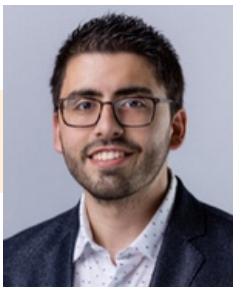
RESEARCH GRANTS AWARDED IN 2023

LEADING EDGE RESEARCH

FRANCISCO EXPÓSITO, PHD
Yale University



Investigating novel synthetic lethal vulnerabilities in EGFR-driven lung cancer

2023 William C. Rippe Award for Distinguished Research in Lung Cancer

This project aims to understand how the loss of SETD2 hinders EGFR-driven tumor growth to leverage these findings to create new precision treatments for the treatment of patients with EGFR-mutant tumors.

BENJAMIN MORRIS, PHD
University of Texas M.D. Anderson Cancer Center

Deep whole genome sequencing of circulating tumor DNA for studying evolution and therapy resistance in small cell lung cancer

This project will use cancer DNA collected from small blood draws to study how SCLC evolves following treatment and identify changes in cancer DNA and gene expression that drive resistance. The study will determine if resistant tumors are composed of one population of resistant cells or if multiple, hard to treat populations emerge after treatment to drive resistance.

UNDERSTANDING RESISTANCE

TREVER G. BIVONA, MD, PHD
University of California San Francisco

Characterization and therapeutic targeting of a tumor-tumor microenvironment network promoting resistance to targeted therapy in lung cancer

The overall goal of this project is to create an entirely new approach to treat lung cancer by developing a suite of precision therapies that are distinct in their mechanism of action against the tumor ecosystem and improve the effectiveness of current therapies against mutant EGFR, KRAS, and ALK as combination therapies, while critically maintaining safety and quality of life for patients. The work accomplished in this project could yield molecular treatments that better control, or potentially cure, lung cancer safely through improved precision medicine in the relatively near future.

ANN PENDERGAST, PHD
Duke University School of Medicine

Uncovering novel vulnerabilities to treat SCLC therapy resistance

Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine lung cancer that is typically metastatic upon diagnosis.The overall 5-year survival rate for SCLC patients is only ~7%, and has remained unchanged for over 30 years. Therefore, there is an urgent need to define the molecular mechanisms that promote metastatic SCLC in order to identify effective treatment strategies to treat this deadly cancer. The Pendergast laboratory recently found that pharmacologic inhibition of ABL kinases with ABL-specific inhibitors impairs SCLC metastasis in mouse models, resulting in prolonged animal survival. This proposal will evaluate whether ABL kinase inhibition sensitizes SCLC to therapies targeting stress response pathways, and/or to metabolic inhibitors.

ANTIBODY DRUG CONJUGATES

AAKASH DESAI, MD, MPH
University of Alabama at Birmingham

Deciphering the ADC code: a proteogenomic quest in lung cancer

This research project aims to improve the treatment of non-small cell lung cancer (NSCLC) using a special kind of therapy called Antibody-drug conjugates (ADCs). These therapies are designed to target cancer cells more precisely. However, it's not fully understood why some patients respond better to these treatments than others. The focus of this project is to study a particular target on cancer cells, known as Trop-2, and to figure out how its presence or absence affects the success of the therapy. By examining the characteristics of cancer cells and their surrounding environment in great detail, the project hopes to find out which patients are more likely to benefit from ADCs. This could lead to more personalized and effective treatments for lung cancer.

NAN SETHAKORN, MD, PHD
Loyola University of Chicago

Leveraging liquid biopsy to identify the optimal clinical niche for Trop2-targeting in NSCLC

A new class of treatments in lung cancer are antibody-drug conjugates (ADCs) that work by detecting proteins on cancer cells. One target is Trop2, a protein found in many cancer cells. Trop2-ADCs show promising anti-tumor activity, but treatments often stop working, or do not work in everyone. Often, as patients receive treatments, their tumors develop changes that allow them to adapt, but often it is difficult to get a sample. New technologies that can analyze tumor cells circulating in blood are thus a way to obtain a "liquid biopsy" through a simple blood draw. This project will study three markers: Trop2, PD-L1, and schlafen-11, in circulating tumor cells, and may identify patients who may benefit from Trop2-ADCs either alone or in combination with currently existing immunotherapy.

