The American Lung Association has been saving lives by improving lung health and preventing lung disease for more than 100 years. An essential cornerstone of that mission is medical research. As the nation’s leading organization fighting for healthy lungs and healthy air, our mission combines medical research with patient resources, educational programs, and public health advocacy in a way that is both comprehensive and beneficial to all Americans.

This year, thanks to your help, the American Lung Association is able to support $6.49 million in research to advance our understanding and further the fight against acute, chronic, and rare lung diseases that touch the lives of millions of Americans.

Our Research Program consists of two distinct programs—the Awards and Grants Program and the Airways Clinical Research Centers. Through our Awards and Grants Program we support the entire research career spectrum, from training awards to early and mid-career grants to grants for established investigators and beyond. We are proud of the depth and diversity of this program, which funds promising research in a wide spectrum of lung diseases like lung cancer, chronic obstructive pulmonary disease (COPD), asthma, influenza, tuberculosis and many others. We also fund research that explores other threats to lung health, such as tobacco use and air pollution.

Our focus on lung cancer—the leading cancer killer of both men and women in America—is particularly robust. American Lung Association has made defeating lung cancer a strategic imperative of the organization, and we have doubled our funding of lung cancer research.

Our Airways Clinical Research Centers (ACRC) network conducts large clinical trials that have a direct impact on care and treatment of patients with asthma, and COPD. We are excited that this past year our ACRC network expanded its scope to include COPD, along with its original focus on asthma.

We are investing in the power of partnership to increase the impact of our research program. Funding partners this year include LUNGevity, the American Academy of Allergy, Asthma & Immunology, Lung Cancer Research Foundation and Free to Breathe. We’re also leveraging the expertise of our researchers in exciting new ways, such as being lung health advocates or expert speakers and panelist for conferences, webinars and media events. By connecting our research and researchers with patients and families, we’re creating opportunities for unique and meaningful experiences.

Our deepest thanks to the many individuals and organizations that provided the support needed to make our research program such a success. I invite you to read about the research being supported by the American Lung Association in 2015-2016, and share our pride in this exciting and groundbreaking work. Together, we are saving lives.

Harold P. Wimmer
We acknowledge and express our sincere gratitude to our research funding partners. We offer a special thanks to The American Lung Association of the Northeast and the American Lung Association of the Upper Midwest for their generous contributions for lung cancer research to the Lung Association’s nationwide initiative LUNG FORCE.
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Expanded Network to Benefit Patients with Obstructive Lung Disease

The American Lung Association Airways Clinical Research Centers conducts large clinical trials to provide vital information about caring for people who have asthma and now, COPD. The network is comprised of 17 Clinical Centers and a Data Coordinating Center, making it the largest non-profit network of its kind. Its unique focus on studying large numbers of patients differentiates it from other current federally funded and commercial research. With the inclusion of COPD, the network will continue and expand meeting its mission to improve patient care for those suffering from obstructive lung diseases.

Data Coordinating Center, Johns Hopkins University, Baltimore, MD
PI: Robert Wise, MD

Baylor College of Medicine, Houston, TX
PI: Nicola Hanania, MD

Duke University Medical Center, Durham, NC
PI: Loretta Que, MD

Illinois Consortium, Chicago, IL
PI: Lewis Smith, MD, Northwestern University

Louisiana State University, New Orleans, LA
PI: Kyle Happel, MD

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

Nemours Children’s Clinic, Jacksonville, FL
PI: Kathryn Blake, PharmD

New York Consortium
PI: Joan Reibman, MD, New York University and Co-PI: Emily DiMango, MD, Columbia University

New York Medical College, Valhalla, NY
PI: Allen Dozor, MD

North Shore-LIJ, New Hyde Park, NY
PI: Arunabh Talwar, MD

St. Vincent Health, Indianapolis, IN
PI: Mike Busk, MD

South Florida Consortium
PI: Adam Wanner, MD, University of Miami and Co-PI: Richard Lockey, MD, University of South Florida, Tampa

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

University of Missouri/Kansas City, Kansas City, MO
PI: Gary Salzman, MD

University of Vermont, Burlington, VT
PI: Charles Irvin, PhD

University of Virginia, Charlottesville, VA
PI: Gerry Teague, MD

Washington University, St. Louis, MO
PI: Mario Castro, MD, MPH

University of Arizona, Tucson, AZ
PI: Lynn Gerald, PhD
**Resistant Airway Obstruction in Children (REACH)**

The purpose of this retrospective chart review is to characterize children with a history of treatment-insensitive airflow obstruction with respect to demographic features, history of respiratory infections, treatment history, atopy, environmental tobacco smoke exposure and pulmonary function.

**Allen Dozor, MD, New York Medical College, Valhalla, NY, REACH Lead-PI**

**Evaluation of Anxiety in Patients with COPD (ACE)**

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and disability in the United States. In a recent prospective cohort study, anxiety was found to be one of the most predictive comorbidity of mortality in COPD patients. Anxiety in patients with COPD has been associated with hospital readmission and compromised quality of life. Since many symptoms of COPD and anxiety overlap, using standard anxiety assessments designed for the general population may not properly identify anxiety in COPD sufferers. The goal of the Anxiety and COPD Evaluation (ACE) study is to validate this scale by administering the AIR questionnaire to 200 participants with COPD. Validating this scale will help us to better understand the association between COPD exacerbations and the prevalence of anxiety and depression in these individuals. This will lead to better understanding of the causes of exacerbations and better methods of treatment for these patients.

**Nicola Alexander Hanania, MD, MBBS, Baylor College of Medicine, Houston, TX, ACE Lead-PI**

**Smoking Asthmatics Pilot Study (SAPS)**

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

About 20 percent of people with asthma smoke, yet smokers are consistently excluded from therapeutic trials for asthma. As a result current asthma treatment guidelines may not be appropriate for smokers. There is evidence that suggests that inhaled corticosteroids, the mainstay for treating persistent asthma, are less effective in smokers. The SAPS trial is designed to test the feasibility of a large scale clinical trial looking at the four main therapeutic options for asthmatic patients who still smoke and are not well controlled on standard asthma therapy. Smoking cessation remains the primary strategy for treating these patients, but this study represents an important step toward improving care for that significant population of individuals with asthma for whom smoking cessation remains a struggle.

**Joe Ramsdell, MD, University of California, San Diego, La Jolla, CA, SAPS Lead PI**

**Use of Mobile Devices and the Internet to Streamline an Asthma Clinical Trial (MICT)**

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

Finding participants for research trials is not easy, likely because of the time and effort required on the participant’s part as well as logistical barriers. The MICT trial will study whether the use of mobile devices and internet technology make clinical trials more convenient and cost effective. Participants in the study will be provided an iPad to complete questionnaires and health information diaries, as well as have real-time interaction with study staff using FaceTime, a live, video-telephone software application developed by Apple, from the comfort of their homes. Depending on the results of this clinical trial pilot, and, if full-scale clinical trials are conducted, this could potentially change the way that clinical trials are completed in the future.

**Kathryn Blake, PharmD, Nemours Children’s Clinic, Orlando, FL, MICT Lead PI**
RECENT ACRC NETWORK PUBLICATIONS


The study used daily diary data collected from participants enrolled in the American Lung Association–Airways Clinical Research Centers’ Trial of Asthma Patient Education (TAPE), to analyze the use of albuterol. Overuse of albuterol is relatively common among patients with asthma and is a risk factor for poor outcomes. The study found that among adults with mild asthma, albuterol use on symptom-free days is the most important driver of overuse. Compared to those who use albuterol less frequently, overusers are at twice the risk for clinical depression. The recommendation for healthcare professionals is that when albuterol overuse is suspected, depression should be considered a potential comorbidity.

*The study was funded by the National Institute of Health’s National Heart, Lung, and Blood Institute.*

Effect of a Soy Isoflavone Supplement on Lung Function and Clinical Outcomes in Patients with Poorly Controlled Asthma: A Randomized Clinical Trial, Journal of the American Medical Association (May 26, 2015)

This study from the American Lung Association’s Airways Clinical Research Centers Networks looked at whether soy isoflavone—a common nutritional supplement—improves the health of people with poor asthma control. During the study, adults and children aged 12 years and older who have poorly controlled asthma took a controller medication. Some study participants also took a soy isoflavone supplement while others took a placebo in place of soy isoflavone.

The study found that the soy isoflavone supplement did not improve participants’ lung function or clinical outcomes. The results may save consumers from spending thousands of dollars on an ineffective treatment, and also potentially help some avoid adverse drug reactions.

*The study was co-funded by the American Lung Association (ACRC Network) and the National Institute of Health’s National Heart, Lung, and Blood Institute.*

Treatment of Chronic Sinusitis and Rhinitis with Nasal Steroids Does Not Improve Asthma Control, Journal of Allergy and Clinical Immunology (2014)

The network’s ninth study, Study of Nasal Steroids in Asthma, examined whether long-term treatment of sinonasal disease with mometasone improved asthma control, lung function and quality of life in patients aged 6 years and older with poorly controlled asthma and chronic rhinitis/sinusitis. In previously conducted ACRC trials, researchers found that more than 70 percent of asthmatics report sinusitis, rhinitis or both.

