CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170090

Project Title:
Novel Regulation and Function of TAK1 in Mutant Kras-driven Development of Pancreatic Ductal Adenocarcinoma

Award Mechanism:
Individual Investigator

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

Lay Summary:

Pancreatic cancer (PDAC) is the fourth leading cause of cancer mortality with 46,420 new cases in 2014 in the USA and is projected to surpass breast, prostate, and colorectal cancers as the second leading cause of cancer-related deaths by 2030 (Rahib et al., Cancer Res, 2014). At diagnosis, approximately 80% of PDAC patients have locally an advanced or metastatic disease and a median survival duration of less than 6 months. The 5-year survival rate has remained at 1%-3% for the past 30 years. Therefore, determining an effective drug target for PDAC is one of the greatest challenges in cancer research. Mutant Kras is detected in almost 90% of PDAC cases and is required not only for the initiation of PDAC but also for maintaining the tumorigenic phenotype in mouse models. Because targeting mutant Kras proteins directly with small-molecule inhibitors have so far proved unsuccessful, one of the new ideas is to identify key signaling pathways that function downstream of Kras and inhibiting such signaling pathways may lead to tumor suppression. We previously identified the KrasG12D-induced constitutive activation of NF-?B in PDAC cells and 70% of PDAC patients through a pro-oncogenic kinase TAK1 overexpression. Our recent study demonstrated that NF-?B activation, the signature molecular alteration, is required for mutant Kras to induce PDAC. Therefore, the goal of our proposal is to study TAK1-dependent and -independent signaling pathways. Inhibiting these signaling pathways functioning downstream of by mutant Kras may be an effective strategy for targeting mutated Kras for treating PDAC. To pharmacologically target the key oncogenic kinases such as TAK1, our proposed aim will study the function of TAK1 in maintaining tumorigenic phenotype, and determine whether TAK1 is a potential novel therapeutic target in pre-clinical animal models of PDAC. Our novel findings and innovative approach may identify a therapeutic target and improve survival of pancreatic cancer patients.