CDMRP
Department of Defense

August 2021

Lung Cancer Research Program

Strategic Plan

INTRODUCTION

The Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas. Programs managed by the CDMRP have formalized strategic plans that identify program-specific research priorities, how to best address these urgencies, short- and long-term goals, investment strategies, and ways to identify and evaluate program successes with respect to the priorities.

The Lung Cancer Research Program (LCRP) Strategic Plan identifies the high-impact research goals that are most important to its stakeholders while providing a framework that is adaptable to changes in the medical research environment to address those goals. This plan has been formulated to provide the public and other stakeholders with greater clarity regarding the program's goals over time. Funding for the LCRP is congressionally appropriated on an annual basis; therefore, there is no guarantee of future funding. The LCRP Strategic Plan will be reviewed during the program's annual Vision Setting Meeting and updated as necessary.

LCRP BACKGROUND AND OVERVIEW

Anyone can get lung cancer. Lung cancer is the leading cause of cancer mortality in the United States, accounting for 22% of all deaths.[1] In 2021, more than 235,000 U.S. men and women will be diagnosed with lung cancer, and over 131,800 will die from the disease.[1] Lung cancer incidence and mortality is highest in African Americans compared with other racial/ethnic groups in the United States, primarily due to very high rates in African American men.[2] Several factors have been shown to contribute to the development of lung cancer, particularly smoking and exposure to environmental carcinogens being the most prevalent; however, 10% to 15% of lung cancers occur in people who are non-smokers. Lung cancer risk for our military is significant, as 24% to as high as 38% of Service Members are smokers, compared to 14% of civilians.[3] Among military Veterans, 29% reported current tobacco use,[4] and an estimated 900,000 Veterans remain at risk due to age, smoking, and other environmental exposures during and after military Service. Despite improved screening methods for lung cancer and advances in treatment, the 5-year survival rate is only 20%. Lung cancer is a global problem that struggles from limited availability of research dollars and research resources. Increased research efforts on lung cancer would significantly help achieve improved detection, treatment, management, and prevention and, ultimately, a cure for this deadly disease.

VISION AND MISSION

The LCRP was established in fiscal year 2009 (FY09) with a congressional appropriation of $20 million (M) to promote innovative and competitive research focused on the development of integrated components to identify, treat, and manage early curable lung cancer. To address this guidance, the LCRP has developed the following vision and mission statements:

LCRP VISION: To eradicate deaths and suffering from lung cancer to better the health and welfare of the Service Members, Veterans, and the American public

LCRP MISSION: Support and integrate research from multiple disciplines for risk assessment, prevention, early detection, diagnosis, and treatment for the control and cure of lung cancer

Since the program's inception, the LCRP has followed Institute of Medicine* (IOM) recommendations[5] to the CDMRP on the peer review procedures to be used in evaluating an application's scientific merit and the preferred programmatic investment strategy for funds. A two-tier peer review system is used in which the primary criterion for awarding grants is scientific excellence (first tier – peer review). Programmatic relevance is a secondary criterion (second tier – programmatic review) to ensure that awards are made to those excellent applications that best meet the programmatic goals.

The IOM also recommended that "consumers" (disease survivors) be included as members of the panel conducting the programmatic review termed the Programmatic Panel. The LCRP has adhered to this guidance; consumers also participate on the peer review panels.