The study found no difference between those taking mometasone versus a placebo in the improvement of their asthma control. Children and adolescents (ages 6 to 17 years) experienced no difference in their asthma or sinus symptoms, but those taking mometasone (versus the placebo) did experience a decrease in their lung function. Adult participants who took mometasone showed a small difference in asthma symptoms measured by using the Asthma Symptom Utility Index and in nasal symptoms, but they didn’t experience a difference in asthma quality of life, lung function, or episodes of poorly controlled asthma.

*This study was funded by the National Institute of Health’s National Heart, Lung, and Blood Institute.*
Methacholine Bronchoprovocation—An Unreliable Diagnostic Tool for White and Nonatopic Patients with Asthma, Annals of Asthma and Clinical Immunology (2014)

This study evaluated whether methacholine challenge in subjects ages 12 to 70 with stable asthma is a sensitive test to diagnose or confirm asthma. The study also looked at whether using high-potency inhaled corticosteroids (ICS) alters methacholine responsiveness.

Results indicated that the methacholine test may not be a reliable tool for conclusively excluding the diagnosis of asthma and that it should not be used as the sole method of diagnosis, especially in white and nonatopic (non allergic) patients. African-American patients were more sensitive to methacholine challenge than whites (95 percent versus 69 percent, respectively). Additionally, the sensitivity was 82 percent in those with atopy, defined as having one or more positive allergy skin test results, compared with 52 percent in those without. There was no significant difference in the change for high- versus low-dose ICS.

The study was funded by the American Lung Association (ACRC Network).

What are the benefits of participating in an ACRC clinical trial?

• Taking part in this study may help doctors understand how to better treat the condition, even if you don’t personally benefit.
• During the study, you will receive lung function testing, study treatment, physical exams, monitoring and education.
• You will have opportunities to learn about living with your disease.
• All study-related care and study-related treatments are provided at no cost to you or your insurance company.
• If you qualify, you will be compensated for your time and expenses.

For more information about American Lung Association Airways Clinical Research Centers studies, go to: Lung.org/acrc-trials.
American Lung Association-funded medical research delivers the hope of a longer, healthier life. We are proud to be currently funding more than $6.49 million in groundbreaking lung health research. This year, the Lung Association is funding a total of 69 investigator-led research projects at 51 institutions throughout 28 states.

The American Lung Association is committed to funding quality groundbreaking research to help find improved treatments and cures for lung disease. Today, the Lung Association funds scientific research through the Awards and Grants Program with one goal in mind: to save lives by improving lung health and preventing lung disease. The Lung Association is particularly interested in highly meritorious research projects consistent with our strategic imperatives:

- Defeat lung cancer
- Improve the air we breathe so it will not cause or worsen lung disease
- Reduce the burden of lung disease on patients and their families, and improve quality of life for those living with lung disease
- Eliminate tobacco use and tobacco-related lung diseases
The American Lung Association Awards and Grants Program funds researchers at important crossroads of their careers, typically those still in training or just gaining independence as faculty at institutions. Through this ‘career ladder’ funding structure, we are building a community of researchers dedicated to lung health and committed to lung disease research. This ensures that there will be scientists and medical experts working to advance the pace of lung disease research progress.

**Steps on the American Lung Association Career Ladder**

![Career Ladder Diagram]

We welcome you to learn more about this year’s American Lung Association Awards and Grants-funded researchers and their important research projects. Please note the research projects have been categorized by the primary research topic. Many projects impact multiple topics. To view and filter by keywords please visit Research Awards Nationwide (RAN) online at [Lung.org/ran](http://Lung.org/ran).
LUNG CANCER

Lung cancer kills more men and women than any other form of cancer. This year it is estimated that more than 158,000 Americans will die of lung cancer, accounting for approximately 27 percent of all cancer deaths. Lung cancer is the second most commonly diagnosed cancer in both men and women, with an estimated 221,000 new cases being diagnosed in 2015.

Known risk factors including cigarette smoking are responsible for the majority of lung cancer cases. But our ability to treat this disease is woefully inadequate, resulting in only 17 percent of patients living five years or longer after being diagnosed. For some, surgery can be effective, but often lung cancer isn’t found early enough to be removed. Currently, standard treatment options include chemotherapy, which kills healthy cells along with cancer cells; and radiation, which targets cancer cells, but may also damage the lungs. The recent understanding of biomarkers—which lead to targeted therapies and new early detection screening—are helping to change the statistics. Low-dose screenings and these therapies have fewer side effects than traditional treatments and can increase survival rates and improve treatment outcomes. Recent studies provide hope that new methods of early detection involving special CT scans may reduce the death rate by 14 percent in the high-risk population. However, even then, lung cancer will remain a major contributor to cancer deaths and cases in the U.S.

The American Lung Association Research Program supports a rich array of studies in lung cancer directed towards finding improved methods of early detection and novel treatments along with understanding basic cancer biology. Through the American Lung Association initiative LUNG FORCE, with additional funding contributed by the American Lung Association of the Upper Midwest and the American Lung Association of the Northeast, we have been able to more than double our funding for substantial innovative lung cancer research.

This year, Lung Association researchers are casting a broad net to find and develop new therapies. Much of the new work is in the area of precision medicine or “personalized treatment.” These targeted therapies focus on finding the unique genetic makeup of a person’s tumor and developing and using drugs that are designed to be most effective for that patient.

We are supporting remarkable new techniques, such as the ability to study genetic material from a single cancer cell. We are funding research into how lung cancer tumors become resistant to drug therapy, and how to stop the process. Our research program is also supporting a study that will assess whether the effectiveness of CT screening for lung cancer seen in a national trial translates into real-world benefits in everyday medical practice.
ANKIT BHARAT, MD
Northwestern University, Chicago, IL
Biomedical Research Grant
The Role of Carbon Dioxide in Stopping Lung Healing After Lung Cancer Surgery

After lung cancer surgery, many patients have an air leak from the cut lung surface. If the leak does not heal, the person will develop abnormal connections in the airways, called alveolopleural fistulae. This can lead to illness and death, as well as delaying the start of additional chemotherapy or radiation. We have observed that high carbon dioxide concentration inside the chest cavity impairs lung healing. We will study the relationship between increased carbon dioxide concentration and lung wound healing. The findings could lead to therapies that would lower carbon dioxide or reverse carbon dioxide-induced changes in the lungs, and promote lung repair.

EMILY CHENG, MD, PhD
Memorial Sloan Kettering Cancer Center, New York, NY
Lung Cancer Discovery Award
Overcoming Resistance to Newest EGFR-Inhibiting Lung Cancer Drugs

Epidermal growth factor receptor (EGFR) is a cell surface protein that promotes cell growth once bound by epidermal growth factor. Some lung cancers have mutations in EGFR, resulting in hyperactivation of the receptor and uncontrolled proliferation of cancer cells. Most patients with EGFR mutant lung cancer initially respond to drugs that inhibit EGFR, but eventually develop resistance. We will develop combination therapy to prevent and/or overcome resistance to the newest EGFR inhibitors by triggering a regulated form of cell death known as apoptosis in cancer cells. We will also investigate the mechanisms underlying resistance to the newest EGFR inhibitors.

ERIC COLLISSON, MD
University of California, San Francisco, San Francisco, CA
Lung Cancer Discovery Award
Funded in Partnership with the American Lung Association of the Upper Midwest
Using Genomics to Attack Lung Cancer

While we are gaining insight into the working of the lung cancer cell by the use of genome sequencing, our efforts at personalizing treatments only help about one in five patients. We will use new therapies being developed to attack lung cancer that use mutant cancer genes against the tumor’s own growth. We will examine how a gene complex responsible for managing the way other genes are packaged affects the transformation of normal lung cells to cancer cells. We will also look at how mutations in a specific gene affect the formation and then the progression of lung cancer.

KRISTINA CROTHERS, MD
University of Washington, Seattle, WA
Lung Cancer Discovery Award
Funded in Partnership with the American Lung Association of the Mountain Pacific
Improving How We Implement Lung Cancer Screening in Diverse Patient Populations

The National Lung Screening Trial demonstrated that lung cancer screening with chest computed tomography (CT) decreases lung cancer death in high-risk smokers. Implementing this screening is challenging, particularly in groups that were underrepresented in prior trials, such as low-income and minority populations. The burden of smoking and lung cancer are disproportionately high in these groups, but rates of use and acceptance of lung cancer screening may be low. We will study the best ways to communicate with patients about the benefits and risks of lung cancer screening, as well as how to best educate patients on lung cancer screening results and subsequent follow-up.
**TUSHAR DESAI, MD, MPH**  
Stanford University, Stanford, CA  
*Lung Cancer Discovery Award*  
**Genetic Tools Help Shed Light on Lung Cancer Progression**  
New methods are desperately needed for earlier detection of lung cancer and improved therapies that can eradicate disease that has spread. Fundamental to developing such approaches is understanding how lung tumors develop, grow and spread. We will use genetic tools to study these events using a mouse model of lung cancer, which will allow us to observe changes at incredibly high resolution. This includes marking and tracing the behavior of individual tumor cells within the 3-D context of a growing lung tumor. These studies will pave the way for devising novel approaches to treat patients.

