitudinal change in lung

function. The researchers will test this novel hypothesis in the Emphysema and Cancer Action Project, a study of 650 current and former smokers in which repeated measures of lung function and CT lung density were collected. In addition, they will study whether elevated blood levels of the chemical 3-nitrotyrosine are associated with lower lung function and density and may reflect cured meat intake. If the researchers' hypotheses are borne out, this may suggest a novel preventive strategy for COPD.

SUN KIM, PhD
University of Massachusetts, Worcester, MA
Social Behavioral Research Grant ● Co-funded by the American Lung Association and the American Lung Association of New England

Finding Effective Ways To Get Korean Americans To Quit Smoking

Predictors Of Readiness For Tobacco Dependence Treatment Among Korean Americans. Korean male immigrants in the United States have the highest rate of current smoking and the highest rate of cancer deaths caused by smoking; however, this is also one of the groups studied least in regards to smoking and smoking cessation. Many Asian Americans, including Korean Americans, tend not to seek treatment for smoking cessation that is available in public health care settings due to language and cultural differences. In an effort to prevent lung diseases caused by smoking, this study will identify psychological, social, cultural, and behavioral factors that may predict Korean Americans' willingness to quit smoking and to seek cessation treatment, and to explore their experiences with the treatment, particularly regarding actual and perceived difficulties accessing the treatment. Information from the study will lead to further understanding of Korean Americans' willingness to quit smoking and receive treatment for smoking cessation. This information will also help other researchers identify ways to develop a smoking cessation program that is more acceptable to and receptive by members of this ethnic minority group.

SUSAN LYNCH, PhD
University of California, San Francisco, San Francisco, CA
Biomedical Research Grant ● Funded by the American Lung Association of California

Unlocking The Role Of Bacteria In COPD Flare-Ups And Remissions

Analysis Of Bacterial Community Dynamics In Adult Patients With Exacerbations Of Chronic Obstructive Pulmonary Disease. Although bacteria are now thought to be responsible for up to 50% of chronic obstructive pulmonary disease (COPD) episodes, little is known about the types and dynamics of bacteria in the airways of people with the disease. Recently, it has been shown that bacterial communities exist in a number of respiratory diseases. To fully understand the contribution of specific members of the airway bacterial community to COPD, it is necessary to identify which bacteria are present when patients develop symptoms. The researchers use a novel tool that allows them to comprehensively describe the types of bacteria present in the airways of COPD patients during flare-ups and remission. They will look at how the microbial community changes over time and with antimicrobial treatment and which microbes are associated with disease progression. Eventually, this research may lead to new treatments for COPD.

A K M SHAMSUDDIN, PhD
University of California, San Diego, San Diego, CA
Senior Research Training Fellowship ● Funded by the American Lung Association of California

Learning About Small Airways Can Lead To Big Gains In Knowledge

Comparison Of Ion Transport Properties In Trachea And Small Airways. Although most significant lung diseases such as asthma, chronic obstruction pulmonary disease and cystic fibrosis are generally thought to start in the small airways, most knowledge of small airways has been inferred from previous studies of large airways. Direct knowledge of the properties and functions of the small airways is difficult to obtain because they are tiny and almost inaccessible. The researchers have designed a novel technique that allows direct investigation of small airways. They will now be able to determine whether early notions mostly based on observations of properties and functions of large airways are in fact valid for small airways. They will focus on ion transport of airway surface fluid, a thin film of salty water that covers the airways of the lung. The thickness and composition of this fluid is crucial to protecting the lung from infection and contamination. A better understanding of the mechanism of ion transport will enable the development of new therapies for airway diseases associated with defects in these mechanisms.

MARTIN STEFFEN, MD, PhD
Boston University, Boston, MA
Biomedical Research Grant ● Funded in partnership between the American Lung Association of New England and the Alpha-1 Foundation

Key Protein In Development Of COPD Could Shed Light On Genetics Of The Disease

An Exploration Of Proteasome Structure And Function In COPD. Chronic obstructive pulmonary disease (COPD) is a complex respiratory disease characterized by decreased airflow and abnormal inflammation. The researchers will explore one potential cause of the abnormal inflammatory response, and how that inflammation may promote disease development. They will focus on the proteasome, a key protein complex known to regulate several processes that cause inflammation and that have previously been implicated in the development of diabetes and heart disease. They will isolate proteasome complexes from people with and without COPD, in order to identify differences between the two groups. Specifically, they will compare the protein and chemical composition of the complexes, and test their functional activity. A positive finding of consistent differences, along with their previous data, will help establish the proteasome as a source of genetic risk for the disease, which can then be used to develop a test to identify susceptible individuals. They also will be prepared to explore the use of drugs that modulate proteasome activity to treat people with this deadly disease.

JANET THOMAS, PhD
University of Minnesota, Minneapolis, MN
Social Behavioral Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the Upper MidWest

Comparing Two Methods To Encourage Home Smoking Bans

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

JIANLIANG ZHANG, PhD
University of Florida, Gainesville, FL
Career Investigator Award ● Funded by the American Lung Association of the Southeast

Pulmonary Arterial Hypertension In Patients With Smoking-Associated COPD

ERK1 / 2-VEZF1 Signaling Regulation Of Lung Endothelial ET-1 Expression. Elevation of pressure in the pulmonary artery, which carries blood from the heart to the lungs, is often seen in a subset of patients with moderate to severe chronic obstructive pulmonary disease (COPD). Tobacco smoking is the leading cause of COPD, responsible for 80-90% of all cases in the United States. Studies suggest a direct effect of tobacco smoke on lung endothelium, a layer of cells covering the inside of blood vessels. Smoking-induced endothelial dysfunction leads to overproduction of a substance, endothelin-1 (ET-1). ET-1 can tighten the vessel and may thicken the walls of pulmonary arteries. This makes the inside of vessels narrower. Experimental results indicate that smoking stimulates ET-1 gene expression in cultured lung endothelial cells. A protein in the nucleus modulates the synthesis of ET-1 through chemical communication within the cell, known as a cell signaling event. The long-term goal of this project is to investigate the process that leads to ET-1 overproduction, elevating lung arterial pressure. This research may lead to additional targets to be tested to reduce the incidence of pulmonary arterial hypertension in COPD patients.

TUBERCULOSIS

Tuberculosis (TB) remains an important disease in the United States and a worldwide epidemic that kills approximately 1.7 million people each year. Since it is transmittable and more and more people are migrating or traveling around the world, this international problem is of great concern to Americans. The worldwide AIDS epidemic has reached frightening proportions and is partly responsible for the increase in TB internationally, as the two infections often coexist. More recently, Americans have learned about the potential threat of a deadly form of TB germ that has no effective therapy and kills rapidly.

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

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

American Lung Association Scholar: Tuberculosis

ROXANA E. ROJAS, MD, PhD
Case Western Reserve University

While one-third of the world's population is currently infected with tuberculosis (TB), only about 10 percent of these people will develop TB disease in their lifetime. The remaining 90 percent have what is called latent or inactive TB, meaning their immune system can successfully fight the infection. The TB infection may remain inactive for a lifetime, although latent TB infection can become active if the person's immune system becomes weakened (such as with HIV).

Roxana E. Rojas, M.D., Ph.D., is investigating how the bacteria that causes TB, Mycobacterium tuberculosis (Mtb), escapes recognition by the immune system and remains latent. "To design better vaccines, we have to be able to understand how the bacteria remains latent and why certain people with latent TB develop the disease," she says.

Mtb appears to inactivate two types of key immune cells: macrophages and T lymphocytes. The TB bacteria primarily reside in macrophages, immune cells that engulf foreign material. Macrophages are activated by proteins called cytokines, which are secreted by T lymphocytes. Dr. Rojas is studying the mechanisms that Mtb uses to inactivate T lymphocytes. "We have made progress in understanding how the bacteria can directly affect T lymphocytes and modify their behavior so they cannot respond to the bacteria," she says.

Dr. Rojas is focusing on molecules called glycolipids on the surface of the bacteria that affect T lymphocytes. "Glycolipids prevent optimal interaction between T lymphocytes and macrophages, which is very important for the development of an effective immune response," she explains. "In addition, mycobacterial glycolipids directly inactivate T cells contributing to immune evasion. Mycobacterial molecules with potent effects on the immune system such as glycolipids need to be taken into consideration when designing new vaccines to fight TB."

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

CELIA GOULDING, PhD
University of California, Irvine, Irvine, CA
Biomedical Research Grant ● Funded by the American Lung Association and Supplemented by the American Lung Association of California

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

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

RUSSELL KARLS, PhD
University of Georgia Research Foundation, Athens, GA
Biomedical Research Grant ● Funded by the American Lung Association

Building A Better Tuberculosis Vaccine

Testing A Novel Tuberculosis Mucosal Vaccine. A vaccine for tuberculosis, BCG, has been used for decades, but a more effective vaccine is needed. The researchers will study how the Mycobacterium tuberculosis (Mtb) bacteria escape early destruction by the immune cells. These bacteria establish infection when inhaled into the alveoli (air sacs of the lungs). Interactions of the tuberculosis bacteria with cells within the alveoli are critical to the infection process and may impact whether the infection is contained at the initial contact site or spreads to other parts of the body. The researchers will study the function of a Mtb gene that appears to affect the fate of cells that line the walls of the alveoli. They will study if tuberculosis bacteria lacking this gene can no longer replicate in, or spread from, the alveolar lining. Bacteria that cannot infect the cell lining are more likely to be engulfed by immune cells that patrol the alveoli. The information gathered from this research will aid in the development of an effective tuberculosis vaccine.

FARAHNAZ MOVAHEDZADEH, PhD
University of Illinois, Chicago, IL
Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the Upper Midwest

Genes May Provide Insight About Latent Tuberculosis

The Biological Function Of Genes Essential For Latency In M. Tuberculosis. Mycobacterium tuberculosis (Mtb) causes tuberculosis (TB), which kills 1.7 million people worldwide every year. TB can reside latently in the human body for many years, but once active, it attacks the respiratory system. Anti-TB therapy is complicated, involving combinations of antibiotics taken over 6-12 months. In certain parts of the world, the rates of drug resistance are increasing rapidly. Thus, there is an urgent need to identify new anti-TB drugs. The ability of Mtb to enter a latent state is considered to be the key to its success as an infectious agent. The researchers will study the mechanism of the genes which are important in maintenance of the latent state of Mtb. Determining the functions of such genes will be key to finding targets for new anti-TB drugs that eliminate latent TB infection and/or shorten the duration of treatment of active TB.