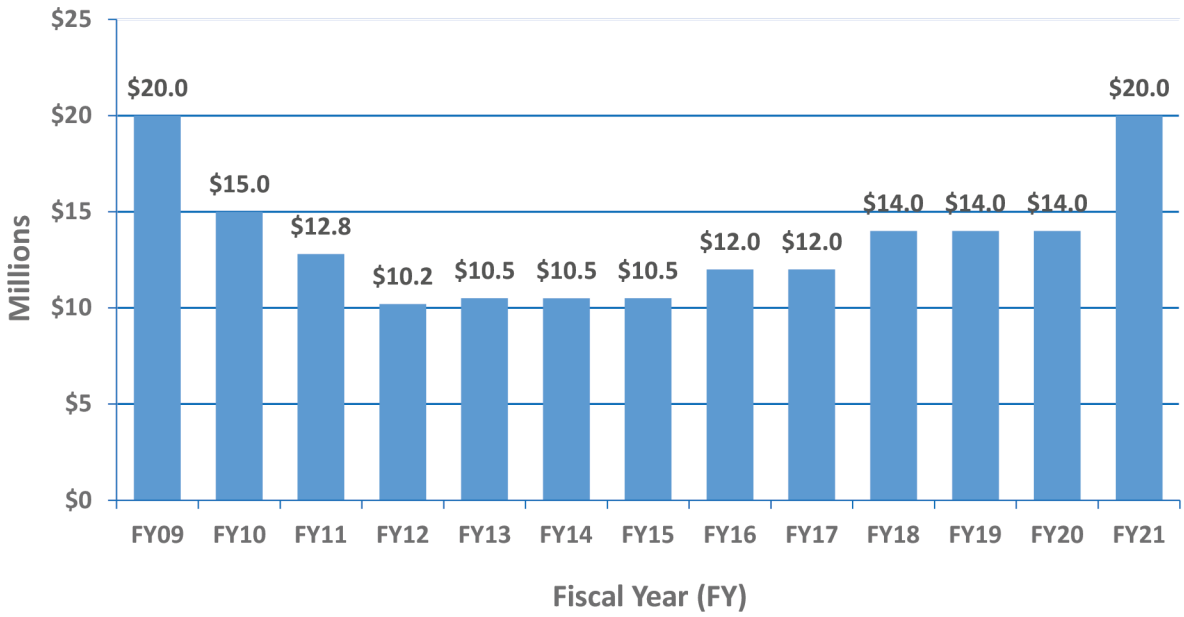
In addition, the IOM recommended that "...the best way to ensure that only first-rate research is funded is not to target specific disciplinary areas but, rather, to create a structure that allows the best ideas to emerge from all disciplines..." The IOM further recommended that CDMRP programs "encourage innovative ideas and cross-cutting proposals that can shed light on the fundamental questions in the causation, prevention, detection, diagnosis, and optimal treatment of and recovery from...cancer."

To this end, the LCRP invests in research across the full spectrum of basic, translational, and clinical research. Consistent with the IOM recommendations, the LCRP designed award mechanisms that meet the following objectives:

- Accelerate high-impact research
- Encourage innovation and stimulate creativity
- Bring new investigators into the lung cancer field
- Facilitate meaningful collaborations

FUNDING HISTORY

Over its 13-year history, the LCRP has received congressional appropriations annually, albeit with some fluctuation from year to year. The figure below shows the program's funding from 2009 to 2021, totaling $175.5M since its inception. From FY09-FY20, the program has supported over 300 awards. An additional 34 awards are anticipated for FY21, depending on the quality and budgets of the recommended applications.



