CDMRP Department of Defense

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. In 2015, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine was assembled to evaluate the CDMRP's two-tier review process and its coordination of research priorities with the National Institutes of Health (NIH) and the Department of Veterans Affairs (VA). As part of their final report,[1] the committee recommended that each CDMRP program "… develop a strategic plan that identifies and evaluates research foci, benchmarks for success, and investment opportunities for 3–5 years into the future," and that these strategic plans "should specify the mission of the program, coordination activities with other organizations, research priorities, how those priorities will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives."

In response to these recommendations, this document presents the current strategy for the CDMRP's Lung Cancer Research Program (LCRP). The LCRP Strategic Plan identifies the high-impact research goals 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 greater clarity of the program's goals over time to the public and other stakeholders. 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 most common cancer worldwide for both men and women and accounts for 25% of all cancer deaths.[2] More than 234,000 people in the United States will be diagnosed with lung cancer this year, and almost 155,000 American lives are lost each year.[3] In addition, more than 33,000 women will be under the age of 65 when first diagnosed, and more than 1,700 of these women will be younger than 45.[3] 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.[3] Of all new lung cancer diagnoses, 60-65% are among people who have never smoked or are former smokers. Despite improved screening methods for lung cancer and advances in treatment, the 5-year survival rate is only 18%. Lung cancer is a global problem that struggles from limited availability of research dollars and research resources. An increase in research investments would significantly help efforts to improve detection, treatment, management, and prevention and, ultimately, find 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: 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 the Institute of Medicine (IOM) recommendations[4] to the Department of Defense (DoD) 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-tiered peer review system is used where 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 the excellent applications that best meet the programmatic goals.

The IOM also recommended that consumers (disease survivors) should be included as members of the panel conducting the programmatic review. The LCRP has adhered to this guidance, and consumers also participate on the peer review panels.

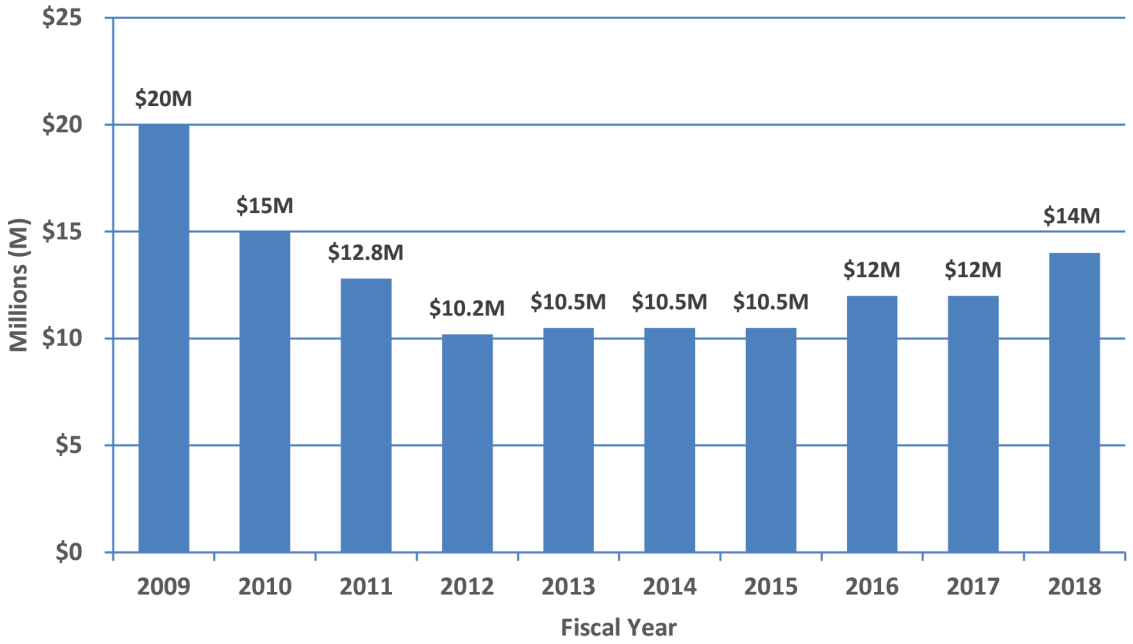
In addition, the IOM recommended that "the best way to ensure that only first-rate research is funded is not to target specific disciplinary areas but, rather, to create a structure that allows the best ideas to emerge from all disciplines." The IOM further recommended to "encourage innovative ideas 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 10-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 2018, totaling $127.5 million since inception. From FY09-FY17, the program has supported over 200 awards. An additional 29 awards are anticipated for FY18, depending on the quality and budgets of the recommended applications.