**ANTHONY FABER, PhD**  
Virginia Commonwealth University, Richmond, VA  
*Lung Cancer Discovery Award*  
**Resensitizing Cells to Lung Cancer Targeted Therapy**  
Genetic variations and cell mutations contribute to the growth and development of cancer. Drugs called targeted therapies are designed for specific gene mutations in particular cancers. One effective targeted therapy is EGFR inhibitors, which target lung cancers with mutations in the EGFR gene. These mutations are often found in nonsmoking young patients. EGFR inhibitors are often effective for many of these patients, but most eventually become resistant to the drugs. This can occur through a process in the cancer called epithelial-mesenchymal transition (EMT). We will screen for drug compounds that can reverse this effect in EMT cells and re-sensitize them to EGFR inhibitors.

**LIDA HARIRI, MD, PhD**  
Massachusetts General Hospital, Boston, MA  
*Senior Research Training Fellowship*  
Funded by the American Lung Association of the Northeast  
**Does Tumor Environment Promote Drug Resistance in Lung Cancer Cells?**  
Despite advances in personalized lung cancer therapy, nearly all patients develop resistance to therapy within 6 to 12 months and prognosis remains poor. We will study how non-tumor cells in the environment can help tumor cells survive during drug therapy, and use a combination of cell culture studies and cutting-edge optical imaging to carefully track tumor cells, their environment and their response to therapy in lung cancer mouse models. Our results will help us determine if and how the tumor environment promotes drug resistance in lung cancer cells. Our findings could uncover methods to detect and inhibit drug resistance, which would improve response to therapy and increase survival in patients with lung cancer.

**HUMAM KADARA, PhD**  
University of Texas M.D. Anderson Cancer Center, Houston, TX  
*Lung Cancer Discovery Award*  
**Changes in Airway Could Signal Early Lung Cancer Development**  
Scientists need a better understanding of how lung cancer develops in order to detect the disease early. We have previously found that seemingly normal airway cells close to lung tumors carry molecular changes that are characteristic of the tumor itself. In a mouse model, we found these changes preceded the onset of lung tumors. Our project aims to uncover, using sequencing technology, how changes in the mouse normal airway evolve following tobacco-carcinogen exposure and up to emergence of nearby lung tumors. We will uncover novel markers associated with lung cancer onset that can serve as tools for early detection of the disease.
**PETER KAISER, PhD**
University of California, Irvine, CA
American Lung Association, Free to Breathe and Uniting Against Lung Cancer Impact Award

**Drugs to Reactivate Tumor Killing Ability of p53**

One of the most commonly mutated genes in cancer and one of the most difficult proteins to target therapeutically is p53. The malfunction of p53 is crucial for the origin and spread of lung cancer. We aim to develop new cancer drugs targeting p53 to help patients suffering from this terrible disease. Drugs able to reactivate the tumor-killing ability of p53 will be a significant new treatment option for thousands of lung cancer patients and will also improve treatment options for patients fighting other types of cancers.

**JI YEON KIM, PhD**
UT-Southwestern Medical Center, Dallas, TX
Senior Research Training Fellowship

**Lung Cancer Mutations Increase Levels of Polyamines**

Polyamines are naturally occurring molecules that are essential for cell growth. They can contribute to tumor growth and survival, but the way in which this occurs is unknown. We have found that polyamine content is dramatically increased by combinations of the three of the most common mutations in lung cancer—TP53, KRAS, and LKB1. We will study how these mutations elevate polyamine levels in lung cancer cells. We will then extend these findings to mouse and human lung tumors. Our research has the potential to provide a foundation for novel therapeutic strategies in lung cancer.

**WENYU LIU, PhD**
Rutgers University, New Brunswick, NJ
Senior Research Training Fellowship

**Preventing Lung Cancer Stem Cells From Self-Renewing**

A major hurdle in lung cancer treatment is reducing cancer stem cells that are responsible for cancer drug resistance, metastasis and recurrence. We will decipher the way in which lung cancer stem cells self-renew after drug treatment. We will be focusing on a cell signaling system called Notch signaling and its role in regulating the self-renewal of cancer stem cells. We hope to discover new methods of identifying lung cancer stem cells and new ways to diminish cancer stem cells by restricting their self-renewal.

**YUTAKA MAEDA, DVM, PhD**
Cincinnati Children’s Hospital Medical Center, Cincinnati, OH
Biomedical Research Grant

**Eradicating Every Last Lung Cancer Cell**

Although lung cancer treatment aims to eradicate tumor cells, in many cases, tumor cells recur after treatment. Identification of recurring lung tumor cells is needed so as not to miss eradicating even one tumor cell. It has been technically difficult to isolate and analyze such cells at the single-cell level. In the past two years, single cell-sequencing technology has been developed and enables scientists to capture individual tumor cells and analyze their genetic profiles. We will use this technology to identify the “Achilles heel” of individual lung tumor cells, including recurring tumor cell populations, and develop strategies to eradicate every tumor cell.
SWETA MISHRA, PhD  
Massachusetts General Hospital, Boston, MA  
Senior Research Training Fellowship  
Funded by the American Lung Association of the Northeast 

Discovering Protein’s Role in Resistance to Lung Cancer Chemotherapy 

Resistance to chemotherapy is a major challenge in the treatment of patients with lung cancer. Cancer cells possess the ability to amplify parts of their genome, which in turn protects the cells from chemotherapy. We have recently discovered a protein responsible for amplifying specific regions of the genome involved in resistance. We will investigate the role of this protein, KDM4A, and how the environment present inside lung tumors, such as low oxygen, can regulate KDM4A levels. We will also determine how tumor cells respond to drugs that inhibit KDM4A regulators. Our research could identify novel therapeutic targets for treating drug-resistant non-small cell lung cancer.

NANCY McNAMARA, OD, PhD  
University of California, San Francisco, San Francisco, CA  
Lung Cancer Discovery Award 

Inhibiting a Protein Might Help Prevent or Treat Lung Cancer 

As cigarette smoke is responsible for 87 percent of lung cancer deaths, there is an urgent need to develop novel strategies to treat lung cancer in smokers. We have previously shown that cigarette smoke initiates tumor formation by disrupting the junctions between airway cells. An important component of the cell membrane that participates in smoke-induced tumor development is a protein called mucin 1 (MUC1). We are studying two methods to inhibit the tumor-promoting potential of MUC1. We will explore the potential of these therapies to prevent and/or treat lung cancer in smokers using an engineered mouse model of lung cancer.

JOHN POIRIER, PhD  
Memorial Sloan Kettering Cancer Center, New York, NY  
LUNGevity/American Lung Association Career Development Award 

Molecular mechanisms of acquired drug resistance in small cell lung cancer 

Small cell lung cancer (SCLC) is a common, aggressive and exceptionally lethal type of lung cancer that is remarkably sensitive to combination therapy with a combination of two drugs, cisplatin and etoposide, even in patients with extensive-stage disease. However, many patients find their SCLC tumors return, now resistant to chemotherapy. We will study how SCLC tumors acquire resistance using two parallel approaches: studying resistance in patient samples and in patient tumors grown in mice. Targeting the key determinants of acquired chemo-resistance could be integrated into first-line treatment, and/or could drive rational targeted therapeutic studies for recurrent disease.

LINDA RESAR, MD  
Johns Hopkins University, Baltimore, MD  
Lung Cancer Discovery Award  
Funded in Partnership with the American Lung Association of the Upper Midwest 

Therapy Blocks Protein Involved in Lung Cancer Growth 

To address the urgent need for more effective lung cancer treatments, we are developing an innovative therapy called Spiegelmers. Spiegel means “mirror.” They are small molecules that bind as “mirror images” to critical regions of a protein to disrupt its function. Our Spiegelmers target a key regulator protein, called HMGA1, which is required by lung cancer cells to grow, invade and spread to distant sites. Spiegelmers that block other proteins have already been shown to be safe and effective in patients with other types of cancer. We therefore expect to rapidly translate our results to the clinics to improve therapy for lung cancer patients.
SAMEEK ROYCHOWDHURY, MD, PhD
The Ohio State University, Columbus, OH
Lung Cancer Discovery Award
Funded in Partnership with the American Lung Association of the Midland States

Identifying Gene Mutations in Lung Cancer That Can Be Attacked With Smart Drugs

We now understand that lung cancer is not one disease, but instead classified by different gene alterations or mutations that are either inherited or arise spontaneously. Despite dramatic advances, up to 50 percent of patients do not have gene alterations that can be targeted by drugs known as “smart drugs.” We will implement a precision cancer medicine study for patients with advanced lung cancer who do not have effective standard treatment options. We will offer them an innovative testing strategy using customized targeted DNA and RNA sequencing to identify genetic mutations that can be attacked with existing smart drugs.

DAVID SHACKELFORD, PhD
University of California, Los Angeles, Los Angeles, CA
Lung Cancer Discovery Award

Compound May Kill Tumors With LKB1 Gene Mutation

We hope to identify new, personalized therapies for treating non-small cell lung cancer patients whose tumors have a mutation in the LKB1 gene, which regulates growth, metabolism and energy balance in the cell. Lung tumor cells with mutations in LKB1 cannot properly regulate their energy balance. The result is severe cellular stress that can selectively kill these tumors. Initial tests of a compound called piperlongumine, which generates high cellular stress in tumor cells, showed it was able to selectively kill the most aggressive tumors with LKB1 mutations. We will study piperlongumine as a potential therapy for treating advanced lung cancer.

SAMIR SONEJI, PhD
Dartmouth College, Hanover, NH
Lung Cancer Discovery Award
Funded by the American Lung Association of the Northeast

Does the Effectiveness of CT Screening Translate into Real-World Benefits?