ANIL OJHA, PhD
University of Pittsburgh, Pittsburgh, PA
Biomedical Research Grant ● Support of this grant comes from the Mary Fuller Russell Research Fund

Uncovering How TB Bacteria Persist Against Current Drug Treatments

Determination Of the Genetic And Environmental Factors That Control Biofilm Development In Mycobacterium Tuberculosis. One of the reasons that tuberculosis (TB) kills millions of people worldwide each year is that it has the extraordinary ability to persist against current drug therapy, which requires multiple anti-TB drugs to be administered for up to 12 months. Patients often don't complete their treatment, which results in the re-emergence of infections with multi-drug resistant or extremely drug resistant strains of the bacteria. A shorter treatment course is essential for an improved control of TB. However, development of new-generation antibiotics for a shorter treatment of TB requires a better understanding of the TB bacteria's ability to withstand drug treatment. The researchers have found that the TB bacteria, Mycobacterium tuberculosis

(Mtb), is able to form a complex drug-tolerant cellular structure called biofilm, but much is still unknown about this structure and the development of drug tolerance behavior. The researchers plan to investigate the factors that control the development of M. tuberculosis biofilm and study its role in persistence against drug therapy. The study may lead to knowledge that can be used to design new strategies that can shorten the duration of treatment.

SARAH K. PARKER, MD
University of Colorado Health Sciences Center, Denver, CO
Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the Southwest

Tuberculosis Bacteria 'Steal' Lipids From Human Host To Grow

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

NAIMISH PATEL, MD
Beth Israel Deaconess Medical Center, Boston, MA
Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of New England

Unlocking How HIV Increases Susceptibility To TB

HIV Alters Macrophage Apoptotic Response To M. Tuberculosis Through IL-10. While the HIV epidemic has resulted in an increased rate of tuberculosis worldwide, the manner in which HIV increases susceptibility to TB disease is poorly understood. TB is caused by a bacterium called Mycobacterium tuberculosis, which is transmitted when a person breathes in the TB bacterium. Specialized lung immune cells called alveolar macrophages serve as the first line of defense against TB bacteria. The bacteria are believed to cause disease by successfully existing inside alveolar macrophages without being killed or detected. Macrophages undergo programmed cell death, a normal suicidal process to selectively remove cells that are no longer needed, damaged or are dangerous. Programmed cell death prevents TB bacteria from existing undetected in infected cells. The investigators' preliminary research suggests that HIV infection of macrophages hinders the normal cell death response of macrophages, making a person more susceptible to TB infection. The researchers seek to further study the mechanism by which HIV is able to prevent cell death and also to identify factors in the lung's immune defense that are responsible for this effect. They will also identify potential novel targets for TB therapy in HIV, which can provide critical information for applications such as vaccine development.

ROXANA ROJAS, MD, PhD
Case Western Reserve University, Cleveland, OH
Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the Midland States

Gaining Insight Into How TB Germ Hides From Immune System

Regulation Of CD4+ T Cell Adhesion And Migration Induced By Mycobacterial Phosphatidylinositol Mannosides. Tuberculosis (TB) is a bacterial disease that primarily affects the lungs and is caused by Mycobacterium tuberculosis (Mtb). Many studies have shown that control of infection requires an intact, healthy immune system. However, control of infection does not eliminate all organisms from the lung and this state is called latent TB. Persons infected with Mtb are at risk of having the latent bacteria become reactivated, especially people with suppressed immune systems such as those with HIV infection. There is a need to improve therapy against TB as well as develop preventive measures such as vaccines. Knowing how Mtb escapes recognition by the immune system and remains latent is important to design new approaches for TB control. Mtb's immune evasion mechanisms can affect two types of cells: macrophages and T lymphocytes. The researchers will study how Mtb affects T lymphocytes and regulates their functions. Ultimately this research will contribute to efforts to develop more effective therapies and vaccines against TB.

OTHER LUNG INFECTIONS

Lung infections are common and often deadly. Influenza (flu) and pneumonia-related illnesses are responsible for approximately 63,000 deaths annually. Studies are being done to understand human susceptibility to the most dangerous flu viruses. American Lung Association researchers continue to study a bacterium called pseudomonas, which affects the injured lungs of people who have chronic obstructive pulmonary disease (COPD) and cystic fibrosis, hoping to find a new means of prevention.

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

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

In a new approach, scientists are asking whether common bacteria may act as "stealth organisms" and be an underlying cause of common diseases such as asthma and COPD that heretofore have not been considered to be caused by infections.

American Lung Association Scholar: Other Lung Infections

MINGQUAN ZHENG, MD
Children's Hospital of Pittsburgh

People with defects in the number and function of infection-fighting white blood cells, called T cells, whether due to HIV infection, cancer, or other diseases that suppress the immune system, are at increased risk from serious influenza (flu).

Studies have shown an increased risk for heart- and lung-related hospitalizations in people infected with HIV during flu season, and a higher risk of flu-related death in HIV-infected people. Other studies suggest that flu symptoms might be prolonged and the risk of flu-related complications such as pneumonia is higher for certain HIV-infected people.

While a flu shot may help reduce the risk of flu-related complications, the reduction in T cells impairs both the immune system itself and the effectiveness of the flu vaccine in promoting an immune-system response in people with HIV/AIDS. A more effective solution is needed to provide adequate protection for people with HIV/AIDS and other immune-damaging conditions.

Mingquan Zheng, MD, is using an American Lung Association Biomedical Research Grant to study the effectiveness of a new DNA-based vaccine in mice with a deficiency in T cells that protect against flu. The long-term goal of this research is to develop new DNA vaccine strategies against flu in patients with AIDS and other conditions that impair the immune system.

In his first year of research, Dr. Zheng found the DNA-based vaccine shows promise in protecting mice with T cell deficiency against flu, which produced antibodies against the flu virus. He is now conducting the study on a larger group, to see whether he can confirm his findings. He also hopes to understand how the DNA vaccine works to protect against flu.

"I'm hoping to get a larger grant based on the results of this research," Dr. Zheng says. "The grant from the American Lung Association has been very important to my scientific career—I would not have been able to start this project without it."

To see a complete description of Dr. Zheng's research project, please go to page 42.

SANTANU BOSE, PhD

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

Can Enzyme That Lowers Cholesterol In Cells Lead To Treatment For RSV?

Role Of Cholesterol 25-Hydroxylase During NF-kB Dependent Innate Anti-Viral Response Against Human Respiratory Syncytial Virus. Human respiratory syncytial virus (RSV) is an airborne virus that infects lung cells to cause a wide variety of diseases among infants, children, and the elderly. RSV infection is associated with high death rates among children, but there is currently no effective anti-viral therapy or vaccine to combat RSV infection. In an effort to identify novel anti-viral factors against RSV, the researchers will study the anti-viral defense mechanisms of lung cells. They have identified a candidate anti-viral protein called cholesterol 25-hydroxylase (C25H). This is an enzyme whose production in cells results in lowering of cellular cholesterol content. Since many viruses, including RSV, require cholesterol for infection, the researchers will study whether C25H acts as an anti-RSV agent and will study the way in which it restricts RSV infection. These studies may lead to the development of novel anti-viral therapies against RSV and other respiratory viruses.

JOHN BOUCHER, PhD

University of Texas at Tyler, Tyler, TX
Biomedical Research Grant ● Funded by the American Lung Association of the Central States

Targeting Protein On Bacteria That Causes Lung Infections

The Role Of IcmP, A Pseudomonas Aeruginosa Insulin-Cleaving Metalloprotease. Pseudomonas aeruginosa (PA) is a type of bacteria associated with many types of infections including those of the lungs. Pseudomonas infections of the lung are typically seen in patients who suffer from cystic fibrosis, HIV, and cancer. The ability of organisms such as PA to cause disease is dependent on proteins and other factors that they produce. Many of these proteins are found within the cells themselves. However, some are located on the outside of the cell anchored into the membrane. PA has a membrane with two layers, with the outer one functioning as a protective barrier. Some proteins on the outer membrane are responsible for adhering to or entering the body, thereby causing disease. These outer membrane proteins may also evade the body's immune system. The researchers are studying one of the PA outer membrane proteins called IcmP. Investigation into the function of this protein may lead to identification of new drug targets and vaccines, both of which would prevent PA from causing disease.

ANN CHEN, MD

University of Washington, Seattle, WA
Senior Research Training Fellowship ● Co-funded by the American Lung Association and the American Lung Association of the Northwest

Protein That Regulates Inflammation Could Help Fight Influenza

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

CORNELIUS J. CLANCY, MD

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

Proteins Involved In Invasive Pulmonary Aspergillosis May Hold Clues To Disease

Identification Of Virulence Factors During Invasive Pulmonary Aspergillosis. Invasive pulmonary aspergillosis (IPA) is an infection of the lungs caused by an environmental fungus called Aspergillus fumigatus (A. fumigatus). Humans normally inhale several hundred A. fumigatus spores into their lungs every

day. If they do not have deficiencies in their immune system function, people might develop allergic symptoms upon inhaling the spores but do not develop more extensive disease. If a person has a damaged immune system, however, the spores might not be cleared from the lungs, in which case they can grow and invade surrounding tissue and blood vessels. The resulting disease, IPA, has become much more common as the numbers of people with damaged immune systems have increased due to medical advances such as organ transplantation and cancer chemotherapy. Even with aggressive treatment with antifungal drugs, over half the patients with IPA die from the disease. In order to develop new treatments and preventive strategies, scientists need a better understanding of the way in which A. fumigatus causes IPA. They will identify A. fumigatus proteins within the lungs and study the specific mechanisms by which individual proteins contribute to the development of IPA. Some of these proteins may represent potential targets for future drugs or vaccines.

ANDREA COOPER, PhD
Trudeau Institute, Saranac Lake, NY
DeSouza Research Award ● Funded by the American Lung Association of the Southwest

Examining Inflammatory Response In Lung Disease Caused By Environmental Bacterium

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

DANNY HSIA, MD
University of Washington, Seattle, WA
Junior Research Training Fellowship – Senior Research Training Fellowship ● Funded by the American Lung Association of the Northwest

Predicting Which Children With RSV Will Develop Asthma

Exhaled Nitric Oxide Output In Infants With Pulmonary Hyperinflation Following Respiratory Syncytial Virus Bronchiolitis. Most lower respiratory tract illnesses with wheezing that occur in the first three years of life are associated with infection with respiratory syncytial virus (RSV). Many studies have shown an association between RSV, subsequent wheezing, and the development of asthma. Between 20-40% of young children who have RSV suffer from recurrent wheezing episodes that resolve on their own as the child gets older. A major challenge for doctors is predicting which infants are at increased risk for developing asthma after RSV and which will resolve on their own. The researchers will use two measurements to see how each alone and in combination predicts recurrent wheezing as the child grows. One measurement, called the thoracic index, measures persistent airway narrowing, while the nitric oxide index measures ongoing airway inflammation. If these measurements prove useful, they will allow doctors to identify which children who have had RSV might benefit from asthma therapy very early in life and thereby avoid complications of asthma in very young children.