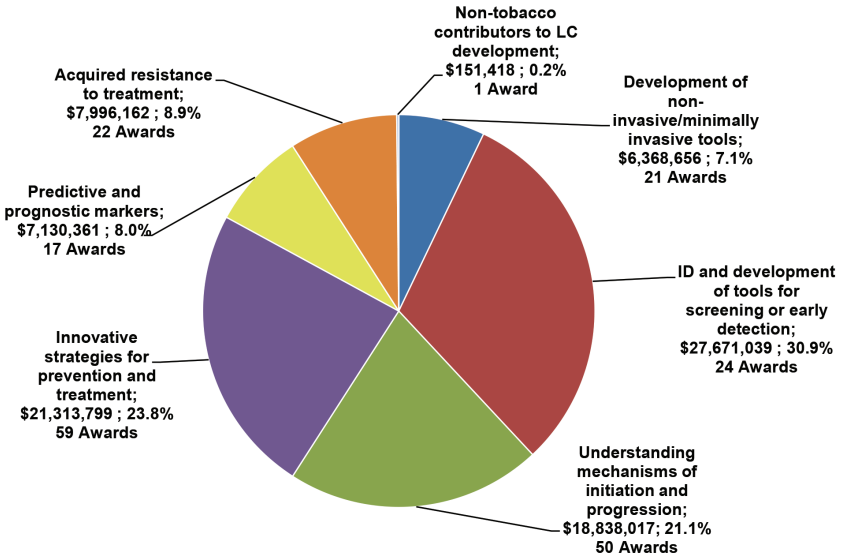


RESEARCH PORTFOLIO

When the LCRP was first established in FY09, the Programmatic Panel developed 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 FY16, the panel introduced a new area of emphasis concerning contributors to lung cancer other than tobacco and consolidated two other areas of emphasis, resulting in the following:

- Development of non-invasive/minimally invasive tools to improve detection
- Development or improvement of tools for screening or early detection
- Understanding mechanisms of initiation and progression to clinically significant lung cancer
- Innovative strategies for prevention and treatment
- Predictive and prognostic markers of responders versus non-responders
- Treatment susceptibility or resistance
- Understanding contributors to lung cancer development other than tobacco

The following pie chart displays the LCRP portfolio from FY09-FY16, 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-FY16)
Total Investment: $89.5M; Total Awards: 194

RESEARCH ACCOMPLISHMENTS

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

- Immunotherapy treatment with mesothelin-targeted CAR (chimeric antigen receptor) T cells is being tested in phase I clinical trials in multiple cancers, including lung cancer.
- Determination that defective apoptosis plays a large role in the emergence of resistance in lung cancer, leading to phase I clinical trial (NCT02520778) testing of a combination therapy of an apoptotic stimulator with a targeted therapy in lung cancer.
- In vivo demonstration that inhibition of focal adhesion kinase (FAK) specifically inhibits high-grade lung cancer, leading to clinical testing of the FAK inhibitor defactinib in non-small cell lung cancer (NSCLC) patients harboring KRAS mutations.
- 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, and 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 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.[5, 6, 7] The risk of developing lung cancer with tobacco smoking is dose-dependent and increases markedly according to the number of cigarettes/cigars/pipes smoked per day and the number of years smoked. Other risk factors for lung cancer include secondhand smoke,[8] family history,[9] HIV infection,[10] environmental risk factors (exposure to air pollution, radon, asbestos, arsenic, chromium, nickel, beryllium, cadmium, tar, and soot),[11] and beta carotene supplements in heavy smokers.[12] 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% of lung cancer cases occur in never-smokers,[3, 13] and 60%-65% of all new lung cancer cases are diagnosed in people who have never smoked or are former smokers.[3, 14] Based on this information, questions raised 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.[15] 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.[15] 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?

Gaining greater knowledge of the molecular biology and genomic landscape of lung cancer will lead to much 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] Currently 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.