For the first time, a tool used in screening for lung cancer has been shown to reduce lung cancer deaths. The National Lung Screening Trial (NLST) concluded that CT screening, compared to chest X-ray, reduced lung cancer mortality by 20 percent. Yet the effectiveness of CT screening demonstrated in NLST may not translate to similar reductions in lung cancer deaths as screening occurs in everyday practice. Barriers, including lack of knowledge and high rates of treatment-related complications, may reduce the benefit of CT screening. We will assess the challenges facing patients to fully realizing the benefits observed in NLST. The study will improve clinical practice and narrow racial disparities in lung cancer mortality.

E. ALEJANDRO SWEET-CORDERO, MD
Stanford University, Stanford, CA
Lung Cancer Discovery Award
Funded in Partnership with the American Lung Association of the Upper Midwest

Examining Cell-to-Cell Communication for Clues About Lung Cancer

Normal cells and tumor cells communicate with each other in similar ways. Often times, the genes involved in communication in normal cells are “hijacked” by tumor cells to promote unregulated growth and survival. One mechanism of communication between cells that seems to be important in lung cancer is called the Notch signaling pathway. We will study how Notch is activated in lung cancer and what changes occur in cells as a consequence of this activation. Understanding how Notch proteins are activated in tumor cells and what the consequences of this activation are may identify novel therapy approaches for non-small cell lung cancer.
SEYEDTAGHI TAKYAR, MD, PhD  
Yale University, New Haven, CT  
*Lung Cancer Discovery Award*

**Enhancing the Targeting of Tumor Blood Vessels in Lung Cancer**

Vascular endothelial growth factor (VEGF) is secreted by lung tumor cells to maintain and enhance the blood vessels in the tumor and in its vicinity supporting further tumor growth and invasion. An anti-VEGF drug is used to treat advanced lung cancer, but its effectiveness is limited as most patients quickly become resistant to its effects. We have found that intracellular concentration of a molecule called microRNA-1 in tumor blood vessels determines their response to VEGF. We will study the effect of this molecule on the growth of blood vessels in lung tumors and their progression in animal models. Our hope is to find a way to prevent resistance to anti-VEGF therapy and to identify a subset of patients who will benefit the most.

PHUOC TRAN, MD, PhD  
Johns Hopkins University, Baltimore, MD  
*Lung Cancer Discovery Award*

**Targeting a Gene Involved in Lung Cancer Drug Resistance**

Many lung cancers have gene mutations that make them highly responsive to targeted treatments, such as the EGFR inhibitor erlotinib. Lung cancers with EGFR mutations initially respond very well to erlotinib, but all patients eventually develop resistance. One way resistance develops is through a change called epithelial-mesenchymal transition (EMT). A gene called Twist1 is one of the key regulators of EMT. Our previous work suggests Twist1 is overly active in many lung tumors and plays a role in development of the cancer. We will study the role of Twist1 in erlotinib resistance in EGFR mutant lung cancers. The findings could lead to therapy that reverses Twist1-induced erlotinib resistance.

NARENDRA WAJAEYEE, PhD  
Yale University, New Haven, CT  
*Biomedical Research Grant*  
Funded in partnership with the American Lung Association of the Northeast

**Targeting p53 Gene to Treat Lung Cancer**

Lung cancer arises due to defects in tumor suppressor genes, which inhibit tumor growth, and oncogenes, which promote tumor growth. One type of tumor suppressor whose malfunction is crucial for the origin and spread of lung cancer is the p53 gene. The p53 gene has been found to be mutated or genetically deleted in over 50 percent of lung cancers. We have identified 14 genes that when blocked can selectively eradicate p53-deficient lung cancer cells in a large percentage of patients. We will determine which of these genes can be targeted for the treatment of p53-deficient lung cancers using cell cultures and mouse models. The results of our experiments will provide a new, but effective treatment option for many lung cancers patients, including those with metastatic and drug-resistant lung cancers.

GUANGHU WANG, PhD  
Georgia Regents University, Augusta, GA  
*Biomedical Research Grant*  
Funded by the American Lung Association of the Southeast

**Fighting Drug Resistance in Lung Cancer**

Lung cancer treatment is hampered by a lack of understanding of how the cancer becomes resistant to treatment, and how the disease spreads. We will study the function of a gene called Spns2 and investigate whether a decrease in activity of this gene causes drug resistance. Additionally, we will examine whether a combination of two FDA-approved drugs reduces lung cancer drug resistance for patients who have reduced Spns2 activity. Our hope is that these results will provide vital insights into the molecular mechanisms of lung cancer drug resistance, which will lead to more comprehensive treatments for patients with advanced lung cancer.
JOHNATHAN WHETSTINE, PhD
Massachusetts General Hospital, Boston, MA
*Lung Cancer Discovery Award
Funded by the American Lung Association of the Northeast

Enzyme Could Help Predict Effectiveness of Lung Cancer Chemotherapy

Abnormal gene expression and mutations contribute to lung cancer risk and drug resistance. The enzyme KDM4A, which is over-produced in lung cancer, leads to genetic changes which have been linked to drug resistance. The overproduction of KDM4A in cancer cells results in reduced response to drug treatment and radiation. We will study how KDM4A works in lung cancer cells, and whether levels of the enzyme are an important predictor of the effectiveness of chemotherapy against lung cancer.

LUNG FORCE is a nationwide initiative led by the American Lung Association to unite women to stand together against lung cancer.

We work to improve awareness of lung cancer and be a force that changes the startling facts.

We aim to change people’s minds about what it means to have lung cancer—so that everyone understands that anyone can get lung cancer.

We raise our voices for research innovation that will lead to early detection for all and better treatments that give everyone a fighting chance.

Learn more—get involved. LungForce.org
TUBERCULOSIS AND NONTUBERCULOUS MYCOBACTERIUM

Tuberculosis (TB) is a worldwide epidemic that kills approximately 1.5 million people each year. Given that TB is transmittable and that global travel and migration has increased, this international problem remains of great concern to Americans.

Many people who are infected with the bacterium that causes TB, called Mycobacterium tuberculosis (Mtbt), do not go on to develop active TB. Their immune system protects them. But those with immune systems damaged by AIDS or other illnesses may develop active TB. The American Lung Association is supporting research looking at how to stop infection with Mtbt from turning into active disease. Another grant recipient seeks to identify genes that contribute to TB susceptibility, which will improve understanding of the body’s response to this deadly disease.

A major problem in the treatment of TB is the development of resistance to standard drugs. Surprisingly little is known about the molecular basis for TB drug resistance. One project we are funding will study critical cellular functions that can be targeted to rapidly kill Mtbt regardless of its tolerance to existing drugs.

A great frustration has been our inability to produce a truly effective vaccine to protect against TB. One study will explore how the immune system recognizes Mtbt, which could be used in developing new TB vaccines.

People who are infected with Mtbt are prescribed antibiotics to reduce the risk they will develop active disease. Since they feel well and have to take the medication for many months, as few as one-third complete treatment. A research project we are funding will investigate whether daily text message reminders improve compliance with TB treatment.
Two billion people, including 12 million U.S. residents, are infected with the bacterium that causes tuberculosis, Mycobacterium tuberculosis (Mtb). Current treatments require a minimum of six months, have adverse side effects and are not fully effective in preventing relapse of disease. Treatment failure is common and has led to the emergence of drug-resistant TB. Surprisingly little is known about the molecular basis for TB drug resistance. We will study critical cellular functions that can be targeted to rapidly kill Mtb regardless of cell tolerance to existing drugs. These studies will enable the discovery of new drugs to accelerate and increase TB cure rates.

Our project focuses on discovering new genetic mechanisms that contribute to pulmonary tuberculosis (TB), which causes disease and death in millions of people each year. We will use three novel strategies. The first is a new experimental mouse population that closely models the human population. The second is the use of computer algorithms to study traits of granulomas (aggregations of cells that are a hallmark of TB) and sites of lung damage. Third, we will integrate the complex data into testable models of TB. This research will allow us to identify genes that contribute to TB susceptibility, and to improve understanding of the body’s response to this deadly disease.

Mycobacterium tuberculosis (Mtb) is the second most common cause of infectious disease death worldwide and remains a significant global health threat. Unfortunately, the existing vaccine for TB, the BCG vaccine, does not confer enough protection in adults to curb the prevalence of Mtb. The difficulties in developing more effective vaccines stem from an incomplete understanding of how the immune system recognizes an Mtb-infected cell. We will focus on a type of immune cells called the Mucosal Associated Invariant T (MAIT) cells, which are capable of recognizing and killing Mtb infected cells. Our research will provide new information that could lead to new avenues for Mtb vaccine development.
EYAL OREN, PhD
University of Arizona, Tucson, AZ
Social Behavioral Research Grant
Using Texting to Encourage People to Take Their TB Medicine

While one-third of the world’s population is currently infected with the TB germ, only about 10 percent of these people will develop TB disease. The remaining 90 percent have latent TB, meaning their immune system can successfully fight the infection. Treatment of latent TB with an antibiotic reduces the risk it will progress to active disease. However, since these individuals feel well and have to take the medication for many months, as few as one-third complete treatment. We will investigate whether daily text message reminders help people to take their medication, preferences for receiving the messages, and whether this approach is affordable for tuberculosis clinics.

