LUNG CANCER RESEARCH FOUNDATION
Living. Breathing. Science.®

INVESTING IN THE FUTURE OF RESEARCH

LCRF's mission: to improve lung cancer outcomes by funding research for the **prevention, diagnosis, treatment,** and **cure** of lung cancer.

Photo: Nikhil Joshi, PhD, Yale University
2014, 2017 & 2021 LCRF Grantee
Two-time Scientific Merit Awardee

"LCRF funding was instrumental in allowing me to complete and publish the project I was working on at the time. The project has fostered cross-institutional collaborations and a clinical trial. It provided support at a critical juncture so I can continue doing research. Now it serves as a springboard for me to compete for Federal funding with the results and publications I generated."

Victoria Wang, MD, PhD
University of California, San Francisco
Two-time LCRF grantee

The Lung Cancer Research Foundation (LCRF) is the leading nonprofit organization focused on funding innovative, high-reward research with the potential to extend survival and improve quality of life for people with lung cancer. We are committed to backing novel lung cancer research that might otherwise go unfunded. To date, LCRF has funded 409 research grants, totaling over $42 million.

Through its Scientific Grant Program, LCRF funds projects across the spectrum of basic, clinical and translational research, including work that addresses disparities, early detection, novel treatments, resistance, and more. LCRF provides critical seed funding to investigators, helping establish proof of concept evidence to pave the way for additional funding from government and other sources.

Learn more about the research LCRF is currently funding: LCRF.org/currentgrants

EARLY DETECTION AND SCREENING

MICHAEL ZIMMERMANN, PhD

European Molecular Biology Laboratory

Identifying risk factors for lung cancer predisposition through systematic evaluation of environmental carcinogens' activation by the respiratory tract microbiota

2020 James B. Dougherty, MD Award for Scientific Merit

The human body harbors trillions of microbes (known as the human microbiome), which collectively encode many more genes than the human genome. These microbial communities colonizing different body surfaces play an essential role in human health and response to environmental factors. Numerous studies have linked changes in the microbiota composition to different diseases, such as the metabolic syndrome and cancer. Based on these observations and the fact that lung cancer prevalence was linked to altered respiratory tract microbiome compositions, Dr. ZImmermann hypothesizes that microbial strains with certain metabolic traits can be identified as predisposition risk factors for lung cancer.

WILLIAM LOCKWOOD, PhD

British Columbia Cancer Agency

SNF2 Histone Linker PHD RING Helicase as a novel tumor suppressor gene and risk factor in lung adenocarcinoma development

Through genetic analysis of lung tumors, Dr. Lockwood's group has recently uncovered the mutation of a gene that is located in a region linked to familial risk of lung cancer development. This gene is known to play a role in repairing damaged DNA, and he hypothesizes that its inactivation leads to increased gene mutations over time, increasing the risk of developing cancer. To test this, he will disrupt the gene in normal lung cells to determine if this allows them to transform into lung cancer. This study will determine whether this gene is associated with lung cancer susceptibility and development, and how this information can be used to improve screening aimed at the early detection of lung cancer in high risk patients.

HILARY ROBBINS, PhD, MPH

International Agency for Research on Cancer

Risk prediction models to ensure equitable eligibility for lung cancer screening in minority populations

2020 William C. Rippe Award for Distinguished Research in Lung Cancer

Screening by low-dose CT (LDCT) can reduce lung cancer mortality, but research has largely neglected racial and ethnic minorities. Criteria for defining screening eligibility fail to acknowledge how lung cancer risk varies across racial and ethnic groups. This means a white individual and an African-American individual might have the same lung cancer risk, but only the white person might meet current guidelines for screening. The most promising solution is to base eligibility on individual risk calculated using a prediction model, but such models must be properly calibrated to perform just as well in racial/ethnic minorities as among whites. This study aims to develop lung cancer risk prediction tools so screening eligibility can be defined in a way that is fully equitable across racial and ethnic groups.