Currently, 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.[16] The caveat to the reduction in mortality using LDCT screening is the high rate of false positives (96.4% of positive screening results), which result in unnecessary follow-ups and thus place burdens on the health care system and the individual. Therefore, there is a significant need to develop other detection methods to use together with or prior to LDCT screening to maximize the benefits of using 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-born 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.[17, 18] 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.[3] 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%.[19]

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.[20] The better prognosis when treated with targeted therapies has only been observed in the advanced disease setting[21]; 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 the development of 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.[22] Other types of immunotherapy currently being explored include adoptive T cell transfer, e.g., chimeric antigen receptors (CAR) T-cell therapy, and therapeutic cancer vaccines with clinical trials that are currently being conducted in lung cancer patients.[23] 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 also need to be made 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.

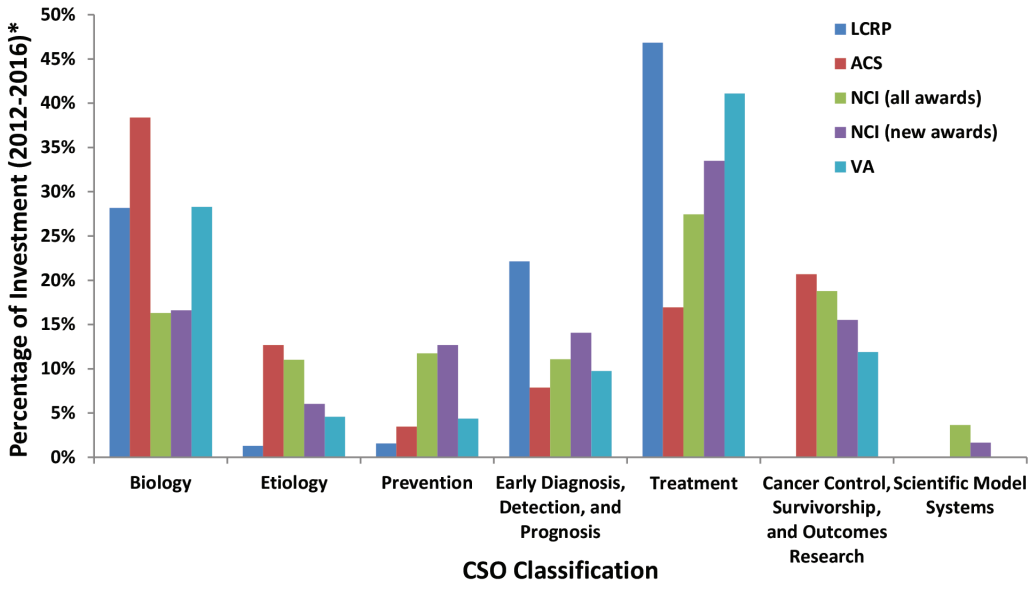
Every year, the LCRP analyzes the: (1) dollar investments and (2) research portfolios of the major lung cancer research funding organizations. The table at right provides data on lung cancer research funding provided by ICRP partners (the LCRP, National Cancer Institute [NCI], and American Cancer Society) and the VA from 2012-2016.

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, whereas the NCI invests about 14% of its funds in new awards, with the remaining funds supporting the out-years of existing continuing awards.

Funding Organization	Dollars Invested
LCRP	$46,248,255
NCI (all awards)*	$1,084,975,753
NCI (new awards)*	$153,913,430
VA	$24,497,346
American Cancer Society	$26,469,988

** NCI funding information for 2016 was not available; data shown are for 2012-2015.*

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



** NCI funding information for 2016 was not available; data shown are for 2012-2015.*
***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 in three: Biology (28%); Early Detection, Diagnosis, and Prognosis (22%); and Treatment (47%). 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) in all research areas, with Treatment (33%) receiving the most funding; followed by almost equivalent funding amounts for Biology and Cancer Control, Survivorship, and Outcomes Research; essentially equivalent amounts for Prevention and Early Detection; and the least for Etiology.

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 NIH, VA, CDMRP and other DoD 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 unanswered research questions that are potentially critical to advancing prevention, detection, treatments, and cures for lung cancer. In studying these unanswered research 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 forward for 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 interested in 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 and are currently working in other areas in 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 get early investigators and early ideas off the ground and capable of transitioning to larger studies and funding opportunities.

STRATEGIC GOALS/PRIORITIES

The LCRP seeks to invest in its priorities (base on its areas of interest); however, we enable investigators to propose their best ideas and are interested in furthering high-impact, innovative lung cancer research by focusing 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; for each priority, the program will focus on specific goals to address these priorities:

- Support research toward understanding the molecular mechanisms of the development of clinically significant 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

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
  - 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 areas leading to clinical research studies or clinical trials
  - 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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