KEVIN WINTHROP, MD, MPH
Oregon Health and Science University, Portland, OR
DeSouza Research Award
Funded by the American Lung Association of the Southwest
Who Will Develop Nontuberculous Mycobacterium Lung Disease?

Chronic lung disease due to nontuberculous mycobacterium (NTM) is increasingly common in the U.S., usually affecting women and people over age 50. Mycobacterium avium complex (MAC) causes most NTM lung disease and is regularly found in municipal water supplies and soil. Most people inhale NTM during their lives but suffer no chronic infection, while others develop chronic, debilitating NTM disease that can require more than two years of antibiotic therapy. We will follow newly infected patients and evaluate whether their immune cell function predicts who will develop disease. These results will help us better prevent and treat NTM.
OBSTRUCTIVE LUNG DISEASES
(ASTHMA, ALLERGY AND COPD)

Asthma, allergy and chronic obstructive pulmonary disease (COPD) are all obstructive lung diseases, characterized by inflamed and easily collapsible airways, obstruction to airflow in and out of the lungs, and frequent doctor visits and hospitalizations. It is estimated that 32 million Americans have obstructive lung disease, with asthma and COPD being most common.

Asthma is a chronic but reversible disease that affects close to 22.6 million Americans, including 6.1 million children under 18. Asthma can be a life-threatening disease if not properly managed.

COPD is not reversible and gets progressively worse over time. COPD, consisting of chronic bronchitis and emphysema, is now the third leading cause of death in the United States, killing 145,000 per year. In 2012, an estimated 11.3 million adults had COPD, with an additional 12 million underdiagnosed. Although the major risk factor for COPD is cigarette smoking, there are other important risk factors such as air pollution and genetics.

This year the American Lung Association has a diverse portfolio of grants related to asthma and COPD. We are funding studies that are exploring the basic properties of the immune system and its role in both asthma and COPD.

Researchers are studying new therapeutic strategies to treat mucus obstruction in COPD airways, as well as ways to reduce mucus production in both asthma and COPD. They are investigating whether early-life exposure to secondhand smoke increases COPD risk, how genes influence the development of cigarette smoke-induced COPD and how cigarette smoke leads to lung damage in emphysema.

We are funding research to seek a better understanding of allergic asthma, and to determine whether prenatal exposure to the environmental pollutant bisphenol A (BPA) increases the risk of developing asthma later in life. One study is exploring ways to block the development of cells involved in steroid-resistant asthma. Other areas of research include the link between asthma and sleep-disordered breathing in children, the relationship between asthma and obesity, and the connection between asthma and influenza.

Lastly, we are funding research directed at finding ways to improve management of obstructive lung disease. This includes a study looking at ways to increase adherence to supplemental oxygen therapy in people with COPD.
**ASTHMA AND ALLERGY**

**SUZANNE CASSEL, MD**
University of Iowa, Iowa City, IA  
ALA/AAAAI Foundation Allergic Respiratory Diseases Research Award

**Blocking Development of Cells Involved in Steroid-resistant Asthma**

It is becoming increasingly clear that asthma is not a single disease with one underlying cause. Treatments including inhaled or oral steroids are effective for many patients but not for all. Some people, most commonly those with severe or steroid-resistant disease, have a different type of inflammation in their airways that involves immune-system cells called Th17 cells. Better understanding of the way in which Th17 cells develop is important to devising new treatments to block them. We will identify the pathways by which different subsets of Th17 cells develop, which will provide insight into new ways to successfully treat these patients.

**DAVID FEDELE, PhD**
University of Florida, Gainesville, FL  
Social Behavioral Research Grant

**Helping Overweight or Obese Children With Asthma Improve Their Health**

Overweight or obese (OV/OB) children with asthma experience serious health difficulties. Weight loss may improve health outcomes in these children, but there are no weight loss interventions specifically targeted for their needs. We have developed the Childhood Health and Asthma Management Program (CHAMP), a combined asthma and weight management intervention for these children and their parents. Child-parent pairs will be randomly assigned to either CHAMP or general health education. Those in the CHAMP group will learn asthma management strategies and behavioral weight management skills tailored for OV/OB children with asthma. We will compare changes in lung functioning, weight, quality of life, nutrition and physical activity between the two groups.

**YOICHI FURUYA, PhD**
Albany Medical College, Albany, NY  
Biomedical Research Grant  
Supported by the Mary Fuller Russell Fund

**Does Asthma Protect Against Getting Sick With Flu and Pneumonia at the Same Time?**

Asthma was the most common chronic condition among adults hospitalized during the 2009 influenza pandemic. However, asthmatic patients who were hospitalized with pandemic influenza were half as likely to die or require intensive care compared to people without asthma. Thus there may be a connection between asthma and less severe disease outcome. We have found that mice with asthma are resistant to being infected with both the influenza virus and bacteria that causes pneumonia. Understanding the mechanism of increased resistance to coinfection may lead to development of new treatments for patients infected with both the influenza virus and pneumonia bacteria.

**JENNIFER INGRAM, PhD**
Duke University Medical Center, Durham, NC  
ALA/AAAAI Foundation Allergic Respiratory Diseases Research Award

**Exploring the Link Between Asthma and Obesity**

Obesity is an important risk factor for the development of asthma. Obese patients often use more medications, suffer worse symptoms and have reduced asthma control than lean patients. Poor asthma control over time can lead to airway remodeling, a feature of asthma that leads to diminished lung function. We would like to gain a greater understanding of the molecular and cellular mechanisms governing airway remodeling in obese people with asthma. We will investigate how these mechanisms contribute to the lack of responsiveness to medications in obese asthma. Our goal is to identify potential therapeutic targets for treatment of airway remodeling in obese people with asthma.
**Obstructive Lung Diseases (Asthma, Allergy and COPD)**

**TERUMI MIDORO-HORIUTI, MD, PhD**  
The University of Texas Medical Branch at Galveston, Galveston, TX  
ALA/AAAAI Foundation Allergic Respiratory Diseases Research Award

**Can Prenatal Exposure to BPA Increase Asthma Risk?**  
We will investigate whether prenatal exposures to the environmental pollutant bisphenol A (BPA) increases the risk of developing asthma later in life. BPA is a chemical that is used to make clear plastic containers and as lining in canned foods. We have found feeding BPA to female mice promoted the development of asthma in their pups and in the next two generations of pups. We hope to identify which immune cells from the infant’s cord blood are altered by exposure to higher BPA levels and whether such exposure leads to an increased risk of asthma in this and subsequent generations.

**VALERIE ROGERS, PhD**  
University of Maryland, Baltimore, MD  
Biomedical Research Grant

**Asthma and Sleep-disordered Breathing in Children**  
Sleep-disordered breathing (SDB), including snoring and sleep apnea, is common among children with asthma. SDB-related upper airway inflammation has been found to trigger exacerbations of asthma, an inflammatory disorder of the lower airways. Our study will collect tonsils and blood from children with asthma undergoing tonsillectomy for treatment of SDB to measure inflammatory markers in these tissues and will test their association with asthma control. Identifying mechanisms of the association between SDB and asthma may provide pathways for improving control of asthma, a common and often debilitating disease in children.

**AMALI SAMARASINGHE, PhD**  
University of Tennessee Health Science Center and Le Bonheur Children's Foundation Research Institute, Memphis, TN  
Biomedical Research Grant  
Funded in Partnership with the American Lung Association of the Midland States

**Molecules Found in Allergic Airways May Protect Against Influenza**  
Although asthma was a risk factor associated with increased hospitalization during the 2009 influenza pandemic, people with asthma were less likely to die from influenza compared with nonasthmatics. Reasons for these seemingly contradictory results are unknown. Our data suggests that small proteins called resistin-like molecules, which are abundant in allergic airways, may play a role in reducing illness from influenza. The function of these proteins in respiratory viral infections has not been thoroughly investigated. We will examine the source and function of these proteins in influenza immunity. Our findings can be used to develop treatments for influenza virus infections.

**COPD**

**CRISTINE BERRY, MD**  
University of Arizona, Tucson, AZ  
Biomedical Research Grant

**Does Early-life Exposure to Secondhand Smoke Increase COPD Risk?**  
While smoking is a major cause of chronic obstructive pulmonary disease, not all smokers develop COPD. The reason for this remains poorly understood. Evidence suggests that early-life environmental tobacco smoke exposure influences harmful responses to adult smoking, thereby increasing COPD risk. To evaluate this, we will measure markers of the lung response to smoking in participants who are followed up to age 32, comparing smokers with or without early life ETS exposure. We will also compare the results of breathing tests to measure lung changes suggestive of early COPD. We hope that this work will identify innovative targets for COPD prevention and treatment.
HITENDRA CHAND, PhD
Lovelace Respiratory Research Institute, Albuquerque, NM
Biomedical Research Grant

Reducing Mucus Production in Asthma and COPD

Patients with chronic airway diseases such as asthma or COPD suffer from abnormally high levels of mucus and chronic productive cough. This condition poses an increased risk for airway infection, decline in lung function and hospitalization. Airway plugging by excess mucus can be fatal if left uncontrolled. Exposure to cigarette smoke is strongly associated with chronic airway diseases like COPD and asthma. We will study the link between cigarette smoke exposure and excess mucus. Our studies have identified the pathways responsible for increased mucus production. We will target this pathway using a small molecule that can help reduce production of mucus.