ARIA VAISHNAVA, PhD

University of Utah

Elucidating the molecular mechanisms of radon-induced lung cancer through a novel mouse model

Chronic exposure to inhaled radon gas is estimated to cause 21,000 lung cancer deaths in the US annually, making it the second leading cause of lung cancer and the leading cause of lung cancer in never smokers (LCINS). Despite this, the precise molecular, cellular and genetic changes that occur in the lung epithelium following chronic radon exposure to environmentally-relevant levels of radon gas are poorly characterized. Moreover, there are no reliable ways to identify radon-induced lung cancer in patients. To address this critical knowledge gap, Dr. Vaishnava plans to develop genetically engineered and human patient-derived mouse models that will enable direct assessment of the molecular, cellular and genetic changes that occur in the lung following chronic exposure to environmentally relevant levels of radon. The findings may be used to identify human lung cancer patients that harbor radon-induced disease in the clinic. An improved understanding of the molecular mechanisms that drive radon-induced lung cancer may result in new or improved therapeutic strategies in this poorly understood disease..

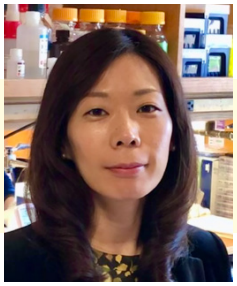
TARGETED THERAPIES

YANG TIAN, PhD
Icahn School of Medicine at Mount Sinai

Targeting lung lineage plasticity to suppress Osimertinib-induced drug-tolerant persisters

2021 LCRF-EGFR Resisters Grant

Genomic discoveries of driver-gene alterations in lung cancer have led to development of effective target therapeutics, but patients who initially respond to the therapy inevitably experience regrowth of the disease. The reversible drug-tolerant persister (DTP) stage, where cells enter a quiescence to ensure survival, is gaining attention as a major source of non-genetic drug resistance. Dr Tian's study seeks to prevent DTP development by targeting the origin of plasticity, thereby avoiding relapse under osimertinib treatment. Preliminary data showed osimertinib-induced DTP cells exhibited increased heterogeneity, and HOPX, a lineage factor important for lung development and differentiation potential, significantly increased at early DTP stage and is necessary for DTP cell survival. Dr. Tian's findings should reveal epigenetic mechanisms by which cancer cells undergo drug resistance transformation and help develop novel therapeutic strategies to manipulate the activity of critical lineage factors during lung regeneration for patients with minimal residual disease and relapse after osimertinib treatment.



HIDEKO ISOZAKI, PhD
Massachusetts General Hospital

Targeting APOBEC3A induction as a new therapeutic strategy to prevent acquired drug resistance in non-small cell lung cancer

The development of therapies that target oncogenic driver mutations has transformed the treatment of lung cancer. Despite notable progress in the design of successive generations of drugs with more potent activity and improved side-effect profiles, the inevitable development of acquired drug resistance continues to limit the clinical efficacy of these agents. Thus, there remains an urgent need for innovative therapeutic approaches to combat drug resistance. This project will test the hypothesis that preventing APOBEC-driven evolution of cancer cells treated with targeted therapies will prevent the development of acquired drug resistance.

ANTJA-VOY HARTLEY, PhD
Dana-Farber Cancer Institute

Overcoming tumor recurrence and therapeutic resistance in EGFR-mutant non-small cell lung cancers

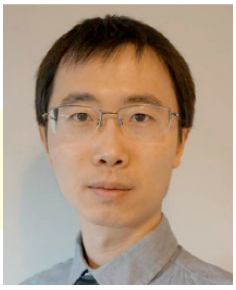
Osimertinib is an effective drug for treating mutant epidermal growth factor receptor (EGFR) non-small cell lung cancers. Many patients respond favorably, but one huge barrier to a cure remains: not all the tumor cells are eradicated. The remaining cells, dubbed "persisters", behave quite differently from typical fast-growing tumor cells. First, they adopt a unique state of dormancy (i.e negligible growth) and second, they depend on the YAP/TEAD cancer signaling pathway as a means of escaping death and surviving lethal exposure to osimertinib. Once the drug is removed, these changes are reversible and the "persisters" can quickly regrow to repopulate the tumor and give rise to osimertinib resistance. In her research, Dr. Hartley will investigate exactly which type of epigenetic changes are responsible for activating YAP/TEAD signaling in "persisters" following treatment with osimertinib. This knowledge will allow clinicians to identify patients that harbor these "epigenetic marks" and correlate them to the frequency at which we see more activated YAP signaling in tumor cells.