TAEG SU KIM, PhD
University of Virginia, Charlottesville, VA
Senior Research Training Fellowship ● Co-funded by the American Lung Association and the American Lung Association of the Atlantic Coast

Deciphering How The Immune System Fights Influenza

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

infection and potential new treatments for other illnesses in the respiratory tract.

GIRISH S. KIRIMANJESWARA, PhD

Albany Medical College, Albany, NY

Senior Research Training Fellowship ● Co-funded by the American Lung Association and the American Lung Association of New York

Attacking 'Stealth' Organisms In The Lungs

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

KEVIN LEGGE, PhD

University of Iowa, Iowa City, IA

Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the Upper Midwest

Finding A Way To Help The Immune System Fight Off Bacterial Infections After Influenza

Respiratory Dendritic Cells: Cell Migration And Induction Of Adaptive Immunity During Virus Infections. The lungs are routinely exposed to foreign pathogens such as bacteria and viruses in the air that we breathe. Often our immune system halts these pathogens before significant infections can occur. However, when these pathogens do establish an infection, the immune system must kick in to fight it. In the lungs, respiratory dendritic cells (rDC) are thought to be responsible for inducing this immune system response. The researchers have found that following influenza infections, rDC rapidly migrate from the lungs to the lymph nodes and induce an immune response that is specific to influenza. But within 24 hours after influenza virus infection, rDC halt their migration. This halt is of particular concern following respiratory virus infections where concurrent or new bacterial infections are common. The researchers will study the way in which rDC migration is stopped following influenza virus infections. They will then determine if manipulating this mechanism can restore rDC migration, thus helping the immune system fight off secondary infections. By boosting the immune system's response to bacterial infections, complications ranging from otitis media and pneumonia in children to potentially deadly pneumonia in elderly adults might be avoided.

LATANIA LOGAN, MD

Children's Memorial Hospital, Chicago, IL

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

How Do Hardy Bacteria In The Lung Withstand Antibiotic Treatment?

Mechanisms of Relapse In Pseudomonas Aeruginosa Acute Pneumonia. Pseudomonas aeruginosa (PA) is a bacteria that is a major cause of lung disease resulting in serious infections. This organism is particularly problematic in patients with hospital-acquired pneumonia, which leads to death in up to 80% of infected patients on ventilators. PA is very difficult to kill once it has infected the lung, and often causes relapses. Most cystic fibrosis patients remain infected with the same strain of PA for life despite long-term therapy with multiple antibiotics. Despite the enormity of the problem, very little is known about how PA is able to withstand antibiotic therapy. The researchers will examine what happens to the bacteria inside white blood cells during antibiotic treatment. A better understanding of the importance of PA's role inside white blood cells in pneumonia may lead to the identification of new antibiotic combinations with increased effectiveness in the treatment of these infections.

SUSAN LYNCH, PhD
University of California, San Francisco, San Francisco, CA
Biomedical Research Grant ● Funded by the American Lung Association of California

Unlocking The Role Of Bacteria In COPD Flare-Ups And Remissions

Analysis Of Bacterial Community Dynamics In Adult Patients With Exacerbations Of Chronic Obstructive Pulmonary Disease. Although bacteria are now thought to be responsible for up to 50% of chronic obstructive pulmonary disease (COPD) episodes, little is known about the types and dynamics of bacteria in the airways of people with the disease. Recently, it has been shown that bacterial communities exist in a number of respiratory diseases. To fully understand the contribution of specific members of the airway bacterial community to COPD, it is necessary to identify which bacteria are present when patients develop symptoms. The researchers use a novel tool that allows them to comprehensively describe the types of bacteria present in the airways of COPD patients during flare-ups and remission. They will look at how the microbial community changes over time and with antimicrobial treatment and which microbes are associated with disease progression. Eventually, this research may lead to new treatments for COPD.

BORNA MEHRAD, MD
University of Texas Southwestern Medical Center, Dallas, TX
Career Investigator Award ● Funded by the American Lung Association

Searching For Genetic Clues To Resistance To Pneumonia

Genetically Determined Host Resistance To Pneumonia. Pneumonia caused by gram-negative bacteria is a common and serious illness, but relatively little is known about inherited factors that predispose a person to this infection. The researchers have identified a strain of mouse that is much more resistant to this infection than another more common strain. These two strains of mice are nearly identical, except for one set of genes. In this study, the researchers hope to determine how the resistant animals fight off the infection more effectively. These experiments should produce results relevant to human disease in two ways. First, it is possible that some humans have genes similar to those that make mice more resistant to pneumonia. Second, understanding the way in which the resistant mice fight off the infection could lead to new treatments to help patients fight off the infection in similar ways.

ALLISON MILLER, PhD
University of California, San Francisco, San Francisco, CA
Senior Research Training Fellowship ● Funded by the American Lung Association of California

Exploring The Role Of A Protein In Fungal Infection In The Lungs

Elucidating The Cell-Type Specific Roles Of Syk Kinase In A Murine Model Of Pulmonary Aspergillosis. Aspergillus fumigatus (A. fumigatus) is the most prevalent airborne fungus in industrialized countries and it has the potential to cause a variety of devastating pulmonary diseases. Colonization of the lung with this fungus occurs mainly in people with compromised immune systems, with lung transplant recipients and people with blood cancers. A. fumigatus also can cause a condition known as ABPA, in which the fungus colonizes the lungs of people with cystic fibrosis or asthma. Further insights into the fungus and the immune response that it generates are critical for the development of effective treatments. The researchers will study a protein called Syk that is found in cells lining the airways called epithelial cells, as well as alveolar macrophages, cells that engulf foreign material, keeping the lungs free of infection. They will investigate whether Syk is involved in fungal clearance from the lung. The researchers will generate mice lacking Syk in either their airway epithelial cells or alveolar macrophages and monitor changes in the lungs when exposed to A. fumigatus.

NAIMISH PATEL, MD
Beth Israel Deaconess Medical Center, Boston, MA
Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of New England

Unlocking How HIV Increases Susceptibility To TB

HIV Alters Macrophage Apoptotic Response To M. Tuberculosis Through IL-10. While the HIV epidemic has resulted in an increased rate of tuberculosis (TB) worldwide, the manner in which HIV increases susceptibility to TB disease is poorly understood. TB is caused by a bacterium called Mycobacterium tuberculosis, which is transmitted when a person breathes in the TB bacterium. Specialized lung immune cells called alveolar macrophages serve as the first line of defense against TB bacteria. The bacteria are believed to cause disease by successfully existing inside alveolar macrophages without being killed or detected. Macrophages undergo programmed cell death, a normal suicidal process to selectively remove cells that are no longer needed, are damaged or are dangerous. Programmed cell death prevents TB bacteria from existing undetected in infected

cells. The investigators' preliminary research suggests that HIV infection of macrophages hinders the normal cell death response of macrophages, making a person more susceptible to TB infection. The researchers seek to further study the mechanism by which HIV is able to prevent cell death and also to identify factors in the lungs' immune defense that are responsible for this effect. They will also identify potential novel targets for TB therapy in HIV, which can provide critical information for applications such as vaccine development.

CARLOS SEREZANI, PhD

University of Michigan, Ann Arbor, MI

Senior Research Training Fellowship ● Co-funded by the American Lung Association and the American Lung Association of the Midland States

Gathering Facts About Inner Workings of Lung's Immune System

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

CHAD STEELE, PhD

Children's Hospital of Pittsburgh, Pittsburgh, PA

Career Investigator Award ● Funded by the American Lung Association

Protecting Against A Deadly Infection In People With Compromised Immune Systems

Dectin-1 And Invasive Pulmonary Aspergillosis. People with defective immune systems are highly susceptible to infection by a variety of organisms, including parasites, bacteria, viruses, and fungi. The fungal organism Aspergillus fumigatus (A.fumigatus) is a particular danger to people with compromised immune systems. Current antifungal treatments are not very effective against this severe infection. Many disease-causing organisms, including A. fumigatus, enter the body through the lung; therefore, understanding how the lung immune system works in defending against these organisms is of critical importance. One of the first lung immune cells that a disease-causing organism comes into contact with is the alveolar macrophage. The researchers will investigate a receptor called Dectin-1 on the surface of the alveolar macrophage that recognizes and responds to inhaled A. fumigatus. They will also study a new therapeutic compound based on the structure of Dectin-1 that could enhance the ability of lung immune cells to fight infection caused by A. fumigatus.

SCOTT WESSELKAMPER, PhD

University of Cincinnati, Cincinnati, OH

Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the Midland States

Seeking Genes That Control Susceptibility To Dangerous Respiratory Infection

Host Susceptibility To Pseudomonas Aeruginosa Respiratory Infection. Pseudomonas aeruginosa (PA) is a common bacteria that is a major cause of respiratory infections in patients who have recently received treatment in a hospital or a health care service unit. Patients whose immune systems are in a weakened state are at increased risk for PA infection. It is also the leading cause of illness and death in patients with cystic fibrosis. The bacteria can develop resistance to antibiotics, and is able to flourish in harsh environments. This also makes PA lung infections difficult for doctors to treat. The researchers hope to identify genetic factors that control susceptibility to PA respiratory infection. They will use several strains of mice and examine the clearance of the bacteria from their lungs, as well as the ability of immune-system cells known as macrophages to engulf the bacteria. They will analyze the results to determine unique genes that link to PA respiratory infection, which can be further studied to develop new therapeutics for the treatment and prevention of infection.

MINGQUAN ZHENG, MD
Children's Hospital of Pittsburgh, Pittsburgh, PA
Biomedical Research Grant ● Funded by the American Lung Association

DNA-Based Influenza Vaccine May Help People With Impaired Immune Systems

CD4-Independent DNA Vaccinations Against Influenza. People with defects in the number and function of infection-fighting white blood cells called T cells, whether due to HIV infection, cancer, or other diseases that suppress the immune system, are at increased risk from serious influenza (flu). This defect in T cells impairs both the immune system itself and the effectiveness of the flu vaccine in promoting an immune-system response. The researchers are studying a new DNA-based vaccine in mice with a deficiency in T cells that protects against flu. The long-term goal of this research is to develop new DNA vaccine strategies against flu in patients with AIDS and other conditions that impair the immune system.

LUNG CANCER

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 a five-year survival rate of approximately 16 percent of patients. The effectiveness of surgery is limited by our inability to detect cancers early enough to cure them. The effectiveness of chemotherapy is limited by its suppression of the immune system, which is vitally needed to control cancer growth and protect against infection. The effectiveness of radiation is limited by its damage to the lungs.