SUZANNE CLOONAN, PhD
Weill Cornell Medical College, New York, NY
Biomedical Research Grant

How Genes Influence Development of Cigarette Smoke-induced COPD

Prolonged exposure to cigarette smoke is the greatest risk factor for the development of COPD, but emerging research suggests that genetic predispositions may influence its development. We have previously shown that patients with a mutation in the gene Irp2 have increased levels of a protein called iron regulatory protein 2 and are more susceptible to cigarette smoke-induced COPD. Mice lacking the protein are protected from cigarette smoke-induced COPD. Using innovative experimental models of COPD, we will study how Irp2 and iron regulate responses of the lung to cigarette smoke. The findings may be useful in identifying therapeutic targets in COPD.

MONICA GOLDKLANG, MD
Columbia University, New York, NY
Biomedical Research Grant

How Does Cigarette Smoke Lead to Lung Damage in Emphysema?

Although we know that cigarette smoke is the primary cause of COPD including emphysema, the way in which cigarette smoke exposure leads to lung damage is still not fully understood. Smoking has recently been found to alter ion channel function essential for normal cellular responses to injury. We plan to study the role of the BK channel in lung destruction. Mice bred with mutant BK channels have reduced lung destruction when exposed to smoke despite developing airway inflammation. Understanding the role for BK channel function in lung injury may provide potential novel treatment approaches for patients with COPD.

KRISTEN HOLM, PhD
National Jewish Health, Denver, CO
Social Behavioral Research Grant

Increasing Adherence to Supplemental Oxygen Therapy in People with COPD

Rates of adherence to supplemental oxygen therapy in people with COPD often are below 50 percent. Factors that likely contribute to poor adherence include embarrassment about using oxygen in public and the need for help from family members to manage heavy oxygen equipment. Currently there are no measures of these challenges to using oxygen. We have developed instruments to measure a range of highly promising personal and family factors likely to influence oxygen adherence. We will examine the extent to which these instruments predict adherence to supplemental oxygen. Findings can be used to develop interventions to change specific, modifiable behaviors, such as increasing family members’ involvement with oxygen logistics.
ALEXA PRAGMAN, MD, PhD  
University of Minnesota, Minneapolis, MN  
Biomedical Research Grant

Can Bacteria from the Mouth Be Used to Study COPD?

In order to better understand how lung microbes affect the progression of COPD, we need to study bacteria found in the lungs of COPD patients over time. Such research would be much easier if we could substitute bacteria that are more easily accessible, such as those found in the mouth, nose or airways. We will compare lung bacteria obtained during lung surgery with bacteria found in the patients’ mouths, noses, airways and sputum. By comparing the lung bacteria to bacteria from the other sites, we will determine if a non-invasively obtained sample can be substituted for an invasive lung sample in future studies.

SAMMETA RAJU, PhD  
University of Alabama, Birmingham, AL  
Biomedical Research Grant

New Therapeutic Strategies to Treat Mucus Obstruction in COPD Airways

Excessive mucus buildup is an important feature in obstructive lung diseases such as COPD and cystic fibrosis (CF). CF is caused by an inherited mutation in the CFTR gene that is necessary for efficient mucus clearance, a crucial defense mechanism of the lung. We have previously identified that cigarette smoking causes defects in CFTR function through a highly reactive compound called acrolein. Our study will determine the overall levels of acrolein in cigarette smoke and how it contributes to CFTR abnormality. We propose to identify drugs capable of overcoming acrolein effects on CFTR and improve mucus transport to relieve symptoms of COPD.

BRADLEY WINSTON RICHMOND, MD  
Vanderbilt University Medical Center, Nashville, TN  
Senior Research Training Fellowship

Infections Could Play Role in Smokers’ Development of COPD

While most patients with COPD are current or former smokers, only some smokers develop severe COPD. Differences in frequency or response to recurrent infection may explain why only some smokers develop COPD. Our preliminary data shows that the small airways of COPD patients frequently lack secretory immunoglobulin A (SIgA), a protein whose main role is to prevent bacteria from penetrating into the lung. Using mice engineered to lack SIgA, we will examine whether the lack of this protein results in COPD-like lung injury after exposure to bacteria, and whether restoring SIgA in the small airways will prevent these changes from taking place.

TAKAYUKI SHIOMI, MD, PhD  
Columbia University, New York, NY  
Alpha-1 Research Grant

Investigating Effect of Smoke Exposure in Alpha-1 Antitryptin Deficiency

Alpha-1 antitrypsin deficiency (AATD) triggers an inherited form of emphysema. It is caused by a lack of a protective protein called alpha-1 antitrypsin (AAT) that is produced by the liver. In humans with AATD, cigarette smoke makes the lungs more sensitive to lung damage. We will use a newly developed mouse model of AATD to provide insight into how cigarette smoke leads to lung inflammation and destruction. The experiments will provide a useful model that can be used to study lung injury caused by the disease. The findings potentially can be used to identify new therapies in COPD.
Cigarette smoke is the major risk factor for the development of chronic lung disease. Chronic inflammation, DNA damage and premature lung aging are some of the key contributing factors in the development of smoking-related lung diseases, including chronic obstructive pulmonary disease, pulmonary fibrosis and lung cancer. Our study will examine how cigarette smoke causes DNA damage that contributes to the premature aging of the lung in cell cultures and animal models. We hope our results will help identify novel therapeutic targets in reducing premature lung aging in chronic lung diseases.
INFLUENZA, PNEUMONIA AND OTHER LUNG INFECTIONS

Lung infections are common and often deadly in those very young, very old and in those with compromised immune systems, such as people receiving chemotherapy or who have AIDS. Pneumonia and influenza are the most common lung infections and together continue to be one of the top 10 leading causes of death in the U.S. Almost 57,000 Americans die each year from influenza and pneumonia.

Influenza is a worldwide problem and a looming threat because of the virus’ uncanny ability to mutate, making previous immunizations ineffective, and because of its potential to transform into a highly contagious deadly organism capable of creating a devastating pandemic.

Pneumonia is a common lung infection caused by bacteria, a virus or fungi. Pneumonia and its symptoms can vary from mild to severe. Most healthy people recover from pneumonia in one to three weeks, but pneumonia can be life threatening. The good news is that pneumonia can be prevented by getting an annual flu shot (as flu often leads to pneumonia), frequently washing your hands, and for people at high risk, getting a vaccine for pneumococcal pneumonia.

This year, the American Lung Association is supporting several studies focused on the relationship between influenza and asthma. The research developed from the findings that while asthma was the most common chronic condition among adults hospitalized during the 2009 influenza pandemic, asthmatic patients who were hospitalized with pandemic influenza were half as likely to die or require intensive care compared to people without asthma. The findings may lead to new influenza treatments.

We are funding research that is looking at whether proteins called cytokines may help boost the immune response to influenza. We are supporting research that aims to understand the immune response to a common cause of bacterial pneumonia. We are also funding a study examining how the immune system fights Respiratory Syncytial Virus, an infectious agent that causes widespread disease in children.
INFLUENZA

ANDREW MEHLE, PhD
University of Wisconsin-Madison, Madison, WI
Biomedical Research Grant
Funded in partnership with the American Lung Association of the Upper Midwest

How Influenza Virus and Immune System Response Damage Lungs

Influenza is a serious public health threat and a major cause of acute lung damage. A robust, yet measured, immune response is essential for successful control of influenza virus infection and to limit damage to lung tissue. Severe disease, however, is associated with a hyperactive immune response that results in lung cell death and can be fatal. We will study the contributions of the virus and the immune system that directs protective versus damaging responses in the lungs. Our findings could lay the groundwork for new treatment strategies and may also have implications for other lung infections.

JOSEPH REYNOLDS, PhD
Rosalind Franklin University, North Chicago, IL
Biomedical Research Grant
Funded by the American Lung Association of the Upper Midwest

Cytokine Proteins May Help Boost Immune Response to Influenza

Influenza virus infection is an important global health threat that is in need of improved treatment. Many people suffer severe and sometimes deadly complications following influenza infection, especially the young, the elderly and those with compromised immune systems. We will study proteins called cytokines for their role in severe influenza infection. We will focus on two cytokine proteins, IL-17 and IL-17B, which have poorly understood roles in the establishment of lung inflammation and the immune response against invading infectious organisms. We will investigate whether IL-17 cytokines promote improved immune responses to influenza. Our research may lead to new treatments for inflammation-based respiratory disorders.

ALEXEI TUMANOV, MD, PhD
Trudeau Institute, Saranac Lake, NY
Biomedical Research Grant
Funded in partnership with the American Lung Association of the Northeast

Regulating Immune System’s Excessive Response to Influenza in Lungs

Lung damage induced by influenza infection is a significant cause of death worldwide. Much of this lung damage results from an excessive immune system response mounted by the body in an attempt to clear the virus. We want to find out how to block the aspects of the immune response that cause harm to the lungs without sacrificing those that provide protection. We will study the ability of a specific immune system regulator called lymphotoxin-beta receptor to inhibit influenza-associated harm without limiting protective immune responses. Our research will lead to new strategies for treating influenza and other respiratory diseases.