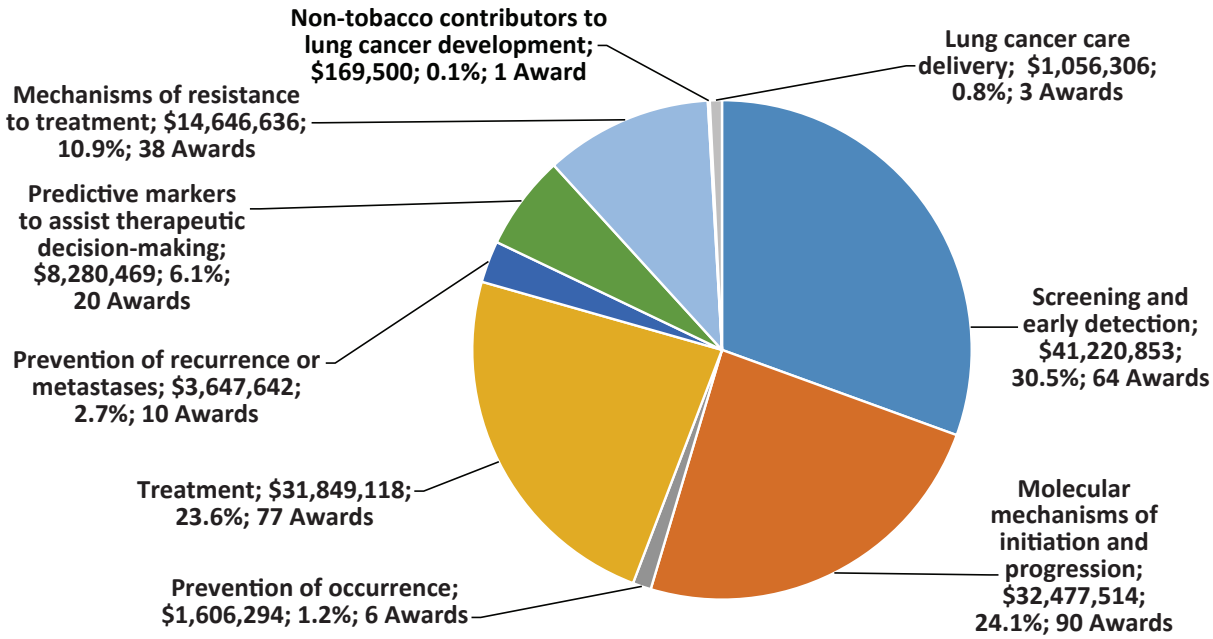
* The National Academy of Sciences changed the Institute of Medicine (IOM) name to National Academy of Medicine in 2015.

RESEARCH PORTFOLIO

When the LCRP was first established in FY09, the Programmatic Panel recommended seven areas of emphasis to assist researchers in concentrating their projects around the program's priorities. Through the years, this framework has been generally followed, although in recent years, the LCRP has introduced four new areas of emphasis and consolidated two other areas of emphasis, resulting in the following areas of emphasis:

- Identify innovative strategies for prevention of the occurrence of lung cancer
- Identify innovative strategies for the screening and early detection of lung cancer
- Understand the molecular mechanisms of initiation and progression to lung cancer
- Understand contributors to lung cancer development other than tobacco
- Identify innovative strategies for the treatment of lung cancer
- Identify innovative strategies for the prevention of recurrence of or metastases from lung cancer
- Develop or optimize prognostic or predictive markers to assist with therapeutic decision-making
- Understand mechanisms of resistance to treatment (primary and secondary)
- Identify innovative strategies for lung cancer care delivery (clinical management/ surveillance/symptom management)
- Understand factors that contribute to the health disparities in lung cancer, such as biological contributors; environmental, social, and cultural factors; and access to health care (new in FY21)

The following pie chart displays the LCRP portfolio from FY09-FY20, based on the program's areas of emphasis; investment in terms of dollars and percentage of funding; and number of awards made for each:



Dollars Invested per Area of Emphasis (FY09-FY20)
Total Investment: $134.95M; Total Awards: 309

RESEARCH ACCOMPLISHMENTS

Multiple LCRP-funded projects have been successful, with results that have been translated to the clinic for testing in humans or have contributed resources for use by the scientific research community. Examples include the following:

- Demonstrated that a novel combination therapy for inoperable stage I lung cancer using an immunotherapy that blocks PD-L1 (TECENTRIQ®) in combination with standard-of-care stereotactic body radiotherapy (SBRT) prevents disease progression with no dose-limiting toxicity. These data became the foundation for the National Cancer Institute (NCI)-supported, ongoing phase 3 clinical trial to examine the benefit of adding atezolizumab to SBRT for non-small cell lung cancer (NSCLC) patients with inoperable stage I-IIA tumors (NCT04214262).
- Determined a novel therapy for K-RAS NSCLC using Rigosertib (RGS), an orally available RAS mimetic, synergized with conventional immune checkpoint inhibitor therapies to reduce the total lung tumor burden in mouse models. Based on these results, a phase 1/2 clinical trial (NCT04263090) was launched to evaluate RGS in combination with immune checkpoint inhibition.
- Immunotherapy treatment with mesothelin-targeted CAR (chimeric antigen receptor) T cells is being tested in phase 1 clinical trials in multiple cancers, including lung cancer.
- Determined that defective apoptosis, or programmed cell death, plays a large role in the emergence of resistance to targeted therapy in lung cancer, leading to phase 1 clinical trial (NCT02520778) testing of a combination therapy of an apoptotic stimulator with a targeted therapy in lung cancer.
- The Lung Cancer Biorepository Network contributed hundreds of samples to the lung cancer-focused APOLLO 1 project of the Cancer Moonshot Program, which is exploring whether specific gene mutations or specific gene expression signatures are associated with disease recurrence, as well as to further test these molecular changes as prognostic markers that can be used in clinical decision-making.