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

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

American Lung Association Scholar: Lung Cancer

MICHAEL P. LISANTI, MD, PhD
Thomas Jefferson University

One way in which the body protects itself against cancer is through tumor suppressor genes, which are protective genes that normally limit the growth of tumors. But when a tumor suppressor gene is altered, or mutated, it stops working properly and may fail to keep a cancer from growing. Michael P. Lisanti, MD, PhD, is seeking to develop replacements for these genes to treat lung cancers.

Dr. Lisanti, Director of the Stem Cell Biology and Regenerative Medicine Center at Thomas Jefferson University, will test the effectiveness of replacing a tumor suppressor gene known as caveolin-1 (CAV-1), using an established mouse model of lung cancer. "We think CAV-1 mutations are involved in many types of cancer, including lung and breast cancer," says Dr. Lisanti.

With the help of a Lung Cancer Discovery Award, funded in partnership between the American Lung Association and the LUNGevity Foundation, Dr. Lisanti will study whether adding back the CAV-1 gene to a mouse bred to develop lung cancer will enable the mouse to suppress the cancer.

"If we can successfully replace the whole gene or a fragment that stops the cancer cells from proliferating, we could potentially use this information to develop a drug that mimics the activity of CAV-1," says Dr. Lisanti, who also leads the Molecular Biology and Genetics of Cancer Program at Jefferson's Kimmel Cancer Center.

The Lung Cancer Discovery Award is critically important to his work, Dr. Lisanti says. "Especially now, during the research funding crisis in this country, we greatly appreciate the support. We wouldn't have been able to do the project without this funding."

To see a complete description of Dr. Lisanti's research project, please go to page 45.

PAO-TIEN CHUANG, MD, PhD

University of California, San Francisco, San Francisco, CA

Career Investigator Award ● Funded by the American Lung Association

Signal Between Types Of Lung Cells May Provide Clues To Lung Development

Fu And Sufu Function Through Different Types Of Cilia In Controlling Lung Development And Function. Proper lung function in adults relies on normal embryonic development. In lung development, a tube-like structure undergoes extensive branching to generate an elaborate respiratory tree that is essential for gas exchange after birth. This structure is comprised of a layer of cells called epithelial cells. Instructive signals for epithelial branching live in a surrounding tissue layer called the mesenchyme. The researchers will use mouse lungs to understand how a secreted protein called the Hedgehog mediates between the epithelial cells and the mesenchyme and regulates their development. When the Hedgehog is received, it activates a series of events in the cell, which is referred to as a signaling pathway. Major signaling pathways including the Hedgehog pathway are thought to control cell proliferation and differentiation as well as stem cell maintenance and cancer formation. This research will lead to a better understanding of the molecular basis of lung development. It also may shed light on the molecular mechanisms of lung cancers and provide cell-based therapy for lung diseases using stem cells. The researchers also will study the link between Hedgehog signaling and cilia, hair-like structures that line the airways and help to clean them out. Their studies will help increase understanding of diseases related to defective cilia, including bronchiectasis and sinusitis.

RANDOLPH HASTINGS, MD, PhD

Veterans Medical Research Foundation, San Diego, CA

Lung Cancer Discovery Award ● Funded in partnership between the American Lung Association and the LUNGevity Foundation

Hormone Therapy May Slow Growth Of Lung Cancer In Men

Hormonal Therapy For Non-Small Cell Lung Carcinoma. This research will focus on parathyroid hormone-related protein (PTHrP) as a basis for developing new treatments for lung cancer. PTHrP modifies the behavior of many types of cancer and is frequently present in lung cancer. The researchers' previous investigations suggest that PTHrP slows the growth of lung tumors that grow in women and improves survival of women with lung cancer, but not men with the disease. The sex difference may arise because male sex hormones interfere with the beneficial effect of PTHrP in slowing lung cancer growth. The researchers will investigate whether blocking these hormones could increase the responsiveness of tumors to PTHrP in men and allow the protein to reduce cancer growth, as it does in women. The results of this research could show that treatments already used for prostate cancer are also useful in men with lung cancers that make PTHrP. In women, the PTHrP-based treatment alone may work. The long-term goal is to develop novel therapies for lung cancer and to identify the best groups of patients to receive those therapies.

MICHAEL P. LISANTI, MD, PhD

Thomas Jefferson University, Philadelphia, PA

Lung Cancer Discovery Award ● Funded in partnership among the American Lung Association, the LUNGevity Foundation, and the American Lung Association of the Mid-Atlantic

Replacing Tumor Suppressor Gene May Lead To New Lung Cancer Treatment

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

PHILIPPE MONTGRAIN, MD

University of California, San Diego, San Diego, CA

Senior Research Training Fellowship ● Funded by the American Lung Association of California

Male Sex Hormone May Inhibit Protein That Slows Growth Of Lung Cancer

Lung Cancer Suppression By Parathyroid Hormone-Related Protein: Antagonism By Androgens. The researchers have found that a protein called parathyroid hormone-related protein (PTHrP), produced by about two-thirds of lung cancers, slows tumor growth in mice and prolongs survival in humans. This survival benefit is seen only in women, however. The researchers have previously found that tumors in males make less PTHrP than tumors in females. They will study how PTHrP

slows lung cancer growth and why the protein's anti-cancer effects depend on gender. They will investigate whether PTHrP decreases the proliferation of tumor cells and whether the male sex hormone testosterone inhibits the production of PTHrP by lung cancer cells, allowing lung tumors in males to make less of the protein and to grow faster. By determining how PTHrP, gender, and hormonal exposure interact to alter lung cancer progression, the researchers hope to advance medical knowledge toward the goal of improved lung cancer therapy.

KWON-SIK PARK, PhD

Stanford University, Stanford, CA

Senior Research Training Fellowship ● Funded by the American Lung Association

Understanding The Origin And Development Of Small Cell Lung Cancer

Mechanisms Of Cancer Initiation In A Mouse Model Of Human Small Cell Lung Carcinoma. The overall five-year survival rate for lung cancer is about 16%; for small cell lung cancer (SCLC), it is only 6%. The high death rate from SCLC is due in part to the fact that only 6% of these cancers are detected in the early stages of the disease, making treatment options fewer and less effective. To understand how to improve detection at earlier stages and identify novel treatments, it is critical to understand the basic biology of how SCLC starts and develops. The researchers plan to investigate the molecular and cellular mechanisms of how SCLC begins and develops by studying genetically engineered mice, in which the disease can be induced in a controlled fashion and cancer progression can be monitored. Previous research indicates these mouse tumors are very similar to human SCLCs. A better understanding of the early stages of SCLC will eventually allow researchers to identify markers for SCLC detection and discover novel therapeutic approaches.

GEORGE C. PRENDERGAST, PhD

Lankenau Institute for Medical Research, Wynnewood, PA

Lung Cancer Discovery Award ● Funded in partnership among the American Lung Association, the LUNGevity Foundation, and the American Lung Association of the Mid-Atlantic

Will Blocking 'Hijacked' Enzyme Shrink Lung Cancer?

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

DAVID ROBBINS, PhD

Dartmouth Medical School, Hanover, NH

Lung Cancer Discovery Award ● Funded in partnership between the American Lung Association and the LUNGevity Foundation with support from Mr. Sylvester F. Miniter III

Identifying Which Lung Cancer Patients Are Sensitive To "Hedgehog" Protein

Uncovering Molecular Markers Of Hedgehog Antagonist Sensitive Lung Cancer. There is a pressing need for new lung cancer treatments, given that lung cancer is the leading cause of cancer death in the United States for both men and women. The researchers will study a secreted protein nicknamed Hedgehog, which plays an important role in large numbers of patients with non-small cell lung cancer, the most common type of lung cancer. When the Hedgehog is received, it activates a series of events in the cell, which is referred to as a signal pathway. These events can lead to mutations that result in different types of cancer. The researchers will identify molecular markers that can identify lung cancer that is sensitive to inhibitors of Hedgehog signal activity. These markers would allow doctors to select which lung cancer patients would be most likely to respond to treatment that targets the Hedgehog signal pathway, maximizing the effectiveness of this novel targeted therapy. The researchers have developed mice that can be used to test Hedgehog pathway antagonists, and treatments that target the Hedgehog pathway. This research has the potential to address the substantial medical need to develop innovative approaches to treat lung cancer.

JULIEN SAGE, PhD

Stanford University, Stanford, CA

Diane Emdin Sachs Lung Cancer Award ● Funded in partnership between the American Lung Association and the American Lung Association of New York with special thanks to the Emdin Family

Targeting A Cell Communication Network In Small Cell Lung Cancer

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

MICHAEL A. TAINSKY, PhD

Wayne State University, Karmanos Cancer Institute, Detroit, MI

Lung Cancer Discovery Award ● Funded in partnership among the American Lung Association, the LUNGevity Foundation, and the American Lung Association of the Midland States

Developing Noninvasive Blood Test To Detect Early Lung Cancer

Autoantibody Biomarkers For The Detection Of Lung Cancer. If lung cancer is detected at an early stage, there is a much greater chance that it can be treated. An inexpensive, noninvasive early detection test that could detect early stage lung cancer would reduce deaths from lung cancer. The researchers have developed a strategy for early detection of cancer that takes advantage of the responses of the human immune system to identify cancer-associated proteins that bind to antibodies present in the blood of cancer patients but not in the blood of healthy subjects or those with noncancerous diseases. They hope to develop a noninvasive screening blood test for early detection of lung cancer using these cancer-associated proteins. Along with blood from lung cancer patients, the blood from other cancer patients will be tested so that the researchers can identify markers for lung cancer that do not falsely identify other cancers or benign lung conditions as lung cancer.

LIN ZHANG, PhD

University of Pittsburgh, Pittsburgh, PA

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

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

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

YANYAN ZHENG, PhD

Stanford University, Stanford, CA

Senior Research Training Fellowship ● Funded by the American Lung Association

Lung Cancer Stem Cells May Help Explain Resistance To Chemotherapy

Lung Cancer Stem Cells And Cisplatin Resistance. Non-small cell lung cancer (NSCLC) is a major type of lung cancer, accounting for approximately 80-87% of cases. Results from the current therapies for NSCLC are poor except in cancers found early that have not spread. In more advanced cancers, chemotherapy plays an important role and can improve survival. However, the long-term survival of patients with chemotherapy is still poor, partly due to cancer relapse from resistance to chemotherapy. Scientists do not know much about the mechanisms responsible for resistance to conventional chemotherapy. Recent evidence suggests that many tumors contain a small population of cells with unique characteristics, called "cancer stem cells" because of their ability to grow a new tumor in transplantation

experiments. The overall objective of this research is to test whether the chemotherapy resistance in NSCLC is contributed by a small subset of lung cancer stem cells. The researchers will use a mouse model of lung cancer to determine whether cancer stem cells show increased resistance to therapy. If they find that these stem cells are present, they can then extend this work to human samples and begin to identify new ways of treating patients with NSCLC.

