CDMRP

Department of Defense

Lung Cancer Research Program

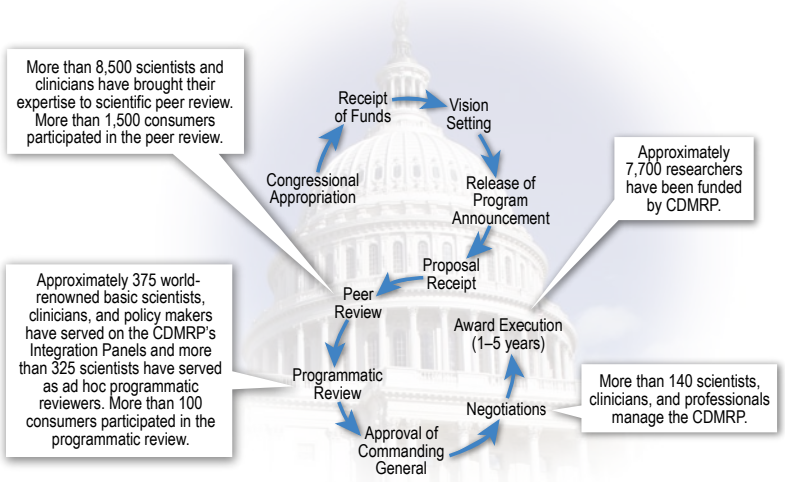
U.S. Army Medical Research and Materiel Command

History of the CDMRP

The Office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since then, the CDMRP has grown to encompass multiple targeted programs and has received more than $7 billion in appropriations from its inception through fiscal year 2012 (FY12). Funds for the CDMRP are added to the Department of Defense (DoD) budget, in which support for individual programs, such as the Lung Cancer Research Program (LCRP), is allocated via specific guidance from Congress.

Application Review Process

The CDMRP uses a two-tier review process for application evaluation, with both tiers involving dynamic interaction among scientists and disease survivors (consumers). The first tier of evaluation is a scientific peer review of applications measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Integration Panel (IP), which is composed of leading scientists, clinicians, and consumer advocates. The IP compares applications to each other and makes recommendations for funding based on scientific merit, portfolio composition, and relevance to program goals.



Lung cancer research is literally a breath of fresh air, giving hope to those who have been diagnosed with lung cancer as well as their families, friends, and colleagues. The LCRP is no exception, providing grants for innovative and unique lung cancer research that we hope will successfully impact the diagnosis and treatment of lung cancer as well as lead to a cure. I am honored to be a member of the LCRP Integration Panel, and I am taken by the passion of the other members, all of whom are dedicated to identifying and encouraging new lung cancer research approaches, which might one day change the grim statistics that have come to define lung cancer.

David Sturges, J.D.
Consumer
FY12 Integration Panel Member
Lung Cancer Foundation of America

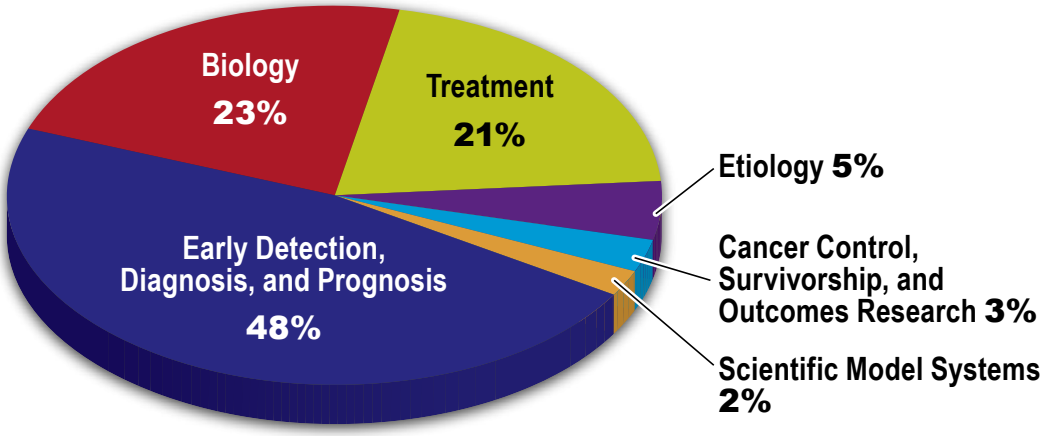
Lung cancer is the leading cause of cancer death for both men and women in the United States. Lung cancer research is sorely underfunded compared to its impact on life. It has been my pleasure to serve on the LCRP for the past 3 years. The funding has provided much needed funds to help us move toward improved detection, better understanding, and treatment of lung cancer. The ultimate goal of a cure is in our sights and with the help of the LCRP will be obtained in the near future.