RESEARCH AND FUNDING ENVIRONMENT

STATE OF THE SCIENCE

Since its initial year in FY09 and in each successive year, the LCRP has reviewed the current state of the science in the lung cancer field and evaluated the major knowledge gaps or significant unanswered questions that remain to be addressed.

PREVENTION

Understanding the biology of carcinogenesis is extremely important for development of effective prevention and treatment strategies. Two key concepts to understanding the biology are the multi-step nature of carcinogenesis and the diffuse field-wide carcinogenic process. Development of lung cancer follows a series of steps extending over years. Before becoming invasive, lung epithelium may undergo morphological changes that include hyperplasia, metaplasia, dysplasia, and carcinoma in situ. The principal premalignant lesions are dysplasia and carcinoma in situ because they are more likely to progress to invasive cancer and are less likely to spontaneously regress. The concept of field carcinogenesis is that multiple independent neoplastic lesions occurring within the lung can result from repeated exposure to carcinogens.

Tobacco smoking is the major cause of lung cancer.[6, 7, 8] The risk of developing lung cancer from tobacco smoking is dose-dependent and increases markedly relative to the number of cigarettes/cigars/pipes smoked per day and the number of years the individual smoked. Other risk factors for lung cancer include secondhand smoke,[9] family history,[10] HIV infection,[11] environmental risk factors (exposure to air pollution, radon, asbestos, arsenic, chromium, nickel, beryllium, cadmium, tar, and soot),[12] and beta carotene supplements in heavy smokers.[13] Some of these risk factors are modifiable and can significantly lower an individual's probability of developing lung cancer, such as not smoking or quitting smoking and lowering exposure to environmental risk factors such as radon, secondhand smoke, and asbestos, to name a few. However, not all environmental risk factors may be avoidable, nor does one always have knowledge of exposure to them.

Ten to 15 percent of lung cancer cases occur in never-smokers,[14, 15] and 60%-65% of all new lung cancer cases occur in never-smokers or former smokers.[14, 16] Based on this information, questions requiring further exploration include the following:

- Which populations of never-smokers are most susceptible to lung cancer, and how do we identify them?
- What are the biological mechanisms of lung cancer development in never-smokers?
- What environmental exposures and gene-environment interactions increase the risk of lung cancer?

BIOLOGY AND ETIOLOGY

The molecular basis of lung cancer is complex and heterogeneous. Lung cancer develops through a multi-step process involving genetic and epigenetic alterations, particularly activation of growth-promoting pathways and inhibition of tumor suppressor pathways. There are two main histological types of lung cancer: NSCLC (representing 80%-85% of cases) and small cell lung cancer (SCLC) (representing 15%-20%). The most common types of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, but there are several other types that occur less frequently. Oncogene activation can be seen in most lung cancers, resulting in persistent upregulation of growth-promoting pathways. Commonly activated oncogenes include EGFR, ERBB2, MYC, KRAS, MET, CCND1, CDK4, MEK, EML4-ALK fusion, and BCL2.[17] Loss of tumor suppressor genes is another important step in lung carcinogenesis. Commonly inactivated tumor suppressor genes include TP53, RB1, STK11, CDKN2A, FHIT, RASSF1A, and PTEN.[17] Despite identification of all of these various genetic alterations in lung cancer, the challenge remains to determine the biologically relevant driver mutations from the vast majority of passenger mutations. In addition, identification of driver genomic aberrations also requires parallel development of effective targeted therapies and, for many of these changes (such as KRAS), such therapies are not yet available. Other questions to be considered include the following:

- What are the events, including molecular genesis, in the initiation, progression, and metastasis of various types of lung cancer?
- What factors influence invasion and metastasis, and how can they be modulated?