THE IMMUNE SYSTEM, INFLAMMATION AND LUNG SCARRING

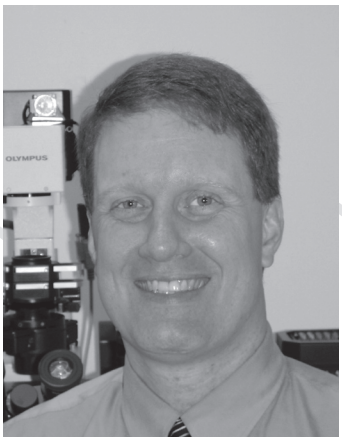
The body defends itself and resists infection by mounting immune (allergic) and inflammatory responses to foreign invaders such as infecting organisms and particulates. Sometimes these defense systems over-respond and identify the body's own molecules as foreign. When the body turns against itself in this way, disease may be created. One example of this is interstitial lung disease or idiopathic pulmonary fibrosis, in which an excessive inflammatory response to seemingly mild stimuli may lead to permanent scarring of the lungs, disability, and death. There has been an unexplainable rise in the incidence of this fatal disease, primarily in middle aged and older men. Because most lung diseases involve inflammation and the cells of the immune system to some degree, the American Lung Association supports an array of investigations into the basic cellular and molecular processes that underlie these systems.

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

One way to treat pulmonary fibrosis is with lung transplantation. Studies are being done that seek to understand the high rate of rejection of lung transplants relative to other organs.

New attention is being paid to the basic biology of Lymphangioleiomyomatosis, or LAM, an uncommon but potentially deadly disease which primarily affects young women.

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



WILLIAM LAWSON, MD
Vanderbilt University Medical Center

Idiopathic pulmonary fibrosis (IPF) is a severe lung disease in which patients develop shortness of breath, decreased exercise capacity, lung scarring (fibrosis) and difficulty with oxygen exchange. Once diagnosed, most IPF patients gradually develop respiratory failure and die within 2-4 years. There is no cure for IPF. While most cases of IPF occur in people who do not have family members with the disease, some cases of IPF are found in families, called familial IPF.

With the assistance of an American Lung Association Dalsemer Research Grant, William Lawson, MD, is studying the role of telomerase in IPF. Telomerase is the enzyme that maintains stability of the end of a chromosome, the region referred to as a telomere, throughout the life of the cell and during cell division. Lack of telomerase can lead to telomere shortening, resulting in cell death. Dr. Lawson's interest in this area stems from previous work in which he and his colleagues found genetic mutations in telomerase in several families with IPF. Dr. Lawson also thinks that similar processes may be at work in non-familial IPF.

Dr. Lawson suspects that in people with IPF, the disease begins to develop in alveolar epithelial cells, which line the air sacs at the end of the airways. "These alveolar epithelial cells are critical for gas exchange—taking in oxygen and releasing carbon dioxide," Dr. Lawson explains. "We suspect that these cells are the ones most adversely affected by telomerase mutations. Based on previous research, we think that these cells are essential not only to the initiation of the disease process, but also to the repair process. If the lung is injured, the behavior of these cells is critical in whether the lung recovers or scars."

If alveolar epithelial cells, do indeed, turn out to be crucial in the progression of IPF, then scientists could begin to develop drugs to target those cells. "If you can intervene in the critical steps in the progression of the disease, you can potentially slow down the process," Dr. Lawson says. "Our hope is that this research is laying the groundwork for the development of future treatments."

To see a complete description of Dr. Lawson's research project, please go to pages 53-54.

KAMRAN ATABAI, MD
University of California, San Francisco, San Francisco, CA
Biomedical Research Grant ● Funded by the American Lung Association of California

Lack Of Protein May Lead To More Severe Lung Scarring After Injury

The Role Of Mfge8 And Apoptotic Cell Clearance In Modulating Pulmonary Fibrosis After Lung Injury. Acute lung injury (ALI) is a common response of the lung to many different types of direct and indirect injury such as pneumonia, multiple bone fractures, and blood transfusions. ALI is characterized by an often escalating spiral of inflammation that can aggravate the lung injury. Despite the same initial degree of injury, some patients recover quickly while others have a progressive and worsening course. When the lung is injured, many cells are killed or undergo programmed cell death, a process called apoptosis in which cells essentially kill themselves when they are under extreme environmental stress. Recent evidence suggests that having too many apoptotic cells in the lung can lead to more severe lung injury and scarring. The researchers will study a protein called Mfge8 that is made in the lung and binds to apoptotic cells, facilitating their removal. They will evaluate whether mice that lack Mfge8 develop more lung scarring after injury. This research has the potential to identify new therapeutic targets for lung injury and scarring.

NAVDEEP CHANDEL, PhD
Northwestern University, Chicago, IL
Career Investigator Award ● Funded by the American Lung Association of the Upper Midwest

Evaluating Immune System Protein's Role In Acute Respiratory Distress Syndrome

Mitochondrial ROS Regulation of TGF-Beta1 Induced Gene Expression. There is no effective treatment for patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). These disorders are associated with an unacceptably high death rate. Transforming growth factor-beta 1 (TGF-B1) has been identified as a critical immune system protein regulating tissue repair in animal models of lung injury and scarring. Too little TGF-B1 activity may prevent resolution of inflammation and impair tissue repair while too much activity may lead to fibrosis, or scarring in the lungs. The researchers will study the relevance to lung disease of a chemical signaling pathway in TGF-B1. The results may provide the rationale for developing and testing novel therapeutic strategies for ARDS and ALI.

PETER CHEN, MD
University of Washington, Seattle, WA
Biomedical Research Grant ● Support of this grant comes from the Mary Fuller Russell Research Fund

Why Is Chronic Rejection So Common After Lung Transplant?

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

ETHAN CORCORAN, MD, PhD
University of California, San Francisco, San Francisco, CA
Junior Research Training Fellowship-Senior Research Training Fellowship ● Funded by the American Lung Association of California

Building A Model To Gain Insight Into Key Immune System Cells

Analysis And Directed Manipulation Of T Lymphocyte Activation At The Single-Cell Level. T lymphocytes, or T cells, are a subset of white blood cells that are central elements of our immune system and have critical functions in infection, autoimmunity and transplantation. Inappropriate activation of T cells can have profound unwanted inflammatory consequences, such as asthma, autoimmune disorders, and anaphylaxis (shock). T cell activation also plays an important role in transplantation, since the ability to perform transplants depends on our ability to regulate the immune response to foreign tissue. Much is still not known about how T cells are activated. The researchers will use new technology to build a better model of T cell activation. They will use

sophisticated mathematical techniques to analyze and model how components of chemical communication within the cell, known as cell signaling, interact and then manipulate those interactions. The researchers believe that a deeper understanding of such signaling networks will help identify new drug targets and predict how to use existing drugs more effectively.

CHEN DONG, PhD

University of Texas MD Anderson Cancer Center, Houston, TX
John L. Kirkwood Career Investigator Award ● Funded by the American Lung Association

Better Understanding Of Lung Inflammation May Shed Light On Many Lung Diseases

Lung Inflammation Mediated By Inflammatory Helper T Cells. Chronic inflammation is the underlying mechanism for many lung diseases including asthma, chronic obstructive pulmonary disease (COPD), sarcoidosis and lung cancers. Development of lung inflammation is complex. The researchers are studying a type of cell that produces a substance called interleukin-17, or IL-17, which has been associated with asthma. They have found that mice that produce too much IL-17 in the lung developed lung inflammation, excess mucus, and changes in the airway. The researchers will study the regulation and function of white blood cells called T cells that produce IL-17 during lung inflammation. The research will provide new explanations of the mechanisms in the development of lung disease and may suggest new treatment.

CAROL A. FEGHALI-BOSTWICK, PhD

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

Insight Into Protein's Lung-Scarring Role May Lead To Pulmonary Fibrosis Treatments

IGFBP-5: Novel Mediator Of Lung Fibrosis. A person with pulmonary fibrosis has tissue deep in the lungs that becomes scarred over time. The development of this scarred tissue is called fibrosis. As the lung tissue becomes thicker, the lungs are less able to move oxygen into the bloodstream. This means that the brain and other organs don't get the oxygen they need. In cases in which the cause of a person's pulmonary fibrosis is not known, the disease is called idiopathic pulmonary fibrosis (IPF). There is currently no effective treatment for this debilitating disease. The researchers have identified a new protein called Insulin-like Growth Factor Binding Protein-5, or IGFBP-5, which is increased in lung tissues of patients with IPF. IGFBP-5 is also increased in cells known as fibroblasts that are grown in the lab from these lung tissues. The researchers have shown that IGFBP-5 can turn normal fibroblasts into IPF-like fibroblasts by increasing their production of certain proteins. They also found that IGFBP-5 can trigger lung scarring in mice that is similar to the fibrosis seen in human IPF and connective tissue diseases. The researchers' goal is to identify the way in which IGFBP-5 causes lung scarring, in order to develop new and more effective treatments to stop the disease's progression.

MONICA FOOTE, PhD

Cornell University, Ithaca, NY
Senior Research Training Fellowship ● Funded by the American Lung Association

Understanding Immune Helper Cells May Lead To Better Treatment For Allergic Asthma

Epigenetic Regulation Of The Neonatal Th2 Bias. Allergic diseases, including asthma, are inflammatory disorders that result when the immune system mounts an irregular response to environmental allergens. It is estimated that half of Americans with asthma suffer from allergic asthma, a condition that is commonly believed to originate in neonatal or fetal life. Certain white blood cells, called T helper (Th) cells, help other immune cells to mount responses by producing and secreting immune growth factors called cytokines. The immune system produces Th1 and Th2 cells, and both are needed for an effective immune response. People susceptible to allergic asthma, however, often mount potent Th2 responses. The researchers will investigate the mechanisms governing the development and persistence of early-life Th2 function, which will provide information that will be valuable in developing targeted, safe, and effective treatments for allergic asthma in children.

MARILYN GLASSBERG, MD

University of Miami, Miami, FL
Career Investigator Award ● Funded by the American Lung Association of the Southeast

Searching For New Targets For Treatment Of Rare Women's Lung Disease

New Directions In The Treatment Of Lymphangioleiomyomatosis. Lymphangioleiomyomatosis (LAM), is an aggressive, destructive, and eventually fatal lung disease of women. In this rare disease an unusual type of muscle cell invades the lungs, forming bundles that

grow into the walls of the airways and form cysts that completely destroy the lungs. Increased activity of enzymes in the lung called matrix metalloproteinases (MMPs) may be involved in LAM. In addition, female sex hormones, particularly estrogen, have been implicated in LAM, since the disease occurs only in women and is predominantly diagnosed during their reproductive years. The researchers will study molecules that inhibit MMPs that are fueled by estrogen. The results of the study could help tailor new therapies for the successful treatment of LAM.