Chuck Mulligan, M.D.
FY12 Integration Panel Member
Helen F. Graham Cancer Center

Program History

The LCRP was initiated in FY09 with a congressional appropriation of $20 million (M). Since then, efforts by lung cancer advocates to increase public awareness and federal funding for research have resulted in a total appropriation of $58M to the LCRP, including $10.2M for FY12. The goals of the LCRP are adapted yearly to target critical research and to be responsive to the needs of the lung cancer community. This year, approximately 226,160 men and women will be diagnosed with lung cancer in the United States and an estimated 160,340 will die from the disease. As such, the LCRP supports innovative research that is focused on identifying, treating, and managing early curable lung cancer. The program's current portfolio includes 60 awards made through FY11.

FY09–FY11 LCRP Portfolio by Research Area



Areas of Emphasis

The LCRP specifically encourages applications that address critical needs of the lung cancer community and concentrate on any of the following areas:

- Identification or development of noninvasive or minimally invasive tools to improve the detection of the initial stages of lung cancer
- Identification, development, and/or building upon already existing tools for screening or early detection of lung cancer. Screening may include, but is not limited to, computed tomography scans, x-rays, other imaging biomarkers, genetics/genomics/proteomics/metabolomics, and assessment of risk factors
- Understanding the molecular mechanisms of progression to clinically significant lung cancer
- Understanding the molecular mechanisms that lead to various subtypes of lung cancer
- Identification of innovative strategies for prevention and treatment of early lung cancer
- Understanding predictive and prognostic markers to identify responders and nonresponders
- Understanding acquired resistance to treatment

VISION

Eradicate deaths from lung cancer to better the health and welfare of the military and the American public.

MISSION

Support and integrate research from multiple disciplines for risk assessment, early detection, diagnosis, prevention, cure, and control of lung cancer.

As a 7-year lung cancer survivor, being a contributing team member with the CDMRP has been an honor and privilege. Knowing that my voice made a difference has given me a sense of accomplishment and the cutting-edge research possibilities have given me hope for the future of lung cancer survivors everywhere.

Jamie Young
Consumer
FY11 Peer Reviewer
National Lung Cancer Partnership

Program Highlights

Role of Ets Proteins in Lung Cancer Progression and Metastasis

Hasmeena Kathuria, M.D., Boston University
FY09 Promising Clinician Research Award

Lung cancer is the leading cause of cancer-related deaths in both men and women. Because patients generally do not experience symptoms in the early stages of the disease, the majority are diagnosed after the cancer has metastasized. While little is known about factors that allow cancer cells to leave the primary tumor and travel to lymph nodes and other distal sites, it is thought that an epithelial-mesenchymal transition (EMT), a process that involves loss of cell-to-cell adhesion and an increase in cell mobility, is a fundamental event in metastatic initiation whereby a subset of tumor cells acquire the ability to invade and disseminate.

Recent studies have revealed that about 30% of human lung cancers have inactivating mutations in the Lkb1 tumor suppressor. Dr. Kathuria hypothesizes that the loss of Lkb1 function induces increased levels of Ets1 and Pea3—members of the Ets family of proteins that are implicated in the regulation of cellular differentiation and proliferation—which in turn promote lung cancer progression and metastasis by driving EMT. With LCRP support, Dr. Kathuria is investigating the effects of Lkb1 loss on Ets1 and Pea3 levels in metastatic lung cancer animal models, as well as how Ets1 and Pea3 drive EMT by identifying their downstream targets. Thus far, Dr. Kathuria has found for the first time in lung cancer cells that Ets1 regulates the expression of the Twist1 transcription factor, which has been shown to initiate EMT in several cancers, by directly binding to its promoter. Inhibition of Ets1 via siRNA resulted in reduced Twist1 levels as well as significant decreases in the migration and invasion potentials of metastatic lung cancer cells.

Based on these promising data, Dr. Kathuria plans to determine whether Lkb1 mutations associate with increased Ets1 and Twist1 activity in tumors of lung cancer patients. Results of this study may lead toward development of novel therapeutic targets against EMT activation and metastasis.