JUSTIN JEE, MD, PhD
Memorial Sloan Kettering Cancer Center

Subclone capture sequencing to guide combination therapy and improve osimertinib response

Therapies such as osimertinib target specific tumor mutations found through DNA sequencing. Matching patients to targeted therapies based on tumor DNA lowers mortality and morbidity and has transformed the treatment of lung cancer. However, resistance to even the best targeted therapies is inevitable, often because a small minority of cells with mutations not covered by the initial targeted therapy emerges to drive tumor growth. These secondary mutant populations are nearly impossible to detect early in disease using standard approaches. This project will use newer, more sensitive DNA sequencing technology and sampling from multiple tumor areas so patients can be treated with combinations of therapies in the front-line setting based on their more detailed DNA profile, allowing for earlier, more stable disease control.

IMMUNOTHERAPY & COMBINATION THERAPIES



LINGTAO JIN, PhD
University of Texas Health Science Center at San Antonio

Targeting tumor-immune microenvironment to improve durvalumab efficacy in SCLC

Small cell lung cancer – around 15% of lung cancer cases – is the most aggressive subtype of lung cancer with a five-year survival rate of less than 5%. The results of numerous clinical trials have been disappointing and treatment options have not had the same progress as NSCLC. Anti-PD-L1 immunotherapy recently received FDA approval as a first line therapy for SCLC – the first new treatment strategy in three decades. Compared with chemotherapy alone, however, adding anti-PD-L1 therapy only moderately extends patient survival, highlighting the unmet need for more effective combination therapies. Dr. Jin's lab explored the role of tumor-derived exosomes in suppressing anti-tumor immunity. These tumor-derived exosomes contain a large quantity of lipids, which can compromise the function of dendritic cells. The lab will further evaluate whether blocking tumor-derived exosome-induced dendritic cell suppression could be used to boost anti-tumor immunity and improve the efficacy of durvalumab in SCLC.

MARJORY CHARLOT, MD, MPH
University of North Carolina

Understanding the immune landscape of non-small cell lung cancer in African Americans

In the United States, 18% more deaths occur among Black men with lung cancer compared to White men with lung cancer. While recent advances in the treatment of lung cancer have led to significant improvements in survival, Black patients are less likely to be invited to participate in cancer research and as a result are less likely to have access to state-of-the art cancer treatments. Having a better understanding of lung cancer that includes the Black population and identifying opportunities to engage Black patients in research will likely help to reduce excess lung cancer deaths experienced by Black men. This project will study the immune landscape in tumor samples obtained from Black patients with lung cancer as well as strategies to enhance participation of Black patients with lung cancer in cancer research.

NIKHIL JOSHI, PhD
Yale University

Manipulating the functions of T cells in lung tumor draining lymph nodes

2021 James B. Dougherty, MD Award for Scientific Merit

Immunotherapy has changed the face of lung cancer treatment over the last decade, but the fraction of lung cancer patients that benefit from immunotherapy remains low. Immunotherapies require T-lymphocytes inside of tumors to kill tumor cells, but in many patients these T-lymphocytes are not present. Dr. Joshi and his team have used animal models and analysis of patient samples to discover that there are also tumor-killing T-lymphocytes located in lymph node glands, but why these cells do not respond to therapy remains unknown. In their LCRF-funded project, Dr. Joshi and his team will test strategies for (1) helping immunotherapy make T-lymphocytes leave the lymph node and to travel into the tumor and (2) making T-lymphocytes more effective once they enter the tumor. The goal of this research is to improve therapy in animal models with a cancer that mirrors the disease that is found in lung cancer patients, so that the findings will be as applicable as possible to the therapies that are used in the clinic.

JOSHUA VEATCH, MD, PhD
Vanderbilt University

Using CD4+ T cells to target the tumor microenvironment in non-small cell lung cancer

"Helper" CD4 T cells coordinate the functions of other immune cells and are important for responses to immune therapies like PD-1 inhibitors in mouse models, but their functions in lung cancer are not well understood. We have recently found that we can identify the subset of CD4 T cells in melanoma patients that are specific for tumors based on a unique signature, and that the presence of these cells correlates with the activation of other immune cells like "Killer" CD8 T cells and macrophages. CD4 T cells with a similar signature exist in lung cancer, and we propose to see whether these cells are also specific for the tumor and whether they correlate with greater immune activation. The eventual goal is to use CD4 T cells targeting tumor antigens as a tool to activate immune cells within lung cancer to enhance other immune therapies including PD-1 inhibitors.