Increasing our knowledge of the molecular biology and genomic landscape of lung cancer will lead to greater promise for prevention, diagnosis, treatment, and eventual eradication of the disease.

DETECTION AND DIAGNOSIS

Early detection of lung cancer is critical to impacting long-term survival. For most patients, lung cancer is detected as advanced disease (stage III/IV), where 5-year survival rates remain low at below 30%, whereas if the disease is detected at an early stage (local), 5-year survival rates are 56%.[16] Today only 16% of lung cancer cases are diagnosed at local stage. Early detection of lung cancer is difficult in part because symptoms tend not to appear until the disease is at an advanced stage.

Detection of lung cancer relies primarily on computed tomography (CT) scans. Results of the National Lung Cancer Screening Trial, using low-dose CT (LDCT) screening, demonstrated a 20% reduction in lung cancer mortality, along with a 6.7% reduction in all-cause mortality when compared with an annual chest X-ray screening of high-risk individuals, ages 55 to 74, with either a cumulative smoking history of greater than 30 pack-years, or former smokers who have quit within the past 15 years.[18] The caveat to the reduction in mortality using LDCT screening is the high rate of false positives (96.4% of positive screening results), resulting in unnecessary follow-ups, which places burdens on both the health care system and the individual. There is a significant need to develop other detection methods to use with or prior to LDCT screening to maximize the benefits of this method and, ultimately, better stratify high-risk individuals.

A step beyond imaging detection is bronchoscopy, which has an established role in diagnosis, despite being an invasive procedure. Collection of tissue biopsies has been the mainstay of diagnosis, but the collected samples are limited in their reflection of the tumor's heterogeneity and its ever-evolving biology. More recently, there has been significant enthusiasm regarding the use of liquid biopsies (blood-borne biomarkers) to assist in diagnosis, screening, prognosis, and recurrence monitoring. These biomarkers include circulating microRNAs, antibodies, ctDNA, circulating tumor cells, and exosomes, to name a few.[19, 20] The challenge remains, however, that these current blood-based biomarkers demonstrate suboptimal sensitivity for cancer diagnostics and require further study. For detection and diagnosis, a key question to be answered is what prognostic indicators can be used to identify the most important screen-detected cancers. Some additional questions for consideration include the following:

- What existing biomarkers or other known risk factors provide the best opportunity for screening never-smokers?
- What pre-lung cancer biomarkers, prodromal indicators, and detection methods can be used to identify at-risk individuals?

TREATMENT

Treatment options can vary, depending on whether the cancer is NSCLC or SCLC and the stage of the disease. The treatment options typically include one or more types of therapy such as surgery, chemotherapy, radiation therapy, targeted therapy, angiogenesis inhibitors, or immunotherapy. NSCLC patients diagnosed with early-stage disease may be cured with surgery or surgery followed by chemotherapy; however, only 16% of cases are diagnosed at early- or local-stage disease. In addition, despite early detection and curative resection, a significant proportion of patients will die from recurrent disease within 5 years.[14] SCLC is found to be most responsive to chemotherapy and radiation therapy. Surgery is rarely used as the main treatment for SCLC because it has a greater tendency to be widely disseminated by the time of diagnosis. SCLC is more aggressive than NSCLC and has an overall 5-year survival rate of 5%-10%.[21]

Identification of genetic alterations in lung cancer has led to development of molecularly targeted therapy or precision medicine to improve the survival of subsets of patients with metastatic disease.[22] The better prognosis when treated with targeted therapies has only been observed in the advanced disease setting[23]; however, studies are underway to investigate these markers in early-stage disease. The biggest challenge for targeted therapies is that a majority of patients with lung cancer who initially benefit from them eventually develop resistance (acquired resistance). Strategies to prevent acquired resistance or delay its development are an area of intense research interest. Questions that are being asked include the following:

- What interventions are best for preventing first-line resistance or treating second-line resistance for patients with known targeted mutations?
- What therapies are best for those without driver mutations?
- What are the best practices for treating tumors of patients with previously untargeted genetic alterations?