A Novel Therapeutic Target for Squamous Cell Lung Cancer

Peter Hammerman, M.D., Ph.D., Dana-Farber Cancer Institute
FY09 Clinical Fellow Research Award

While lung cancer continues to be the principal cause of cancer-related deaths in the United States, treatment of lung adenocarcinomas with inhibitors of the epidermal growth factor receptor tyrosine kinase or the anaplastic lymphoma kinase has led to remarkable responses in a subset of lung adenocarcinoma patients whose tumors harbor genetic alterations in either of these kinases. However, little progress has been made in the treatment of lung cancer patients with lung squamous cell carcinoma (SCC), the second most common type of lung cancer. With LCRP support, Dr. Peter Hammerman is identifying and characterizing novel therapeutic targets for SCC by utilizing a functional genomic approach. Dr. Hammerman discovered that the discoidin domain receptor 2 (DDR2) kinase gene is a target of recurrent somatic mutations in squamous lung tumors. He identified 11 novel mutations in DDR2 from 290 human SCC samples with a mutation frequency of 3.8%. In addition, he found that dasatinib, a drug currently used for leukemia, can inhibit the proliferation of DDR2-mutated SCC cell lines both in vitro and in vivo, suggesting that DDR2 may be the first therapeutic target in lung SCC with existing clinically approved drugs. Dr. Hammerman opened a clinical trial of dasatinib in lung SCC at the Dana-Farber Cancer Institute, which recently expanded to a nation-wide study and is recruiting patients at this time. Dr. Hammerman is currently working on identifying novel DDR2 inhibitors as well as understanding mechanisms of acquired resistance to dasatinib and other tyrosine kinase inhibitors in lung cancer.

Developing Needed Resources

Christopher Moskaluk, M.D., Ph.D., University of Virginia
FY09 Lung Cancer Biospecimen Resource Network Award

Early detection of malignant lung lesions in their potentially curable stages is essential in improving the prognosis and long-term survival of lung cancer patients. Development of diagnostic tools, candidate biomarkers (indicators of disease), and novel therapies is desperately needed to improve the care of lung cancer patients. Unfortunately, lung cancer research has been hindered by the lack of high-quality, well-annotated specimens obtained in a systematic and reproducible fashion. To address the needs of patients and clinicians alike, the LCRP awarded Dr. Moskaluk a $3.8 million grant in FY09 to establish the first national early lung cancer biospecimen repository. This repository is designed to collect, annotate, store, and distribute early lung cancer patient samples to serve the research community, and ultimately, lung cancer patients. The specimens in the Lung Cancer Biospecimen Resource Network (LCBRN) will include tissues from thoracotomies, bronchoscopy washings, blood, saliva, and urine. Each specimen is linked to clinical and outcome data. The LCBRN collects patient samples at three participating sites, which are the University of Virginia, the Medical University of South Carolina, and Washington University in St. Louis. Importantly, the LCBRN has established collaborations with some Department of Veterans Affairs hospitals to address the needs of military personnel. Military personnel and veterans are at an increased risk for developing lung cancer due to increased exposure to environmental toxins and increased smoking rates. The LCBRN is the first national lung cancer biospecimen resource created outside of a clinical trials network that will be available to all biomedical researchers. The LCBRN aims to assist clinical investigators in the study of lung cancer genetics, novel diagnostic and prognostic tests for cancer, and candidate biomarkers.

Use of Plant Extract Parthenolide and Chemical Analogues to Kill Chemotherapy-Resistant Human Non-Small Cell Lung Cancer Cells

Richard Pietras, M.D., Ph.D., University of California, Los Angeles
FY09 Concept Award

Lung cancer is often incurable and is the leading cancer killer in men and women. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. Unfortunately, the majority of such lung cancers are diagnosed at advanced stages where surgery is no longer curative. The poor prognosis of advanced NSCLC is further due, in part, to emergence of tumor resistance to chemotherapy. Resistance to chemotherapy may be modulated by cancer stem cells (CSCs), which are theorized to arise from normal regenerative lung epithelial stem cells. CSCs may be responsible for initial tumor growth as well as tumor regrowth after chemotherapy. To address this important issue, Dr. Pietras seeks to develop novel therapeutics that can specifically target drug-resistant lung CSCs.

