CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170721

Project Title:
Enhancing Immunotherapy of Pancreatic Cancer by Disrupting Mutant K-Ras Using CRISPR/Cas9

Award Mechanism:
High Impact/High Risk

Principal Investigator:
Bao, Gang

Entity:
Rice University

Lay Summary:

Pancreatic cancer remains a major clinical challenge claiming more than 40,000 lives yearly in the US. Pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer that accounts for 95% of cases, is excruciatingly resistant to current chemo-radiation therap. Complete surgical removal of the tumor remains the only chance for cure, however 80-90% of PDAC patients are not eligible for curative surgical approaches at the time of clinical presentation. The overall 5-year survival is 5%. Unfortunately, many of the emerging immune-oncology approaches that have shown dramatic effects in certain solid cancers, such as antibodies against immune checkpoint proteins, have been ineffective in treating PDAC. The goal of the proposed research is to enhance immunotherapy by gene disruption thus triggering the tumor suppressive mechanisms and mediating a synergistic highly effective long-term anti-tumor response. This approach is especially valuable for applying immunotherapy for PDAC which is an immune privileged tumor.

To achieve this goal, we will develop a CRISPR/Cas9 based strategy for gene disruption in PDAC cells, and optimize the guide RNA designs to achieve high specificity and efficiency. The optimal CRISPR/Cas9 system will be packaged into protease-activatable viral vectors for in vivo delivery. We will quantify the efficiency of the approach in vivo using a mouse model of PDAC by examining the enhancement of tumor suppression as a result of combination immunotherapy. We have assembled a strong interdisciplinary team with expertise in pancreatic cancer research, cancer immunotherapy, genome editing and viral vector engineering. Success of the project will lead to additional funding from NIH and/or other funding sources, with the potential to significantly reduce morbidity and mortality of this otherwise incurable disease for the majority of PDAC patients.