CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170336

Project Title:
Preclinical Analyses of NAD Kinase as a Redox Vulnerability for the Treatment of Pancreatic Cancer.

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

A major effort in cancer research is focused on identifying genes directly responsible for promoting cancer progression (referred to here as “drivers”) that could represent new drug targets. Perhaps nowhere is this need more acute than for pancreatic ductal adenocarcinoma (PDAC), an aggressive disease without durable treatment options. To identify new PDAC drivers, we developed novel technologies to identify genes found in PDAC that promote tumor development. Our approach identified the NAD Kinase (NADK), which is known in other organisms to influence cell growth. Our data indicate that NADK robustly drives PDAC growth, and NADK depletion significantly decreases PDAC growth concomitant with changes in redox state. Work by others has demonstrated the importance of redox pathways such as the glutamine reprogramming pathway (GRP) in PDAC. We hypothesize that interplay between the GRP and NADK centrally influences redox state and PDAC growth. We further hypothesize that inhibiting NADK in patient tumors would selectively kill PDAC cells or sensitize them to chemotherapeutics. In Aim 1 we will use a panel of PDAC cell lines and tumors to genetically evaluate the relative roles of NADK and GRP in influencing redox state and PDAC growth. We will also examine the combined effect of NADK depletion and PDAC chemotherapeutics to determine whether use of NADK inhibitors would synergize to kill PDAC cells. Finally, we will measure NADK protein and oxidative stress on PDAC patient tumors to correlate levels with clinical outcome. In Aim 2 we will evaluate the in vivo role of NADK and therapeutic potential of NADK inhibitors by employing a novel electroporation model that allows rapid and cost-effective NADK expression and depletion in the context of activated KRAS in the mouse pancreas. In addition, we will examine NADK’s role in PDAC development and maintenance of tumor redox state using a genetically engineered mouse model of PDAC harboring a NADK conditional knockout allele.