Parthenolide (PTL), a naturally occurring compound found in the plant feverfew, has previously shown strong antitumor activity in leukemia and prostate cancer cells. Importantly, PTL selectively kills tumor cells while sparing normal cells. Despite this, PTL's clinical use has been limited by its poor water solubility and limited bioavailability. Dr. Pietras aims to develop novel PTL analogs with improved pharmacological properties while retaining their efficacy. With support from the LCRP, Dr. Pietras isolated drug-resistant lung CSCs (i.e., CD133+/ALDH+ cells) from several human lung tumor xenografts by first treating the tumors with cisplatin and docetaxel, then selecting only those that were CD133+/ALDH+ from the surviving population. CSCs were significantly more resistant to cisplatin and docetaxel than non-CSCs, and CSCs exhibited constitutive activation of NF-kappaB. Additionally, they more readily formed tumors when injected in mice when compared to non-CSCs.

Next, Dr. Pietras synthesized several analogs of PTL designed for superior water solubility and antitumor properties, and he compared their efficacy in several NSCLC human cell lines and CSCs in vitro. While studies are ongoing, the investigator found several lead compounds that effectively suppress NF-kappaB signaling, inhibit lung cancer cell proliferation, and induce cell death in low concentrations. Moreover, the compounds significantly enhanced the cancer cells' sensitivity to cisplatin, a standard chemotherapeutic used in the clinic. These results suggest that PTL analogs may be a new nonsurgical option for treating lung cancer patients.

Spotlight on Clinical Consortia

Detection of Early Lung Cancer Among Military Personnel (DECAMP)

Avrum Spira, M.D., Boston University
FY10 Lung Cancer Early Detection Clinical Consortium Award

Early detection of malignant lung lesions in their potentially curable stages is essential in improving the prognosis and long-term survival of lung cancer patients. Each year, lung cancer takes more lives than all other cancers combined, largely due to delayed diagnoses. Because patients often lack signs and symptoms, lung cancers are generally diagnosed at an advanced, incurable stage. Currently, low-dose computed tomography (LD-CT) scans are one of the primary imaging modalities for detecting pulmonary nodules. While LD-CT scans are invaluable in detecting lung cancer, they have high rates of false positives due to their inability to distinguish between benign and malignant disease. These false positive results often lead to unnecessary, invasive follow-up procedures and surgery. Therefore, there is a critical need for effective tools that can identify individuals at highest risk for developing lung cancer and differentiate benign radiographic abnormalities from malignant lesions. Such tools would greatly benefit the American public as well as military personnel. Military personnel are at a higher risk of developing lung cancer because of their increased rates of smoking (up to 50% higher than the general population) and increased exposure to environmental toxins during deployment and often during routine military duties.

The LCRP supports high-impact translational research through multiple mechanisms with its most notable being the establishment of a clinical consortium for lung cancer research. In FY10, the LCRP granted a $13.5M Lung Cancer Early Detection Clinical Consortium Award to the DECAMP Consortium to conduct research studies focused on characterizing, developing, and/or improving early detection modalities for lung cancer. This consortium was established in partnership with four large military medical treatment facilities that serve military personnel, their families, and Veterans. Investigators from Naval Medical Center Portsmouth, Naval Medical Center San Diego, San Antonio Military Medical Center, and Walter Reed National Military Medical Center are working with multiple civilian organizations to design and conduct clinical studies.

The DECAMP Consortium is led by Dr. Avrum Spira at Boston University and his co-investigator Dr. Peter Schnall at the American College of Radiology Imaging Network (ACRIN). This consortium seeks to improve the process of diagnosing individuals at high risk of developing lung cancer by developing and validating noninvasive biomarkers that can indicate who needs additional screening (i.e., LD-CT scans) and distinguish between benign and malignant pulmonary nodules found in LD-CT scans.

In collaboration with the military treatment facilities, seven Department of Veterans Affairs hospitals, and additional clinical sites, Dr. Spira's team will first evaluate whether four existing airway and blood-based biomarkers can distinguish malignant pulmonary nodules from benign nodules in 500 Veterans with indeterminate lung nodules found on LD-CT scans. Dr. Spira hypothesizes that lung cancer affects the molecular profiles of tissues distal to the sites of disease (i.e., the field of injury effect) and that these changes can be measured in relatively noninvasive samples, such as in the blood or the nasal epithelium, even before lung cancer occurs. The investigators will evaluate the predictive value of these four biomarkers in combination with routine clinical tests and imaging data to develop the most robust predictor of developing lung cancer.