Recently, the treatment landscape has evolved with the introduction of immunotherapy for lung cancer. There has been success using immune checkpoint inhibitors for NSCLC with several Food and Drug Administration-approved drugs (nivolumab, atezolizumab, and pembrolizumab). Most recently, in a trial with metastatic non-squamous NSCLC patients who received the drug pembrolizumab plus chemotherapy, there was observed improvement of overall survival and progression-free survival compared to patients who received chemotherapy alone.[24] Other types of immunotherapy currently being explored include adoptive T cell transfer, e.g., CAR T cell therapy, and therapeutic cancer vaccines with clinical trials that are currently being conducted in lung cancer patients.[25] Use of immunotherapies does come with concerns, especially regarding treatment-related toxicity associated with the use of immunotherapy agents, and thus requires further investigation and optimization. In addition, combinations of treatments using immunotherapy and chemotherapy or radiotherapy require exploration. Efforts are also needed to develop new and more reliable predictive markers that can identify those patients who will most benefit from immunotherapy treatments. Other questions and areas requiring further investigation include the following:

- Which treatments are most effective for early-stage lung cancer?
- Which biomarkers can be used to determine the benefits/risks of adjuvant therapies following resection for patients with early-stage lung cancer?
- What care and monitoring options can improve long-term survival?

RESEARCH FUNDING LANDSCAPE

To maximize the LCRP's ability to fill gaps and leverage the findings of others in the lung cancer research field, it is important for the program to consider (1) how much is invested and (2) which research areas are funded across major federal and non-federal organizations. The CDMRP is a founding partner of the International Cancer Research Partnership (ICRP), a unique alliance of cancer organizations working together to enhance collaboration and strategic coordination of research. The ICRP currently includes over 100 partnering organizations worldwide. The ICRP developed the Common Scientific Outline (CSO) coding system, which is used by the ICRP partners and enables coordination of research and funding efforts. Portfolio data coded using the CSO system is shared among the ICRP partners and is publicly available.

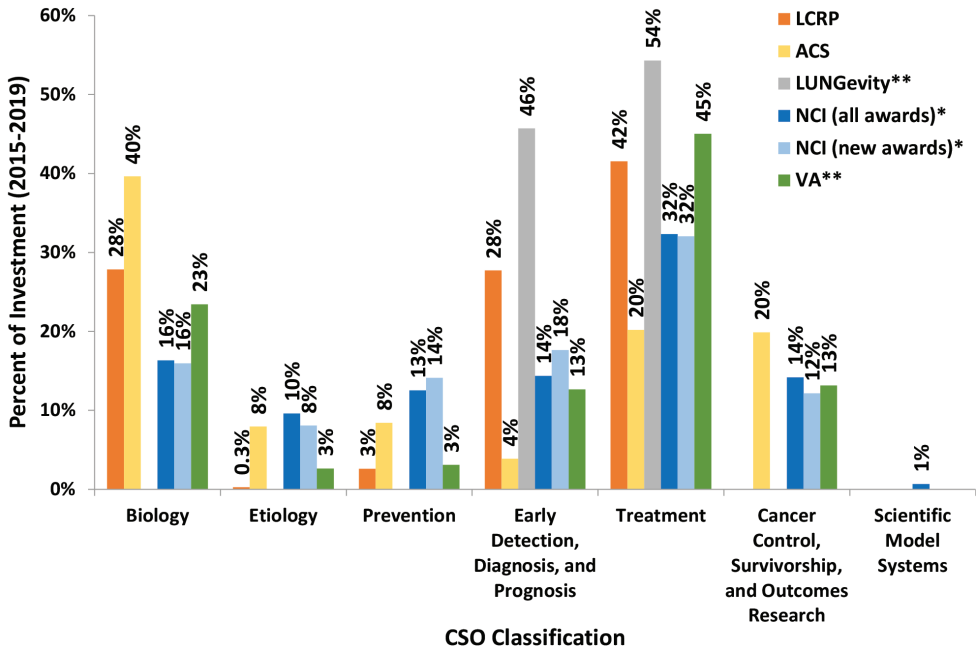
Every year, the LCRP analyzes (1) dollar investments and (2) research portfolios of the major lung cancer research funding organizations. The table below shows data on lung cancer research funding provided by ICRP partners (the LCRP, NCI, and American Cancer Society) as well as LUNGevity and the Department of Veterans Affairs (VA) from 2015-2019.

