CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140216

Project Title:
Context-Specific In Vivo Screening for KRAS-Associated Gene Aberration Drivers Using Genetically Engineered Mouse Models of Lung Cancer

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

A major effort in cancer research is focused on identifying early cancer indicators, or biomarkers, and other genes directly responsible for promoting cancer progression (referred to here as drivers). The identification of oncogenic driver genes and characterization of their biological function has been the moving force behind much of the recent progress in cancer treatment. Nowhere is this need more acute than for lung cancer, a notoriously aggressive disease and leading cause of cancer-related deaths worldwide. The challenge now is to develop efficient means to identify genes directly responsible for lung tumor progression and resistance to cancer therapies. Discovery of such genes is a significant challenge given the large number of cancer gene candidates and the fact that their activity is shaped by each tumor's surrounding cell environment within the lung. To identify such drivers, we propose to develop a novel screening platform that employs (1) our robotics-driven collection of over 32,000 human genes and (2) an innovative strategy that enables rapid modeling of barcoded (i.e., tagged) normal and mutant genes chosen from large-scale mouse and human lung cancer genomics datasets. We will deliver these cancer gene candidates directly to mouse lungs as viruses in a manner that simultaneously activates the KRAS oncogene found in approximately 30% of human lung tumors. Our studies will reveal genes that function with KRAS, thus illuminating targets and activated pathways for new therapies desperately needed by patients with no other effective treatment options since KRAS itself cannot be inhibited by cancer drugs. Once developed, our mouse screening strategy can be applied to other cancer models permitting assignment of disease relevance to thousands of genes with an emphasis on the appropriate cellular, genetic, and microenvironment contexts in which these genes function to expedite their translation into actionable diagnostic and drug development endpoints.