Award ID:
RP160652

Project Title:
Defining and Defeating Mechanistic Subtypes of KRAS-mutant Lung Cancers

Award Mechanism:
Multi-Investigator Research Awards (Version 2)

Principal Investigator:
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Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Lung cancer is the primary cause of cancer-related death worldwide. Underlying this problem, conventional chemotherapies and radiation therapy are frequently ineffective once lung cancer has spread from the lung to other parts of the body in a process called metastasis. Newer therapies have begun to make inroads into this problem based on the discovery that lung cancer cells become “addicted” to alterations (“mutations”) in genes that cause a normal lung cell to become a cancer cell. For example, mutations in genes called EGFR and ALK found in lung cancer dramatically respond to erlotinib and crizotinib, drugs that directly target EGFR and ALK, respectively, and prolong survival in lung cancer patients with those mutations.

However, some genetic alterations important in lung cancer development have been more difficult to treat. For example, a gene called KRAS is mutated approximately 10 times more frequently than EGFR, but we currently have no approved therapies for tumors with KRAS mutations. Our research group has recently discovered that KRAS mutations are often accompanied by mutations in other genes (“co-mutations”), which can be important in dictating the behavior of KRAS-mutant lung cancers (KMLCs) and controlling processes amenable to therapeutic targeting. Hence, we propose that KMLCs can be effectively treated by targeting vulnerabilities regulated by key co-mutations. This hypothesis forms the basis for this application.

Our MIRA application has 4 projects and 3 cores; our goal in each project is to determine whether the vulnerabilities we have uncovered are specific to single or multiple co-mutations, and to better understand how to target these co-mutations or their sequelae. Findings from each project will be further evaluated for biological impact on preclinical disease models by investigators in the MD Anderson Center for Co-Clinical Trials, a novel translational unit that focuses on advancing projects of therapeutic relevance towards the clinic. We will also validate, at the clinical and pathologic levels, our findings using a lung cancer tissue bank that is fully annotated genetically and clinically, and is the largest available in the United States. In Project 1, we have shown that a co-mutation in a gene called LKB1 controls the ability of KMLCs to survive under cellular stress, a condition that is heightened in cancer, so we will be working to understand how we can inhibit survival responses to stress, thereby killing the KMLCs that have LKB1 co-mutations. In Project 2, we have shown that LKB1 co-mutations cause KMLCs to become particularly sensitive to

conditions of low fatty acids, so we plan to target the production of fatty acids to selectively kill KMLCs with LKB1 co-mutations. In Project 3, we have shown that a co-mutation in a gene called TP53 causes KMLCs to metastasize by increasing PD-L1, which suppresses the immune system's ability to attack tumors, so this project will study if PDL1 might be targeted to inhibit metastasis of KMLCs with TP53 co-mutations. In Project 4, we have shown that a co-mutation in a gene called CDKN1A increases the metastatic ability of KMLCs by increasing the production of an enzyme called lysyl hydroxylase 2 that modifies collagen; we will further explore this novel target to determine its potential for new drug development against KMLCs.

These 4 projects will be carried out by investigators from UT MD Anderson, UT Southwestern Medical Center, and Rice University who have diverse areas of expertise that span cancer genetics, tumor biology, tumor immunology, protein structure, collagen metabolism, genetically engineered mouse models of human cancer, molecular pathology, and medical oncology. They have long-standing productive collaborations through a joint UT Southwestern/MD Anderson Lung Cancer NCI SPORE grant currently in its 16th year of funding. Our comprehensive lung cancer tissue bank is a unique resource that has resulted from these SPORE interactions and will serve to both probe and confirm the clinical relevance of our lab-based findings. All of the four project leaders are physician-scientists actively engaged in both clinical and laboratory research and are capable of rapidly translating findings from the MIRA to the clinic.

Our research team is tightly integrated to maximize the synergistic value of the proposed research studies. Findings from our projects and cores will be mutually informative, spawning ideas that would not be realized from individual projects performed in isolation. Furthermore, data obtained in this MIRA will be made available to the greater scientific community in Texas by creating a publically available database of our preclinical and clinical findings, providing a unique resource for future collaborations between academia and industry that may lead to new therapeutic approaches for lung cancer patients.