



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP130189

Project Title:
Development of Therapeutics Targeting Truncated Adenomatous Polyposis Coli (APC) as a Novel Prevention and Intervention Strategy for Colorectal Cancer

Award Mechanism:
Individual Investigator

Principal Investigator:
Shay, Jerry W

Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Colorectal cancer (CRC) is the third leading cause of cancer related mortality in the United States with an estimated 141,000 cases of colon and rectal cancer diagnosed in 2011. Thus, 1 in 19 Americans will be diagnosed with CRC in their lifetime. Despite the enormous burdens placed on the U.S. healthcare system, treatments for CRC is primarily reliant upon chemotherapeutic agents that act with minimal specificity for the underlying genetic basis of disease. The adenomatous polyposis coli (APC) gene is specifically altered in more than 80% of colon tumors. Our proposal seeks to develop a small molecule targeted therapy for the vast majority of CRC patients expressing a truncated APC protein. We have already conducted a high-throughput 200,000 small molecule screen and have identified a small number of compounds that show selective toxicity to human colon cancer cells expressing a truncated APC protein but not normal human colonic epithelial cells. We will develop analogs of our lead compounds and test them both in cell culture and in mice in order to identify those compounds with improved stability that also have favorable characteristics to move forward into clinical trials. As part of these studies, we will conduct an initial assessment of toxicity and pharmacodynamics/pharmacokinetics of our lead compounds. Finally, we will attempt to understand the mechanism of action of these lead compounds. This proposal is a new paradigm in colon cancer research and challenges existing approaches to treating CRC patients. This is an under explored area, with a high degree of relevance to cancer research, and if successful will lead to substantial advances in the field.