The LCRP is the second largest funder of lung cancer research after the NCI. However, it should be noted that the LCRP invests only in new awards each year, whereas the NCI invests about 19% of its funds in new awards and the remainder in supporting the out-years of existing continuing awards.

Funding Organization	Dollars Invested
LCRP	$55,676,563
American Cancer Society	$37,874,322
LUNGevity	$8,315,000
NCI (all awards)*	$1,609,675,463
NCI (new awards)*	$307,342,005
VA	$35,222,476

** NCI funding information for 2019 is preliminary and unpublished.*

The following figure compares the project portfolios of the major lung cancer research funders using the CSO coding system:



** NCI funding information for 2019 is preliminary and unpublished.*
*** CSO codes for LUNGevity and the VA were assigned by LCRP staff.*
**** In April 2015, the CSO code, "Scientific Model Systems," was incorporated into the other six CSO codes as a subcategory.*

Of these seven project portfolios, the LCRP invested the majority of its funds (2015-2019) in three: Biology (28%); Early Detection, Diagnosis, and Prognosis (28%); and Treatment (42%). It should be noted that the LCRP did not invest in Cancer Control, Survivorship, and Outcomes Research, which is consistent with the program's focus on research directed at eradicating deaths and suffering from lung cancer.

The NCI invested funds toward new awards (2015-2019) in all research areas, with Treatment (32%) receiving the most funding, followed by Early Detection, Diagnosis, and Prognosis (18%) and Biology (16%), and less but almost equivalent funding amounts for Etiology, Prevention, and Cancer Control, Survivorship, and Outcomes Research.

Today's medical research environment is dynamic. New research data sets are being created and made available to researchers at an ever-faster rate, and new technologies are emerging that will enable research that is impossible today. Funding for research comes from a variety of sources through a variety of programs. Many are funded by the government through the National Institutes of Health, VA, CDMRP, and other Department of Defense organizations; other funding is provided by non-government organizations that are focused on disease-specific areas. The LCRP must fit within this environment and effectively respond to changes in it to maximize the value and impact of LCRP-funded research.

STRATEGIC DIRECTION

The LCRP considered a broad range of unresolved research questions that are potentially critical to advancing prevention, detection, treatments, and cures for lung cancer. In studying these questions, it is clear that the LCRP plays a unique role in funding lung cancer research. As evidenced by the noted gaps in knowledge in the state of the science, the domain of lung cancer research still has substantial, unfinished work and, to date, has been largely underfunded and underrepresented relative to the high rates of lung cancer prevalence, morbidity, and mortality. The LCRP's strategic priorities therefore seek to address an important gap in the funding of lung cancer research – specifically, the seeding of new and innovative ideas that, once proven, can proceed toward further translational development and clinical trial testing under the auspices of other funding agencies, as well as the LCRP if congressional funding is available.

