LUNG CANCER RESEARCH FOUNDATION

RESEARCH GRANTS AWARDED IN 2024

LEADING EDGE RESEARCH

LINDSAY LAFAVE, PHD
Albert Einstein College of Medicine

Investigating chromatin-mediated mechanisms of immune response in lung cancer

2024 William C. Rippe Award for Distinguished Research in Lung Cancer

This research focuses on understanding how lung adenocarcinoma, particularly in smokers, develops and progresses. By investigating how chronic inflammation and immune responses drive cancer development and affect treatment outcomes, the project aims to improve current therapies and develop new strategies, benefiting both smokers and non-smokers with lung cancer. This could lead to new therapeutic rationales for both smokers and non-smokers.

DIAN YANG, PHD
Columbia University
Irving Medical Center

Investigating the molecular basis of cancer plasticity in LKB1-mutant lung adenocarcinoma

2024 James B. Dougherty, MD Award for Scientific Merit

This project aims to understand how aggressive lung adenocarcinomas develop and how they adapt to treatment. LKB1-deficient tumors are a type of lung cancer that can adapt and resist treatment through a process called cell plasticity, in which cancer cells switch states to survive challenges. Investigators will explore how LKB1-deficient tumors influence this plasticity, focusing on a stage called the pre-EMT state, which may drive disease progression and drug resistance. With advanced mouse models that mimic human tumors, the study aims to uncover the unique genetic mechanisms behind LKB1-deficient tumors. This information could lead to new therapeutic strategies to target these aggressive tumors.

UNDERSTANDING RESISTANCE

MEGAN BURGER, PHD
Oregon Health & Science University

Optimizing immunotherapy sequencing to overcome resistance

This project aims to enhance cancer immunotherapy by combining immune checkpoint blockade (ICB) therapy with cancer vaccines to overcome resistance and extend the benefits of treatment to more patients. Using a mouse model of lung adenocarcinoma, the study will explore how these therapies work together, optimizing vaccine dosing and timing relative to ICB treatment for maximum effectiveness. The findings could inform clinical trials, improve response rates, prevent disease recurrence, and ultimately lead to better outcomes for lung cancer patients.

WILLIAM FENG, PHD
Dana-Farber Cancer Institute

Targeting AP-1 in KRAS-mutant lung cancer

This research explores a potential weakness in lung cancer by targeting AP-1, a group of transcription factors that act as an “on/off switch” for genes essential to cancer cell survival. Previous studies show that EGFR-mutant lung cancers rely on AP-1 for resistance to therapies, and this study investigates whether KRAS-mutant lung cancers do the same. The project will evaluate AP-1 as a drug target, test whether inhibiting it can effectively treat KRAS-mutant lung cancers and develop a new drug to block AP-1 function. This work could lead to groundbreaking therapies for currently untreatable lung cancers.

EARLY DETECTION & PRE-NEOPLASIA

PEGGY HSU, MD, PHD
University of Michigan

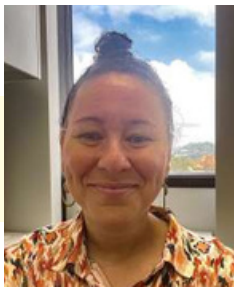
Understanding the origin of ALK-driven lung cancer

ALK-positive lung cancer, often affecting non-smokers and diagnosed at advanced stages, has unclear origins. This research aims to uncover the earliest events driving ALK-driven lung cancer using advanced single-cell technologies. By studying patient samples, lung organoids, and mouse models, the team will map how ALK activation leads to tumor initiation. The findings could reveal novel molecular features, enhance our understanding of cancer cell plasticity, and pave the way for earlier detection and prevention strategies, improving survival rates for ALK+ lung cancer patients.

> *I was once a young investigator who received seed funding through LCRF. Funding young investigators is key to keeping the smartest people in the field and coming up with new ideas of tomorrow."*
>
> *Lecia Sequist, MD*
> *Massachusetts General Hospital Cancer Center*
> *Harvard Medical School*
> 2010 *LCRF Grantee*

MINORITY CAREER DEVELOPMENT AWARDEES

TIKVAH HAYES, PHD
David Geffen School of Medicine, UCLA



Advancing preclinical cell line diversity and decoding TKI-resistance landscapes in EGFR-mutant lung cancer

2024 Cynthia M. Page Merit Award

Treatment resistance remains a major challenge for patients with EGFR-mutant lung cancer. This project aims to shed light on how different mutations in EGFR affect cellular biology and response to treatment. The team will develop new models to study understudied mutations and use advanced genetic techniques to identify mutations that cause resistance to current therapies. By uncovering these mechanisms, the study could lead to better treatments and improved outcomes for patients with EGFR-mutant lung cancer, advancing the field of lung cancer research.