OCTAVIAN HENEGARIU, MD
Yale University, New Haven, CT
Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of New England

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

Changes In Th2 Responses And Lung Inflammation In Mice With Conditional PPARG Deletion In CD4 T Cells. Certain white blood cells, called T helper (Th) cells, help other immune cells to mount responses by producing and secreting immune growth factors called cytokines. The immune system produces Th1, Th2, Th17 and regulatory T cells, and all are needed for an effective immune response. People susceptible to allergic asthma, however, often mount potent Th2 responses. The researchers are studying whether a commonly used class of anti-diabetes drugs called thiazolidedinediones (TZD) may promote Th2 responses in the immune system. TZD drugs bind to a protein called PPARG that is present in many cells, including cells of the immune system. TZD agonist drugs promote PPARG function and lead to a better control of the number of harmful activated immune cells, as well as a reduction in the release of pro-inflammatory cytokines, thus decreasing inflammation. Several studies have shown that the anti-inflammatory action of TZD is beneficial in treating asthma. But the researchers think that in addition to inhibiting PPARG, TZD may also be activating asthma-promoting Th2 cells, and the effects are being obscured by the drug's anti-inflammatory effect. They will use a mouse in which PPARG is deleted from some T cells to investigate the effect of TZD on asthma-promoting cells in the immune system. They hope to discover whether using TZD in asthma has a long-term harmful effect, due to its Th2 activation.

DANIEL KASS, MD
Columbia University Medical Center, New York, NY
Research Grant-Clinical Grant ● Funded by the American Lung Association of New York

Researching Protein's Role in Pulmonary Fibrosis

Cytokine Receptor-Like Factor 1 And Pulmonary Fibrosis. Idiopathic pulmonary fibrosis (IPF) is a chronic illness leading to progressive scarring of the lung. There are no known effective therapies, except possibly lung transplantation. The researchers have performed gene expression profiling, a technique designed to screen thousands of genes simultaneously on lung samples from patients with IPF and normal controls. Their experiments revealed highly significant increased expression of a protein called cytokine receptor-like factor I (CRLF-1) in lungs from patients with IPF versus normal controls. CRLF-1 is important in the developing human central nervous system, but its role in IPF is unknown. CRLF-1 belongs to the interleukin-6 (IL-6) family of proteins. IL-6 family members have been shown to be important in the growth of cells that produce collagen, a key component of scarring. The researchers will study whether high levels of CRLF-1 in human lungs are essential for the development of IPF, and whether blocking CRLF-1 prevents fibrosis. The ultimate goal of this study is to uncover a novel therapeutic target for the treatment of IPF.

WILLIAM LAWSON, MD
Vanderbilt University Medical Center, Nashville, TN
Dalsemer Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the Midland States

Genetic Mutations May Yield Information On Idiopathic Pulmonary Fibrosis

Dysfunction In The Alveolar Epithelium In Pulmonary Fibrosis. Idiopathic pulmonary fibrosis (IPF) is a severe lung disease in which patients develop shortness of breath, decreased exercise capacity, lung scarring (fibrosis) and difficulty with oxygen exchange. Once diagnosed, most IPF patients gradually develop respiratory failure and die within 2–4 years. There is no cure for IPF. While most cases of IPF occur in people who do not have family members with the disease, some cases of IPF are found in families, called familial IPF. The researchers found genetic mutations in telomerase in several families with IPF. Telomerase is the enzyme that maintains stability of the end of a chromosome, the region referred to as a telomere, throughout the life of the cell and during cell division. Lack of telomerase can

lead to telomere shortening, resulting in cell death. The researchers suspect that telomerase dysfunction in cells lining the alveoli, or air sacs at the end of the airways, is responsible for the development of lung fibrosis in people with IPF with telomerase mutations. They also think that similar processes may be at play in non-familial IPF. They will determine how telomerase dysfunction and telomere shortening affect alveolar cells and impact IPF. These studies will identify key components that may serve as future therapeutic targets in IPF.

ZHUGONG LIU, MD, PhD
UMDNJ-New Jersey Medical School, Newark, NJ
Biomedical Research Grant ● Support of this grant comes from the Mary Fuller Russell Research Fund

"Hygiene Hypothesis" Investigated In Allergic Asthma's Rise

The Role of IL-17 In Parasite-Induced Immune Modulation Of Asthma. Asthma is commonly divided into two types: allergic asthma and non-allergic asthma. Allergic asthma is the most common form of asthma, and its prevalence has increased dramatically in recent decades, particularly in highly developed countries like the United States. The reason for this increase is still not known, but it may be related to the "hygiene hypothesis," which proposes that a lack of exposure to infectious agents may result in a dysfunctional immune system, that predisposes a person towards the development of allergic inflammation. Due to both improved hygiene and the widespread use of vaccines and antibiotics in recent decades, a lack of exposure to infectious agents, particularly intestinal parasites called helminths, may increase susceptibility to allergic diseases. The researchers will examine the mechanism through which helminth infection controls the development of asthma. They will focus on a type of white blood cell called a Th17 cell, which has recently been implicated as a major player in the development of tissue inflammation that may lead to asthma. They will investigate how Th17 cells are suppressed by helminth infection and the role of this effect on the development of allergic asthma. Results from these studies are expected to provide important insights into developing preventive/therapeutic methods to suppress the harmful immune response that initiates and sustains allergic asthma.

ANDREW C. MELTON, PhD
University of California, San Francisco, San Francisco, CA
Junior Research Training Fellowship-Senior Research Training Fellowship ● Funded by the American Lung Association of California

Analyzing Protein's Role In Allergic Asthma May Lead To New Treatments

Regulation Of Allergic Asthma By Integrin-Alpha(v) beta8. Transforming growth factor-beta (TGF-beta) is a protein that protects against excessive immune system responses, such as those seen in people with allergic asthma. However, the mechanisms that regulate the activity of this protein in allergic asthma are unclear. Previous studies have shown that another protein, integrin-alpha(v)beta8, plays an important role in regulating the activity of TGF-beta. To investigate the role of integrin-alpha(v)beta8 in allergic asthma, the researchers will study this disease in mice that lack integrin-alpha(v) beta8. Without the ability of integrin-alpha(v) beta8 to regulate TGF-beta in these mice, the researchers expect to find that the mice will develop exacerbated airway responses when challenged with agents that induce allergic asthma. The experiments in this proposal will provide insight into the regulation of TGF-beta in allergic asthma and could facilitate the development of new treatments for this and other diseases.

ERIC B. MELTZER, MD
Duke University Medical Center, Durham, NC
Dalsemer Research Grant ● Support of this grant comes from the Mary Fuller Russell Research Fund

Molecule May Provide Insight Into Development Of Pulmonary Fibrosis

Insulin-Like Growth Factor-1 Regulation Of Pulmonary Fibrosis. Pulmonary fibrosis is a slowly progressive but ultimately fatal disease that affects millions of people worldwide. There is currently no effective treatment for pulmonary fibrosis. Insulin-like growth factor-1 (IGF-1) is a potent natural chemical that is known to be elevated in the lungs of patients with pulmonary fibrosis. The researchers will investigate whether IGF-1 is an important regulatory molecule that controls the development of the disease. They will use several strains of genetically engineered mice to study the effect of IGF-1 in a model of induced pulmonary fibrosis. They will use mice that have been engineered so that each strain of mouse produces IGF-1 within a different compartment of the lung. This will allow the researchers to determine the effects of IGF-1 on different types of cells involved in the formation of fibrosis, or scarring,

in the lung. It will also allow them to study the effects of IGF-1 on the separate phases of development of pulmonary fibrosis. They hope to gain insight into the biology of pulmonary fibrosis that in the future will lead to the discovery of new medications to treat the disease.

RICHARD NHO, PhD

University of Minnesota, Minneapolis, MN

Biomedical Research Grant ● Funded by the American Lung Association of the Upper Midwest

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

A Pathologic Integrin Growth Signaling Pathway Regulates Aberrant IPF Fibroblast Proliferation On Extracellular Matrices. Idiopathic pulmonary fibrosis (IPF) is a deadly lung disease of unknown cause. Short of lung transplantation there is no proven effective treatment for the disease process. IPF is characterized by progressive scarring of the lungs. The primary cell type responsible for the progressive scarring is the lung fibroblast. Recent work suggests that the lung fibroblast in IPF has distinct properties enabling it to abnormally proliferate and survive. However, much is still not known about the differences between the out-of-control growth of fibroblasts in IPF responsible for progressive proliferation and the limited production of normal fibroblasts necessary for proper lung repair. In preliminary studies, the researchers have discovered abnormal changes in chemical pathways that regulate IPF fibroblast proliferation. The researchers will further investigate key differences between normal and IPF fibroblasts that underlie the ability of IPF fibroblasts to proliferate and scar the lungs. These experiments could suggest new therapeutic strategies for this lethal disease.

TIMOTHY ORISS, PhD

University of Pittsburgh, Pittsburgh, PA

Biomedical Research Grant ● Funded by the American Lung Association

Can A Drug That Combats Inflammation In Diabetes Help People With Allergic Asthma?

Effects Of PPAR-gamma On Lung Dendritic Cell Maturation And Migration. In people with allergic asthma, certain types of allergens can trigger asthma attacks and symptoms such as coughing, wheezing, and shortness of breath. Non-allergic individuals do not have an immune system reaction to things they encounter every day in their diet or the air they breathe, a state known as immunologic tolerance. Allergy occurs when tolerance breaks down and an inflammatory response occurs to these common substances. Many people tend to "grow out of" their allergies, suggesting that tolerance has been re-established since these people presumably are still exposed to the environmental triggers that prompted the inflammatory response leading to allergic asthma in the first place. The researchers seek to understand how tolerance is established and maintained by the immune system, and to explore ways to re-establish or initiate tolerance in people where it has failed. The researchers will study one of a class of compounds that has shown effectiveness as an anti-inflammatory agent in the treatment of diabetes, and shows initial promise in the treatment of asthma-like conditions. This research might lead to the future use of these drugs to re-establish immunologic tolerance and thus to effect a "cure" for certain types of asthma.

BEATRIZ QUINCHIA-RIOS, PhD, DDS

University of Wisconsin, Madison, WI

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

Airway Remodeling Research May Benefit Patients With Asthma

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

PING-HUI TSENG, PhD
University of California, San Diego, San Diego, CA
Junior Research Training Fellowship ● Funded by the American Lung Association of California

Unraveling The Protective And Destructive Roles Of Immune Cell Receptors

Developing Peptide Inhibitors Targeting Different Components Of Toll-Like Receptors (TLRs) Signaling Pathways. Toll-like receptors (TLRs) are proteins of immune cells that serve as a key part of the innate immune system, which recognizes infectious threats. When TLRs are activated, the immune system responds to these threats. TLRs are involved in many lung diseases such as asthma, acute respiratory distress syndrome, and lung cancer. In addition to their protective function, TLRs can also cause damage for reasons that are not understood. The researchers will try to develop a novel tool that can improve understanding of how TLR proteins communicate and how this impacts lung health. This tool could allow for development of new therapeutic approaches that could selectively block undesired TLR-triggered responses without affecting the protein's beneficial responses for lung diseases.