PNEUMONIA

NICOLE BYERS, PhD
Indiana University, Indianapolis, IN
Senior Research Training Fellowship

Learning Role of Tumor Suppressor in MRSA Infection Could Lead to Treatment

Methicillin-resistant Staphylococcus aureus (MRSA) pneumonia, which is resistant to the antibiotic methicillin, results in high death rates, despite early treatment with appropriate antibiotics. Uncontrolled MRSA infection causes a deadly overwhelming response by a person’s immune system. We recently identified a novel anti-inflammatory function of a protein expressed in many cells, named PTEN. This protein may dampen uncontrolled inflammation in MRSA infection. The goal of this project is to understand the mechanisms used by PTEN to inhibit overactive immune responses. The findings can help scientists develop new therapies to treat MRSA, and could have a broad impact on diseases associated with lung inflammation.
DANE PARKER, PhD
Columbia University Medical Center, New York, NY
Biomedical Research Grant
Funded in partnership with the American Lung Association of the Northeast

Preventing Immune Cells from Helping Bacteria Cause Lung Infection

We will study the ability of the major respiratory bacterium Staphylococcus aureus to interact with, and activate, a major immune system cell, the T cell. We have shown that the T cell contributes to the ability of S. aureus to cause infection. We will investigate the interaction between the bacteria and the immune system, studying both the host and bacterial factors involved. We will use currently approved drugs that are in clinical use to modulate the ability of the T cell to function with the aim of reducing disease. Our studies will provide a potential target for therapeutic intervention.

SHUYU YAO, PhD, DVM
Indiana University, Indianapolis, IN
Senior Research Training Fellowship
Funded in partnership with the American Lung Association of the Upper Midwest

Helping the Immune System Fight RSV

Respiratory Syncytial Virus (RSV) is the most common cause of lower respiratory tract infections in children. No fully effective active vaccine or treatments exist. Complete understanding of how RSV works still remains unclear. Studies have suggested that uncontrolled inflammatory responses of the immune system play a major role in disease development in the lower airways. We will study factors that can regulate these inappropriate immune-system responses without affecting the body’s ability to fight the virus. We will investigate the role of proteins called PD-1 and HMGB1 in the development of severe bronchiolitis and pneumonia during RSV infection. Our research could be valuable in developing new treatments and preventive strategies for RSV.

Combined influenza and pneumonia are a leading cause of death in the United States. The risk of contracting potentially life threatening respiratory infections, such as influenza and pneumonia, increases sharply among those 65 years and older. Learn more about these lung infections, their symptoms, and treatment and prevention options at the American Lung Association’s newly redesigned website: Lung.org/lung-health-and-diseases.
RISK FACTORS

Most major lung diseases are, to an important degree, preventable. The American Lung Association is working to save lives by reducing exposure to risk factors for lung disease.

Smoking is the leading cause of preventable illness and death in the U.S., causing an estimated 480,000 deaths each year. Tobacco use is the leading cause of lung cancer and chronic obstructive pulmonary disease (COPD), in addition to being a major risk factor for other cancers and respiratory diseases.

This year the American Lung Association Research Program is focusing on a number of aspects of risk factors related to smoking. One study is examining whether early-life exposure to secondhand smoke increases COPD risk. Another is investigating whether mobile devices can help smokers quit. A third is seeking to understand electronic cigarettes’ effect on health. We are also funding research that is exploring whether the effectiveness of CT screening for COPD and lung cancer seen in national clinical trials will translate into benefits in clinical practice in the community.

We are funding several studies related to risk factors and asthma. One study is examining and trying to determine whether prenatal exposure to the environmental pollutant bisphenol A (BPA) increases the risk of developing asthma later in life. We are also supporting research on why asthma is a risk factor for sleep apnea.

Air pollution is another major risk factor for lung disease. One project we are funding is looking at the impact of climate change on lung disease, using a large dataset to study long-term exposures to both air pollution and temperature and their interactive effects on mortality. We are also supporting research on indoor air pollution and how it affects lung health in rural Africa.

Are you ready to commit to quit smoking?

The American Lung Association has lots of help available. Our proven tools, tips and support can help you end your addiction to tobacco and begin a new, smokefree phase of your life. The Lung Association’s Freedom From Smoking® program has helped hundreds of thousands of people quit smoking since it’s first release in 1981. Learn more about the program and how it can help you, too! For an online version use Freedom From Smoking® Online and get started today. Lung.org/stop-smoking
ROBERT DVORAK, PhD
North Dakota State University, Fargo, ND
Social Behavioral Research Grant
Funded in partnership with the American Lung Association of the Upper Midwest

Mobile Device May Help Smokers Quit

Despite serious medical problems associated with smoking, 19 percent of adults in the U.S. continue to smoke. More than one-third of smokers attempt to quit each year, though most attempts end in relapse. People who try to quit often find treatment cost and availability are barriers to their success. We will test a novel cognitive retraining program implemented on a mobile device. The program retraining behavioral responses to smoking images in an attempt to modify brain circuits that control basic impulses to smoke. If successful, our research will provide a low-cost treatment option that can be widely distributed.

PEGGY LAI, MD, MPH
Massachusetts General Hospital, Boston, MA
Biomedical Research Grant
Supported by the Mary Fuller Russell Fund

How Indoor Air Pollution from Chickens Can Affect Lung Health in Rural Africa

Indoor air pollution leads to premature deaths worldwide, and is one of the most important risk factors contributing to the global burden of lung disease. We will study how microbes in the indoor environment change after the introduction of chickens to the environment in rural Uganda, and how these microbes can colonize in the airways of people in contact with the chickens and affect lung health. We will also study whether immune suppression due to HIV affects the ability of microbes in our environment to colonize the airways. The findings will allow us to develop future interventions to protect the health of susceptible populations.

CHRIS LIM, MS
New York University School of Medicine, New York, NY
Lung Health Dissertation Grant
Funded by the American Lung Association of the Northeast

Studying the Effect of Climate Change on Health

Climate change is predicted to alter temperature patterns, resulting in increased frequencies and intensities of extreme-temperature days. While the effects of short-term temperature variability have been extensively studied, it is not yet known whether there is an association between long-term chronic exposure to temperature variability and adverse health outcomes. In addition, there is little information on how individual-level characteristics influence the effects of temperature on adverse health outcomes. Recent evidence also suggests temperature may have an effect on the relationship between air pollution and mortality. To address these concerns, we will study long-term exposures to both air pollution and temperature and their interactive effects on mortality.

JESSICA OAKES, PhD
University of California, Berkeley, Berkeley, CA
Senior Research Training Fellowship

Determining Electronic Cigarettes’ Effect on Health

Electronic cigarettes (e-cigarettes) are widely used by people who believe they are a safe alternative to conventional cigarettes. Yet their safety has not been scientifically proven. Nicotine and glycol, two main ingredients in e-cigarette aerosols, have been linked to disease. Therefore, it is crucial to determine if these ingredients have significant negative impact on human health. We will use computers to simulate the transport and deposition of e-cigarette aerosols in models of the human airways created from CT images. These simulations will provide answers to where and how much of the e-cigarette aerosols are retained in the various regions of the lung. Simulation results may be used in future toxicology studies that aim to relate e-cigarette concentration to airway disease.
ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) AND OTHER DISORDERS OF THE LUNG BLOOD VESSELS

Acute lung injury, also known as acute respiratory distress syndrome (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. It can develop in anyone over the age of 1 who is critically ill. A person with ARDS has rapid breathing, difficulty getting enough air into the lungs and low blood oxygen levels.

Approximately 190,000 Americans are affected with ARDS each year. ARDS can be life-threatening because the body’s organs need oxygen-rich blood to function well. It is often the major complication of extensive infection, surgery, trauma, chemotherapy and lung transplantation. No effective treatment yet exists.

The American Lung Association is supporting a number of research projects on ARDS this year. Much of this research is aimed at understanding the underlying mechanisms of acute lung injury, with an eventual goal of developing new treatments. This year researchers are studying the cellular mechanism of leaky blood vessels in the lung; the inflammatory properties of proteins involved in acute lung injury; and how to prevent lung damage from oxygen used to treat ARDS.

Pulmonary hypertension is an abnormal elevation of blood pressure in the vessels going from the heart to the lung. One form of pulmonary hypertension is called pulmonary arterial hypertension (PAH), which worsens over time and is life-threatening because the pressure in the arteries rises to dangerously high levels, putting a strain on the heart. Currently, a researcher is investigating a molecule that could play a role in improving treatment for PAH.
PATRICK BELVITCH, MD
University of Illinois-Chicago, Chicago, IL
Biomedical Research Grant
Funded by the American Lung Association of the Upper Midwest

Preventing Leaky Blood Vessels in the Lungs in ARDS

Acute respiratory distress syndrome (ARDS) is a devastating form of acute lung injury that is common among critically ill patients. In a person with ARDS, protein-rich fluid leaks from blood vessels into the lungs. These leaky blood vessels can cause respiratory failure that requires prolonged stays in the intensive care unit. This leads to significant rates of illness and death. We will study the cellular mechanisms of leaky blood vessels in the lung, focusing on how specific proteins regulate the formation of gaps between cells that lead to the leakage of fluid into the lung airspaces. By understanding these mechanisms, we hope to be able to develop treatments for this condition.