LUISA ESCOBAR-HOYOS, MSC, PHD
Yale University

Altered RNA splicing as a driver of Osimertinib resistance in lung cancer

Resistance to Osimertinib is a significant challenge with 40-50% of cases lacking a clear genetic cause. This project will investigate whether alternative pre-mRNA splicing (AS) – a process where cells alter RNA to change protein production – might explain this resistance. Lung cancers are known to have widespread changes in AS compared to healthy tissue, suggesting it could play a role. This research will explore how AS differs in resistant vs. sensitive cancers and test whether blocking AS with a drug can restore sensitivity to Osimertinib, potentially leading to new treatment strategies for resistant lung cancers.

View all current funded research projects: **LCRF.org/currentgrants**
For further information about our research grant program, contact: **grants@LCRF.org**

TEAM SCIENCE AWARD

IASLC/LCRF Team Science Award on Advancing Therapies Towards Curing Oncogene-Driven Lung Cancers

Immune elimination of drug tolerant persister cells in oncogene-driven lung cancer

Lung cancer remains one of the deadliest cancers worldwide, particularly in its advanced stages. Metastatic non-small cell lung cancer (NSCLC) patients face poor prognoses despite recent advances in targeted therapies against EGFR, ALK, and KRAS mutations. These therapies, although initially effective, often lead to relapse driven by drug-tolerant persister (DTP) cells that develop resistance. This research aims to tackle this critical challenge, focusing on innovative immune-based strategies to eradicate these persistent cells and improve patient outcomes.

The project is aimed at exploiting vulnerabilities in DTP cells leveraging activating the innate immune programs and targeting of cell surface markers making them susceptible to immune attack. By leveraging the team's expertise in patient-derived models, targeted therapy, and immunotherapy, the project will take a multi-faceted approach to target DTP cells, utilizing cutting-edge CAR T-cell therapy and modulation of the tumor microenvironment (TME).

Project 1: Co-opting innate immunity to eliminate drug tolerant persister cells

Project 1 aims to co-opt innate immunity by inhibiting TREX1, a negative regulator of STING-IFN signaling, to enhance immune response against DTP cells. Preliminary data suggest that TREX1 inhibition can unleash a potent antiviral response, making DTP cells vulnerable to immune attack. By targeting this pathway, we hope to stimulate a robust immune response capable of eliminating these resistant cells.

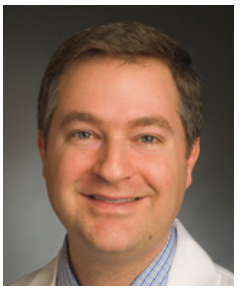
Project 2: Enhancing CAR T cells to eliminate drug tolerant persister cells

Project 2 focuses on enhancing CAR T cellular therapy to specifically target DTP cells in EGFR mutant NSCLC. While traditional CAR T therapies face challenges in solid tumors due to off-target toxicity and poor Tcell infiltration, the team's approach incorporates a novel strategies to address and overcome both these limitations.

This research is poised to make significant strides in the treatment of metastatic NSCLC. The success of this project could rapidly translate into first-in-human clinical trials, offering new hope for patients who have exhausted other treatment options. The team has a track record of working collaboratively, as well as translating discoveries from lab into clinical trials which have led to improved the lives of patients by offering more effective and less toxic therapies. By advancing our understanding and ability to combat DTP cells, we aspire to turn the tide against this resilient form of cancer and pave the way for more effective, long-lasting treatments.

DAVID A. BARBIE, MD

Dana-Farber Cancer Insititute
Lead Investigator



AARON HATA, MD, PHD

Massachusetts General Hospital

ERIC SMITH, MD, PHD

Dana-Farber Cancer Institute

PASI JÄNNE, MD, PHD

Dana-Farber Cancer Institute

SHUNSUKE KITAJIMA, PHD

Japanese Foundation for Cancer Research