Given the substantial need for further lung cancer research across the entire research spectrum (from prevention to biology/etiology, screening and detection, and treatment and cancer control/survivorship), the LCRP is not limiting its focus to one or only a few of these research areas. Rather, the program's focus is defined better by the types of award mechanisms it typically offers, which include but are not limited to the following:

- Researcher Development Awards – Encompassing Career Development Awards, Clinical Fellow Awards, and New Investigator Awards:
  - Designed to support promising scientists or research clinicians who are not yet established investigators, scientists, or research clinicians or are currently working in other areas and are shifting their research focus to lung cancer.
- Early Idea Awards – Includes Concept Awards, Idea Development Awards, and Expansion Awards:
  - Designed to encourage higher-risk/higher-return research and to provide opportunities for continued investigation and further development of promising research.
- Clinical/Translational and Team Science Awards:
  - Designed to support projects with the potential to have a major impact on therapy by applying promising and well-founded preclinical research findings to the care of patients.

By remaining open to a wide range of research projects across the lung cancer research continuum, the LCRP strives to leverage small projects to promote early investigators and launch early ideas and transition to larger studies and funding opportunities.

STRATEGIC GOALS/PRIORITIES

The LCRP seeks to invest in its priorities, which in turn are based on its areas of interest. We do this by enabling investigators to propose their best ideas and by furthering high-impact, innovative lung cancer research focused on underfunded and underrepresented areas. The program does not define which specific projects or products will be funded. The overarching strategic priorities for the LCRP are listed below; the program will focus on specific goals to address each priority:

- Support research toward understanding the molecular mechanisms of the development of lung cancer
  - Early events, including molecular genesis, in the initiation, progression, and metastasis of various types of lung cancer
  - Biological mechanisms of lung cancer developed by never-smokers
  - Risk associated with pre-malignant lesions
- Support research toward understanding contributors to lung cancer other than tobacco
  - Populations of never-smokers most susceptible to lung cancer
  - Genetic factors associated with increased risk of lung cancer
  - Exposure risk associated with military Service
- Support research that develops or improves tools for screening and early detection of lung cancer
  - Non-invasive or minimally invasive tools to improve detection of initial stages of lung cancer
  - Existing biomarkers or other known risk factors to screen never-smokers
  - Pre-lung cancer biomarkers, prodromal indicators, and detection methods to identify at-risk individuals
  - Prognostic indicators to identify the most important screen-detected cancers
- Support research to identify innovative strategies for prevention of lung cancer
  - Preventive measures for occurrence and reoccurrence
- Support research to identify innovative strategies for treatment of lung cancer
  - Mechanisms behind development of resistance to treatment (primary and secondary)
  - Biomarkers to identify responders and non-responders
  - Biomarkers to determine benefit/risk of adjuvant therapies
  - Most effective treatments for early-stage lung cancer
- Support research to identify innovative strategies for lung cancer care delivery
  - Care and monitoring options for long-term survival
  - Health disparities

INVESTMENT STRATEGY

Looking forward to the next 3 to 5 years, the LCRP has developed an investment strategy that will allow it to solicit the type of research that will facilitate accomplishment of its strategic goals. After each FY, the program will evaluate the following award mechanisms supporting each strategic investment to determine whether they may need to be modified or discontinued:

- Researcher Development
  - Career Development Award
  - Idea Development Award (New Investigators)
- Innovative Early Ideas
  - Concept Award
  - Idea Development Award
- Clinical and Translational
  - Investigator-Initiated Translational Research Award
  - Clinical Translational Research Partnership Award

MEASURING PROGRESS

The LCRP will measure its near-term success based on making successful investments in those areas that are important to its strategy. Longer-term success may be evaluated based on contributions to the scientific community and following research linked to LCRP-funded projects.

- Near Term
  - Investments in each strategic priority/goal
  - Encourage more research in strategic priorities that are understudied
  - Contributions to the scientific community, including numbers of publications, patent applications, patents, and clinical trials, which will vary based on the stage of the research project
- Medium to Long Term
  - Proportion of funded investigators receiving additional awards to continue successful research
  - Tracking new investigators who are establishing their careers as lung cancer researchers and their contributions to the lung cancer research field
  - Funded projects leading to clinical research studies, clinical trials or research resources
  - Contributions to the scientific community, including the numbers of publications, patent applications, patents, clinical trials, successful commercialization efforts, and changes in standard of care accomplished

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