TUNG CHAN, PhD
Thomas Jefferson University, Philadelphia, PA
Biomedical Research Grant

Protecting Lungs by Stimulating Molecule Important to Cell Survival

Lung cell injury and death often leads to irreversible airway remodeling and contributes to the progression of various lung diseases. A molecule known as Akt is essential for cell survival. We have previously found a way of stimulating Akt to render lung cells resistant to death and more capable of repairing themselves if injured. We will now attempt to develop novel drugs that will stimulate Akt’s activity in lung cells for their use in treating patients with acute lung injury, chronic obstructive pulmonary disease and fibrotic lung disease. It is possible that these drugs could be used shortly after an event such as acute lung injury, as a way to limit the damage that occurs to the lung cells and may also be able to stop or repair chronic lung degeneration.

ANDREAS SCHWINGSACKL, MD, PhD
University of California, Los Angeles, Los Angeles, CA
Biomedical Research Grant
Funded in Partnership with the American Lung Association of the Midland States

Identifying New Targets to Treat Acute Lung Injury

Mechanical ventilation and oxygen therapy are common treatment options for acute lung injury (ALI), although both therapies are known to cause further damage to the lungs. Recent studies suggest that a particular type of ion channel, 2-pore domain potassium (K2P), can sense signals at the cell membrane and convert them into specific cellular functions. The central hypothesis of this proposal is that the K2P channel is regulated by the treatments above and, in turn, regulates the release of inflammatory mediators. We will identify these channels as new potential targets for the development of novel treatment strategies against ALI.

BINOY SHIVANNA, MD, DM
Baylor College of Medicine, Houston, TX
Biomedical Research Grant
Supported by the Mary Fuller Russell Fund

Preventing Lung Damage from Oxygen Used to Treat ARDS

Acute respiratory distress syndrome (ARDS) is a life-threatening condition in people whose lungs are severely injured. These patients need oxygen to save their lives. But the high oxygen levels that these patients need can escalate their underlying lung injury. We will study whether a hormone named adrenomedullin (AM) can protect and help the lungs to heal from oxygen damage. In particular, we will investigate whether AM protects the lungs by decreasing the levels of an enzyme called NOX that causes lung damage from oxygen. Our studies can lead to improved therapies such as the use of AM to prevent and treat ARDS.
BARTOSZ SZCZESNY, PhD
University of Texas Medical Branch at Galveston, Galveston, TX
*Biomedical Research Grant*

**Damage to Mitochondrial DNA May Trigger Inflammation in Airway Cells**

Airway inflammation is the initial event in the development of several lung diseases. Although the connection between inhaled environmental pollutants and inflammatory lung disease is well established, we still do not fully understand what happens at the molecular level. We will study the role of mitochondrial DNA in inflammatory lung disease. Mitochondria are structures within cells that convert the energy from food into a form that cells can use. They have a small amount of their own DNA. We will study whether damage to mitochondrial DNA triggers the inflammatory response in airway epithelial cells. The findings may lead to new ways to prevent or treat inflammatory lung diseases.

JING ZHAO, PhD
University of Pittsburgh, Pittsburgh, PA
*Biomedical Research Grant*

**Reducing Anti-inflammatory Effects of Protein Involved in Acute Lung Injury**

Acute lung injury (ALI) 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. We will examine the inflammatory property of two proteins, FBXL19 and USP14, involved in ALI. FBXL19 exhibits an anti-inflammatory property, while the effect is reversed by USP14. Results from these studies could be used to develop treatments that inhibit USP14 and lessen the severity of lung injury.

DANIEL GREIF, MD
Yale University, New Haven, CT
*Biomedical Research Grant*

**Smooth Muscle’s Role in Pulmonary Hypertension**

Pulmonary hypertension (PH) is a devastating disease with elevated blood pressure in the blood vessels of the lung. In PH, there is increased smooth muscle in blood vessels, which raises blood pressure. Current treatments, which are of limited benefit, aim to decrease blood pressure by widening blood vessels. None of these treatments directly alter the accumulation of excessive smooth muscle, because the pathways governing smooth muscle accumulation are not well understood. We will use mouse models of human PH to identify key steps that contribute to excess smooth muscle, which could suggest new treatment approaches.

MOHAMMAD SHATAT, MD
Case Western Reserve University, Cleveland, OH
*Biomedical Research Grant*

**Molecule Could Play Role in Improving Treatment of PAH**

Pulmonary arterial hypertension (PAH) is a serious disease characterized by elevated pressure in the vessels that carry blood from the heart to the lungs. This causes the right side of the lung to become strained and, over time, can lead to heart failure. We have found that KLF4, a molecule present in the endothelial cells lining the blood vessels, has a protective effect against the development of PAH. We will study the role of KLF4 in regulating endothelial progenitor cells (EPCs), which participate in repairing damaged endothelial cells and are being studied for treating PAH. Understanding the role of KLF4 in regulating EPC function may help enhance their use in therapy.
INTERSTITIAL LUNG DISEASE AND FIBROSIS

Interstitial lung disease is a group of disorders that cause scarring of the lung. The disease eventually affects a person’s ability to breathe and get enough oxygen into the bloodstream. It can be caused by long-term exposure to dangerous materials such as asbestos. In most cases the cause is not known. Once lung scarring occurs, it usually cannot be reversed.

Idiopathic pulmonary fibrosis (IPF), a type of interstitial lung disease, has no known cause. Risk factors include smoking and viral or bacterial infections. Approximately 34,000 new cases of IPF are diagnosed in the U.S. each year with fewer than 50 percent of affected patients surviving five years. Unfortunately, there is no effective treatment for this disorder.

The American Lung Association supports an array of investigations into the basic cellular and molecular processes that underlie interstitial lung disease. One researcher is looking at an enzyme that could increase susceptibility to IPF. Another researcher is investigating why the same genetic mutation causes interstitial lung disease in only some family members. A third is looking at a rare inherited disease called Hermansky-Pudlak Syndrome, which causes scarring of the lungs. The findings could help increase understanding of the problem of excessive lung scarring and lead to new treatments.
**ROBERT BARRINGTON, PhD**  
University of South Alabama, Mobile, AL  
*Biomedical Research Grant*  
Funded by the American Lung Association of the Southeast  

**Gaining Insight into Rare Lung Disease, APAP**

Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare lung disease characterized by the build-up of grainy material in the alveoli (air sacs) of the lungs. This grainy material is composed mainly of phospholipid (a fat-like substance) and protein. Phospholipid and protein are the key components of lung surfactant, an important substance that coats the alveoli to prevent lung collapse and which promotes oxygen absorption by the lungs. We will use the first mouse model for aPAP to examine the underlying immune mechanisms that cause aPAP. Insights gained through our research could translate into treatment for human patients.

**ARGYRIOS TZOUVELEKIS, PhD**  
Yale University, New Haven, CT  
*Senior Research Training Fellowship*  
Funded by the American Lung Association of the Northeast  

**Enzyme Could Play Key Role in Idiopathic Pulmonary Fibrosis**

Idiopathic pulmonary fibrosis (IPF) is a devastating chronic lung disease in which lung tissue becomes scarred over time in response to unknown injuries. This leads to shortness of breath and dry cough that gradually progresses, culminating in death in 3 to 5 years. The IPF lung is characterized by increases in cells in the lung called fibroblasts. We have discovered an enzyme called SHP-2 is decreased in the lung fibroblasts of patients with IPF. We will study whether reduced levels of SHP-2 from the lungs of patients with IPF render them susceptible to disease development, and whether restoring its levels in a mouse model of lung fibrosis may exert a therapeutic role.

**JENNIFER WAMBACH, MD**  
Washington University in St. Louis, St. Louis, MO  
*Biomedical Research Grant*  
Funded in partnership with the American Lung Association of the Upper Midwest  

**Why Does the Same Mutation Cause Lung Disease in Only Some Family Members?**

Mutations in the surfactant protein-C gene (SFTPC) can cause severe respiratory distress in newborns, interstitial lung disease in children, and pulmonary fibrosis in adults. In families where multiple members have the same SFTPC mutation, not all of them develop lung disease, the same type of disease or at the same age. Variation in other genes may determine who develops lung disease and who remains healthy despite the SFTPC mutation. These genes are unknown. We will study several families with SFTPC mutations using genetic sequencing to determine additional genes that may contribute to either prevent or cause lung disease.
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Our Mission
The American Lung Association is the leading organization working to save lives by improving lung health and preventing lung disease through education, advocacy and research. For more than 100 years, we have led the fight for healthy lungs and healthy air, whether it’s searching for cures to lung diseases, keeping kids off tobacco, or fighting for laws that protect the air we all breathe.

Our Mission: To save lives by improving lung health and preventing lung disease.

Our Vision: A world free of lung disease.

About the American Lung Association
The American Lung Association is the leading organization working to save lives by improving lung health and preventing lung disease, through research, education and advocacy. The work of the American Lung Association is focused on four strategic imperatives: to defeat lung cancer; to improve the air we breathe; to reduce the burden of lung disease on individuals and their families; and to eliminate tobacco use and tobacco-related diseases. For more information about the American Lung Association, a holder of the Better Business Bureau Wise Giving Guide Seal, or to support the work it does, call 1-800-LUNGUSA (1-800-586-4872) or visit the newly redesigned website: Lung.org.

About the New Lung.org
As the nation’s premier resource for lung health, the new Lung.org has been redesigned with a focus on user experience on desktop, tablet and mobile devices. From the doctor’s office to the family dinner table, individuals with a lung disease and their support teams are able to access lung health resources and information the moment they need it.