HUAJING WAN, PhD
Children's Hospital Medical Center, Cincinnati, OH
Senior Research Training Fellowship ● Co-funded by the American Lung Association and the American Lung Association of the Midland States

'Master' Regulatory Gene In The Lung Influences Disease And Repair Of Injury

Roles Of KLF5 In Lung Morphogenesis And Injury. KLF5 is a master regulatory gene that influences many genes in the cells lining the embryo's airways during formation of the lung. This gene is also found in respiratory cells that play a role in repair after injury. The researchers found that mice without the gene died from respiratory failure at the time of birth. Their initial studies demonstrated that the loss of the gene resulted in abnormalities in the growth of airway smooth muscle, a lung tissue that plays a key role in airway inflammation and bronchial hyper-responsiveness (airway "twitchiness"). Overgrowth of airway smooth muscle can lead to respiratory disorders, including asthma, chronic obstructive lung disease, and bronchopulmonary dysplasia in preterm infants recovering from respiratory distress. Preliminary data also showed that KLF5 is rapidly induced following extensive injury of the adult lung. The researchers will study mice to identify genes and processes that KLF5 regulates in the surface of the airway walls that signal to the underlying smooth muscle. Understanding the roles of KLF5 in the lung will provide knowledge to better understand lung diseases and find novel ways to treat them.

JIAN ZHANG, MD
University of Chicago, Chicago, IL
Career Investigator Award ● Funded by the American Lung Association of the Upper Midwest

Controlling IgE Production Key To Treating Allergic Asthma

Regulation Of IgE Production By E3 Ubiquitin Ligase Cbl-b. The body releases immunoglobulin E (IgE) antibodies when it comes in contact with an allergen such as dust, pollen or mold spores. For most allergy sufferers, the release of IgE produces symptoms such as a runny nose, sneezing, and itchy or watery eyes. However, for those with allergic asthma, the release of IgE can trigger a full-blown asthma attack. Therefore, controlling IgE levels is crucial for treatment of allergic asthma. The researchers will study a specific protein, called Cbl-b, and determine whether and how it regulates factors that control IgE production. This research could provide information that will lead to better treatments for allergic asthma.

DISEASES OF INFANTS AND CHILDREN

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 leading causes of death in infants up to one year of age. There is still no cure for CF, and the problems of treatment have increased as people with this condition live longer. New technologies allow delivery of more and more premature infants at risk for RDS. Many of those who survive develop a chronic illness called bronchopulmonary dysplasia, which is caused by the use of pressure ventilators with oxygen used to support life in these fragile infants. More than 75,000 to 125,000 children are hospitalized each year due to respiratory syncytial virus (RSV), and an estimated 2-7% of them die of complications related to the disease.

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

CF, the most common heritable disease of Caucasians, continues to take many lives. Basic studies at the level of the abnormal gene and the cell channels that it codes for, seek to discover the rationale for fundamental new treatments.

American Lung Association Scholar: Diseases of Infants and Children

YOHEI NORIMATSU, PhD
Oregon Health and Science University

Current treatments for cystic fibrosis (CF) fight infection in the lungs but don't correct the cause of the disease. With the help of an American Lung Association Senior Research Training Fellowship, Yohei Norimatsu, PhD, is conducting basic science research that one day may lead to the development of drugs that prevent damage to the lungs in people with CF.

CF is an inherited disease that causes the body to produce an abnormally thick, sticky mucus that clogs the lungs and leads to life-threatening lung infections. A person born with CF has a mutation in the CF gene. This gene is responsible for the production of a protein called "the cystic fibrosis transmembrane conductance regulator" (CFTR). A healthy CFTR helps the lungs to prevent microbial infection. But many mutated CFTRs degrade and disappear before they can function. Even if mutated CFTRs escape degradation, they often do not function well. The result is an accumulation of mucus and microbial infection in the lungs.

Dr. Norimatsu's experiments will allow him to gain a clearer picture of the structure of CFTR. The information he gains from these experiments will be used to refine a 3-D model of the protein in collaboration with a group at Oxford University. Once this model is developed, his lab will work with a company (Schrodinger) that has developed software that screens chemical libraries, narrowing down the vast number of chemicals to a subset that show promise as candidates that could be tested as corrective treatments for mutated CFTRs.

"If we are successful, then drugs could be developed that prevent damage to the lungs, improving survival and quality of life in patients with CF," Dr. Norimatsu says.

To see a complete description of Dr. Norimatsu's research project, please go to page 61.

SANTANU BOSE, PhD

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

Can Enzyme That Lowers Cholesterol In Cells Lead To Treatment For RSV?

Role Of Cholesterol 25-Hydroxylase During NF-kB Dependent Innate Anti-Viral Response Against Human Respiratory Syncytial Virus. Human respiratory syncytial virus (RSV) is an airborne virus that infects lung cells to cause a wide variety of diseases among infants, children, and the elderly. RSV infection is associated with high death rates among children, but there is currently no effective anti-viral therapy or vaccine to combat RSV infection. In an effort to identify novel anti-viral factors against RSV, the researchers will study the anti-viral defense mechanisms of lung cells. They have identified a candidate anti-viral protein called cholesterol 25-hydroxylase (C25H). This is an enzyme whose production in cells results in lowering of cellular cholesterol content. Since many viruses, including RSV, require cholesterol for infection, the researchers will study whether C25H acts as an anti-RSV agent, and will study the way in which it restricts RSV infection. These studies may lead to the development of novel anti-viral therapies against RSV and other respiratory viruses.

PAO-TIEN CHUANG, MD, PhD

University of California, San Francisco, San Francisco, CA
Career Investigator Award ● Funded by the American Lung Association

Signal Between Types Of Lung Cells May Provide Clues To Lung Development

Fu And Sufu Function Through Different Types Of Cilia In Controlling Lung Development And Function. Proper lung function in adults relies on normal embryonic development. In lung development, a tube-like structure undergoes extensive branching to generate an elaborate respiratory tree that is essential for gas exchange after birth. This structure is comprised of a layer of cells called epithelial cells. Instructive signals for epithelial branching live in a surrounding tissue layer called the mesenchyme. The researchers will use mouse lungs to understand how a secreted protein called the Hedgehog mediates between the epithelial cells and the mesenchyme and regulates their development. When the Hedgehog is received, it activates a series of events in the cell, which is referred to as a signaling pathway. Major signaling pathways including the Hedgehog pathway are thought to control cell proliferation and differentiation as well as stem cell maintenance and cancer formation. This research will lead to a better understanding of the molecular basis of lung development. It also may shed light on the molecular mechanisms of lung cancers and provide cell-based therapy for lung diseases using stem cells. The researchers also will study the link between Hedgehog signaling and cilia, hair-like structures that line the airways and help to clean them out. Their studies will help increase understanding of diseases related to defective cilia, including bronchiectasis and sinusitis.

XANTHI COUROUCLI, MD

Baylor College of Medicine, Houston, TX
Biomedical Research Grant ● Funded by the American Lung Association of the Central States

Protecting Premature Babies' Lungs Against Damage From Oxygen Therapy

Role Of Cytochrome P4501A Enzymes In Hyperoxia-Induced Lung Injury In The Newborn. Therapy with supplemental oxygen is frequently used in preterm and full-term infants and in adults with acute respiratory distress syndrome (ARDS). Every year, about 70,000 newborns in the U.S. experience breathing problems, which, if severe, will require high concentrations of supplemental oxygen and mechanical ventilation. While oxygen therapy may be life-sustaining, it may also injure the lung. Considerable evidence links too much oxygen to the development of bronchopulmonary dysplasia (BPD), the major source of illness and death in premature infants. The molecular mechanisms responsible for oxygen-caused damage are not completely understood. The researchers will investigate whether enzymes called P450 (CYP)1A play a protective role against lung injury caused by oxygen. This research should provide critical information that can be used to develop novel strategies for the prevention and treatment of BPD associated with excessive oxygen exposures in premature infants.

LIANWU FU, PhD

University of Alabama, Birmingham, AL
Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the MidSouth

Blocking Disintegration Of Mutated Gene In Cystic Fibrosis

Regulation Of CFTR Degradation Under Cystic Fibrosis. Cystic fibrosis (CF) is an inherited disease that affects the lungs and digestive system of about 30,000

people in the United States. CF is caused by mutations in the gene called CFTR. Most people with CF have a mutation in the CFTR gene that results in the misfolding and premature degradation of the protein. The best way to treat CF is to prevent the mutant gene from degrading, and restore the function of CFTR. The researchers will study the regulation of CFTR degradation in conditions that exist in CF lungs. The information gained will provide critical therapeutic information to treat CF patients by preventing CFTR degradation.

ALEJANDRO P. HEUCK, PhD

University of Massachusetts, Amherst, MA

Biomedical Research Grant ● Co-funded by the American Lung Association and the American Lung Association of New England with Support from the Massachusetts Thoracic Society

Blocking Formation Of Channel For Bacterial Infection In Cystic Fibrosis

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

DANNY HSIA, MD

University of Washington, Seattle, WA

Junior Research Training Fellowship – Senior Research Training Fellowship ● Funded by the American Lung Association of the Northwest

Predicting Which Children With Respiratory Syncytial Virus Will Develop Asthma

Exhaled Nitric Oxide Output In Infants With Pulmonary Hyperinflation Following Respiratory Syncytial Virus Bronchiolitis. Most lower respiratory tract illnesses with wheezing that occur in the first three years of life are associated with infection with respiratory syncytial virus (RSV). Many studies have shown an association between RSV, subsequent wheezing, and the development of asthma. Between 20-40% of young children who have RSV suffer from recurrent wheezing episodes that resolve on their own as the child gets older. A major challenge for doctors is predicting which infants are at increased risk for developing asthma after RSV and which will resolve on their own. The researchers will use two measurements to see how each alone and in combination predicts recurrent wheezing as the child grows. One measurement, called the thoracic index, measures persistent airway narrowing, while the nitric oxide index measures ongoing airway inflammation. If these measurements prove useful, they will allow doctors to identify which children who have had RSV might benefit from asthma therapy very early in life and thereby avoid complications of asthma in very young children.