Concurrently, the investigators will study a cohort of 1,000 military personnel and Veterans who are former smokers and at high risk for developing lung cancer. The study will attempt to discover biomarkers that can distinguish individuals who will develop lung cancer—independent from other risk factors—from those who will remain disease-free. The patients will receive annual follow-ups for up to 4 years where they will be assessed for the development of lung cancer. Serum and nasal epithelial cell samples will be collected during the clinical visits and the researchers will then compare samples from patients who develop cancer to those who did not and analyze them for biomarkers that differentiate the two groups. If successful, these biomarkers will be used to identify individuals at highest risk for lung cancer who will benefit from more intense lung cancer screening.

The success of this two-part study may lead to sensitive, specific, and noninvasive tools for early detection of lung cancer. The goal is that the early detection of malignant lesions will lead to earlier diagnosis and improved outcomes for individuals at high risk for lung cancer and the reduction of lung cancer-related deaths.

Serving as a peer reviewer gave me a chance to make a very big difference in the fight against lung cancer… There are so very few lung cancer survivors out here and of those so few who were diagnosed early as I was and are physically able to carry on this fight. I am passionate and dedicated to this effort.

Charles Florsheim
Consumer
FY09–FY11
Peer Reviewer
National Lung Cancer Partnership

Consumer Story:
Stephanie Dunn Haney – A Repurposed Tenacity

Stephanie Dunn Haney sits with her daughters Allie (left) and Libby (right) on the girls' first day of school.

The phrase "lung cancer patient" would most likely lead people to picture a man in his 50s or 60s who has been a heavy smoker for decades. Picturing a young wife and mother of two girls who never smoked would be the furthest thing from our mind. It was for Stephanie Dunn Haney, and she was the one receiving the diagnosis.

"What I thought I knew was that lung cancer happened only to smokers, so it must be their own fault," Stephanie said. "I fell into exactly the same discompassionate and inaccurate traps as so much of the general public."

After coming to terms with her diagnosis, a process Stephanie called "scraping myself off the floor," she began learning about her disease, a process that included interacting with other lung cancer patients through online forums. At the same time, she met with an oncologist, who encouraged her as much by what he did not say than what he did say.

"He never once tried to give me a life expectancy," Stephanie said. "I am sensitive to doctors giving expiration dates to their patients. He also told me that he had many tools to fight the disease and that, while my cancer might be incurable, so were heart disease and diabetes!"

A previous doctor told Stephanie that while working with patients who fight their disease is an admirable quality, he was challenged by her tenacity. He had no idea.

Discovering her voice as an advocate led Stephanie to assisting the National Lung Cancer Partnership, which does fundraising for private research and advocacy training, and the Lung Cancer Alliance, a group that is active in soliciting federal support and developing specific patient support programs. She credited both organizations for focusing on different paths while working toward the same goal. Working side-by-side with scientists when reviewing research proposals gave her the opportunity to share her experiences, which was as important for the scientists as it was for her.

"Frankly, when I started in advocacy, the only area that I thought really wouldn't suit me was as a consumer advocate for research projects, but I have learned to love it," Stephanie said. "Because I don't fit the public's view of what a lung cancer patient must be, I have the opportunity to be heard in a way that many don't. It's incredibly unfair, so I feel a responsibility to speak for all of us."

Stephanie also has worked with the American Lung Association and was nominated to serve as a peer reviewer for the LCRP.

"Thanks to my peer review experience, I understand more about the disease, more about the research process, and how it works, and why it takes so long!" Stephanie said. "I know that as a non-scientist, I am limited in some ways as to what I can contribute, but my experience has been that I have something different to offer that may be as valuable."

Her tenacity, noted earlier by her first doctor, still exists; however, Stephanie now selectively uses those thoughts and feelings.

"I believe sharing my experience has informed the ideas and work of the other scientific reviewers," Stephanie said. "The scientists and medical professionals who are part of the process look to us for our passion, our perspective, and our common sense. And the very bottom line is we keep them honest—they remember what, and who, they are there for!"

I spent two incredible days sitting at a table with two other advocates/survivors and approximately 14 lung cancer researchers from across the country. It was rewarding to see that the researchers welcomed our perspective and questions. Some opinions on both sides were changed and in the end we walked away knowing that the submitted grants would reflect not only the important science but also how that project would affect patients. The experience was wonderful.

Joan Tashbar
Consumer
FY11 Peer Reviewer
Moffitt Cancer Center

For more information, visit
http://cdmrp.army.mil
or contact us at:
CDMRP.PublicAffairs@amedd.army.mil
(301) 619-7071

09-2012