CARL GAY, MD, PHD
University of Texas M.D. Anderson Cancer Center

Pulmonary high-grade neuroendocrine carcinomas as indications for ADCs targeting TROP2 and HER2

Small cell lung cancer (SCLC) and large-cell neuroendocrine carcinoma (LCNEC) are similarly aggressive lung cancers with poor prognosis due, in part, to limited personalized treatment options. Preliminary data demonstrate that TROP2 and HER2 are viable targets for treatment of these malignancies if the correct patients are selected. Antibody-drug conjugates targeting TROP2 and HER2 rely upon both expression of the antibody's target and sensitivity to the drug to which the antibody is conjugated – each of which is heterogeneous in SCLC and LCNEC. This project highlights a strategy to delineate the precise patient population to which to apply these agents making use of an unparalleled collection of patient samples and patient-derived models for validation.

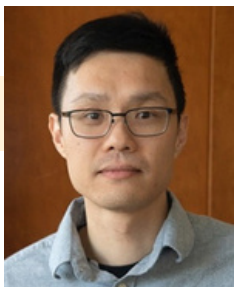
> *I was once a young investigator who received seed funding through LCRF. Funding young investigators is key to keeping the smartest people in the field and coming up with new ideas of tomorrow."*

Lecia Sequist, MD
Massachusetts General Hospital Cancer Center
Harvard Medical School
2010 *LCRF Grantee*

EARLY DETECTION & PRE-NEOPLASIA

DARREN CHIU, MD, MMSC
Boston University

The spatial B cell landscape in lung squamous premalignant lesions



Bronchial premalignant lesions (PMLs) develop in the airway from cellular and molecular changes, and they are precursor lesions of lung squamous cell carcinoma. While some PMLs progress to cancer, some of them regress spontaneously or remain stable. The presence and distribution of B cells in lung cancer has been associated with prognosis and survival, however, the role of B cells in the lung premalignancy is poorly understood. Using single cell sequencing technology and multiplex multiomic imaging, the study will identify B cell subpopulations in bronchial PMLs and characterize the spatial microenvironment that recruits and modulates B cells associated with PMLs severity and progression. The findings are expected to reveal new biomarkers for early diagnosis or interception of lung cancer.

> *"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*

MINORITY CAREER DEVELOPMENT AWARDEES

LLOYD BOD, PHD
Massachusetts General Hospital

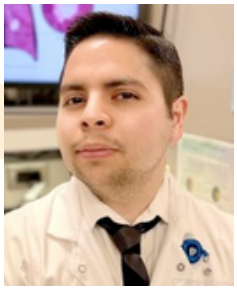
Harnessing B cell specific checkpoint molecules in lung cancer

2023 James B. Dougherty, MD Award for Scientific Merit

Immunotherapy has transformed the paradigm of lung cancer treatment, yet its efficacy remains restricted, benefiting only a minority of patients—typically, two to four individuals out of every ten. Dr. Bod's research focuses on unraveling the functions of B cells, a critical component of the immune system. These cells are abundant in lung tissue and hold the capacity to assist T cells in their anti-cancer activities while directly combatting cancer cells themselves. This translational project's objective is to leverage genomics to identify and assess new molecules present on B cells, which could serve as innovative immunotherapy targets, thereby paving the way for new therapeutic strategies in lung cancer.

LUIS PIETRO, PHD
Mayo Clinic

Impact of senescent cells on lung tumorigenesis



This study focuses on naturally occurring senescent (aging) cells to determine if they promote late-life development of lung cancer. Aging cells accumulate and promote the development of lung tumors by suppressing immune T cells. The next step will be to use treatments aimed at killing senescent cells to see if this effects the formation and/or growth of tumors.

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