ANNE MOON, MD, PhD

University of Utah, Salt Lake City, UT

Career Investigator Award ● Co-funded by the American Lung Association and the American Lung Association of the Southwest

Growth Factor That Stimulates Air Sac Development May Help Premature Babies

A Novel And Required Role For Fgf8 In Pulmonary Development. The researchers will investigate a critical but previously unknown role for a molecule called Fibroblast Growth Factor 8 (Fgf8) in the formation of the tiny air sacs in the lungs, called alveoli. Using a mouse model, the researchers hope to define the role(s) of Fgf8 during lung development. Alveolar underdevelopment is a common, frequently deadly complication of premature birth and of other poorly understood conditions present at birth. The alveolar phase of lung development normally begins in the final months of fetal development and continues after birth; disruption of early al-

veolar formation impacts lung development both before and after birth. It also impacts lung function and, ultimately, survival. In spite of treatment for this condition, the rate of early death and long-term illness in affected infants is high. Even in babies born full term, alveolar underdevelopment and abnormal development are serious immediate threats to life and cause long-term illness. If the researchers can identify a growth factor that stimulates normal alveolar development, this could represent a major development for treatment of infants with this condition.

YOHEI NORIMATSU, PhD
Oregon Health and Science University, Portland, OR
Senior Research Training Fellowship ● Co-funded by the American Lung Association and the American Lung Association of the Mountain Pacific

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

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

BREATHING MECHANICS, CONTROL OF BREATHING, AND SLEEP DISORDERED BREATHING

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

The American Lung Association supports research designed to define the relationship between sleep apnea and cardiovascular disease as well as studies looking at newer, simpler therapies. In related fields, the knotty practical issues of why obesity causes breathlessness and how to administer pain killers to patients with lung disease without impairing their breathing are being studied.

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

ZHENXIONG ZHANG, PhD
Lovelace Respiratory Research Institute

Morphine and other opiate drugs are widely used to relieve pain. But the pain relief sometimes comes with a price: for unknown reasons, even at normal doses opiates can substantially depress breathing, which can be lethal.

Zhenxiong Zhang, PhD, is investigating why opiates depress breathing. This depression in breathing is mainly due to a decrease in the body's response to carbon dioxide (CO2), which is important for maintaining normal breathing. He will study a certain area of the brain called the medullary raphe region (MRR), which is affected by opiates through the activation of micro-receptors, sites on the outside of cells where particular messenger molecules can attach.

With funding from an American Lung Association Senior Research Training Fellowship, Dr. Zhang is studying whether these micro-receptors regulate the function of nerve cells that are sensitive to CO2. "This information can help us better understand the mechanisms by which opiates depress breathing," says Dr. Zhang.

He hopes his research leads to new approaches for developing opiates that produce pain relief with less impact on breathing. He also thinks the research may have implications for preventing sudden infant death syndrome (SIDS). Previous studies have shown the abnormality of the MRR region and elevated levels of opioids produced by the brain in SIDS, he says. "This research may lead to information that could be used to prevent life-threatening infant respiratory disorders."

To see a complete description of Dr. Zhang's research project, please go to page 66.

CYNTHIA D. BROWN, MD
University of Virginia, Charlottesville, VA
Clinical Patient Care Research Grant ● Co-funded by the American Lung Association and the American Lung Association of the Atlantic Coast

New Device Could Improve Sleep In COPD Patients

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

SANJA JELIC, MD
Columbia University Medical Center, New York, NY
Clinical Patient Care Research Grant ● Funded by the American Lung Association

Targeting Link Between Sleep Apnea And Heart Disease May Yield New Treatments

Targeting Endothelial Dysfunction In Sleep Apnea. Untreated obstructive sleep apnea (OSA) causes excessive daytime sleepiness, which results in increased risk of accidents at work and while driving. OSA has been linked to high blood pressure, heart failure, stroke, and increased risk of death. However, the mechanism underlying the association between OSA and heart disease is not well understood. Patients with OSA experience repetitive low blood oxygen levels while asleep, resulting in increased blood vessel wall stiffness. Repetitive decrease in blood oxygen levels causes increased production of toxic substances that can damage blood vessel walls and ultimately lead to development of heart disease. The researchers will study the molecular mechanism of abnormal blood vessel wall function and determine whether and how treatment with continuous positive airway pressure (CPAP), the most common treatment for OSA, restores normal blood vessel wall function in patients with sleep apnea. This information will help explain why OSA patients have a higher incidence of heart disease and whether treatment with CPAP reduces their risk for heart complications. This may help to identify new treatment strategies for OSA that would target specific molecular abnormalities and further reduce the risk of heart disease in these patients.

JONATHAN C. JUN, MD
Johns Hopkins University, Baltimore, MD
National Sleep Foundation Pickwick Award ● Funded in partnership between the American Lung Association and the National Sleep Foundation

Clarifying The Relationship Between Sleep Apnea And Cardiovascular Disease

Role Of NADPH Oxidase In Chronic Intermittent Hypoxia-Induced Atherosclerosis. Obstructive sleep apnea (OSA) is a condition in which breathing is repeatedly interrupted at night as a result of upper airway closure. Not only does OSA lead to sleep deprivation, but it also increases the risk of cardiovascular diseases such as high blood pressure, stroke, and heart attack. There is growing evidence that OSA is associated with advanced hardening of the arteries (atherosclerosis), which may be responsible in part for its cardiovascular complications. However, the exact reason for these detrimental effects of OSA is unclear. When a person with OSA falls asleep, the upper airway periodically collapses and the body's oxygen levels fall. Safeguards in the central nervous system detect the plummeting oxygen levels and cause the person to awaken, restoring oxygen to the body. This repetitive rise and fall of oxygen levels is called intermittent hypoxia (IH). Prior studies have shown that cells exposed to IH release free radicals, highly reactive particles that can cause disease. When free radicals attack fat in the bloodstream, oxidized lipids are generated, one of the key ingredients of atherosclerosis. The researchers will study the pathways by which IH induces atherosclerosis using a mouse model. The results may have implications for developing new treatments for OSA.

ANDREAS KAVAZIS, PhD
University of Florida, Gainesville, FL
Junior Research Training Fellowship-Senior Research Training Fellowship ● Funded by the American Lung Association of the Southeast

Reducing Diaphragm Weakness Due To Mechanical Ventilation

Mechanical Ventilation, Diaphragmatic Oxidant Injury, And Proteolysis. Mechanical ventilation is used in intensive care units to maintain breathing in patients who are incapable of doing so on their own. The removal of patients from mechanical ventilation is termed "weaning" and problems in weaning from mechanical ventilation are extremely common. Studies indicate that mechanical ventilation weakens the diaphragm and this is a significant contributor to weaning difficulties. The researchers have found that two proteases (proteins/enzymes that digest muscle, such as the diaphragm) are activated during mechanical ventilation. They have recently shown that by blocking the activity of each individual protease in an animal model during mechanical ventilation they prevented the breakdown of the diaphragm muscle. However, the mechanisms that regulate the activation of these proteases in the diaphragm during prolonged mechanical ventilation are currently unknown. The researchers will study these mechanisms. The information gathered can be used for developing methods for the prevention of mechanical ventilation-induced diaphragmatic weakness.

HELEN WOOD, PhD
University of Texas Southwestern Medical Center, Dallas, TX
Senior Research Training Fellowship ● Funded by the American Lung Association

Do Obese Men Get Breathless When Exercising Because of Lung Function Limits?

Shortness Of Breath During Exertion In Obesity. Physical activity is very important in the prevention and treatment of obesity; however, many obese adults have symptoms of breathlessness when they exercise ("exertional breathlessness") and, as a result, do not exercise regularly. Most obese patients with exertional breathlessness are generally thought to be unfit; however, it isn't clear whether exertional breathlessness in otherwise healthy obese adults is due to their being unfit, or to having limitations in lung function that are related to their obesity. In preliminary studies of obese women, the researchers found that neither obese women with exertional breathlessness nor those without were unfit; however, the breathing muscles of the obese women with exertional breathlessness used significantly more oxygen. Obese men tend to have more fat in the abdomen than obese women, which may be related to breathlessness. The researchers will investigate whether exertional breathlessness in obese men is due to their being unfit or to having an increased oxygen cost of breathing, and whether this is linked to having more fat on the chest and in the abdomen. The results could potentially alter the approaches used to prevent and treat obesity, and could help obese people stay active and healthy and free of obesity-related conditions.

ZHENXIONG ZHANG, PhD
Lovelace Respiratory Research Institute, Albuquerque, NM
Senior Research Training Fellowship ● Co-funded by the American Lung Association and the American Lung Association of the Southwest

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

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

GLOSSARY

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

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

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

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

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

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

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

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 lungs, oxidant molecules are suspected of contributing to a variety of serious conditions; antioxidants can be an important defense.

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

asbestosis
A disease in which the lungs become scarred with fibrous tissue. It results from a high occupational exposure to asbestos.

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

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

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

bacteremia
The usually transient presence of bacteria in the blood.

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

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

biochemistry
The chemistry of living organisms.

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

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

bronchiolitis obliterans
Extensive scarring (fibrosis) of the small airways.

bronchitis
Inflammation of the bronchial tubes.

bronchoconstriction
Reduction in the caliber of a bronchus or bronchi.

calcium channels
Pores that allow calcium to get inside of a cell.

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

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

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

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

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

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

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

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

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

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

COX-2
A protein thought to play important roles in cancer development, but that has many other functions as well.

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

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

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

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

cytotoxic
Toxic to cells.

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

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

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

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

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

edema
Accumulation of excessive fluid in tissues.

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

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

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

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

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

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

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

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

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

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

gland
An organ that secretes a substance.

graft vs. host disease
A serious complication of transplantation in which transplanted donor immune cells recognize the body as foreign and attack the recipient's cells.

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

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

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

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

idiopathic pulmonary fibrosis (IPF)
A chronic and usually progressive lung disorder of unknown cause.

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

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

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

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

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

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

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

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

lipoprotein
A molecule made of a lipid and a protein.

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

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

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

metabolism
The chemical processes of the body.

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

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

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

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

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

neutrophil
A white blood cell important in the immune process.

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

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

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

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

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

Pneumocystis carinii
A microorganism now considered to be a fungus that 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; one of the major constituents of plant and animal cells.

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

pulmonary edema
Excess fluid in the lungs.

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

pulmonary hypertension
Abnormally high blood pressure in the arteries of the lungs.

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

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

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

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

SIDS
(Sudden Infant Death Syndrome)
The unexplained and sudden death of an infant, one month to one year of age.

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

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

streptococcus
A form of bacteria that may cause pneumonia.

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

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

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

toxicity
Ability to cause harm.

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

tumor
An abnormal collection of cells into a distinct physical entity.

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

type I cells
The cells that line the alveoli that produce surfactant.

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

ventilator
A device that provides for mechanically assisted breathing.

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

TOPIC INDEX

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