



## CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:  
RP160089

Project Title:  
Carbamoyl Phosphate Synthase-1: A new metabolic liability in non-small cell lung cancers

Award Mechanism:  
Individual Investigator

Principal Investigator:  
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Entity:  
The University of Texas Southwestern Medical Center

### Lay Summary:

Lung cancer is the most common cause of cancer-related deaths worldwide and has been highlighted as an area of priority by CPRIT and the Texas Department of State Health Services. Among the various subtypes of non-small cell lung cancer (NSCLC), tumors with mutations in both the oncogene KRAS and the tumor suppressor LKB1 are particularly aggressive. Because both KRAS and LKB1 regulate energy metabolism at the cellular level, we explored whether cells harboring mutations in these two genes have specific metabolic requirements that could be exploited to kill them selectively. We discovered that KRAS/LKB1 NSCLC cells use an unconventional form of metabolism in which the building blocks for DNA synthesis are produced by an enzyme called carbamoylphosphate synthase-1 (CPS-1). Silencing CPS-1 induces the depletion of DNA precursor pools, excessive levels of DNA damage, and rapid cell death. These effects were only observed in cells containing both KRAS and LKB1 mutations, suggesting that CPS-1 inhibition might provide an effective therapy for this aggressive form of lung cancer. We propose to understand the molecular basis of CPS-1 addiction in cultured KRAS/LKB1 co-mutant cells and to test whether silencing CPS-1 reduces the growth of KRAS/LKB1 co-mutant tumors in mice. We will also explore the relationship between CPS-1 expression and KRAS/LKB1 co-mutation in human NSCLC. Our work will capitalize on a suite of mouse models of cancer and state-of-the-art techniques in the analysis of tumor metabolism. If successful, the work will have a major impact on cancer. First, it will uncover what seems to be a unique pathway of DNA synthesis required to avoid DNA damage and maintain cancer cell proliferation, thereby challenging long-standing paradigms about the mechanisms by which cancer cells produce DNA and other nucleic acids. It will also allow us to directly evaluate a potentially actionable metabolic vulnerability in a particularly aggressive subtype of human NSCLC.