CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP160180

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:

Despite the enormous burdens placed on the U.S. healthcare system, treatments for colorectal cancer (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 ~80% of colon tumors. We have developed a small molecule targeted therapy for the vast majority of CRC patients expressing truncated APC proteins. We have conducted a high-throughput 200,000 small molecule screen and identified a lead compound that shows selective toxicity to human CRC cells expressing a truncated APC protein but not normal human colonic epithelial cells. This lead compound reduces tumor burden in mouse models of CRC with no toxicities to normal tissues or cells. We have also shown reduced cancer progression in human CRC cell lines established as xenografts. Importantly, we have recently identified the protein target of this compound. We will now investigate the mechanism of how this compound kills CRC cells while sparing normal cells. Furthermore, we will examine this compound's activity in human tumors introduced orthotopically into mouse models as well as in patient derived primary tumors in xenografts that better recapitulate human CRC. Finally, we will continue to develop analogs of our lead compounds and test them both in cell culture and in mice to identify those compounds with improved stability that also have favorable pharmaceutical characteristics to move forward into clinical trials. Those analogs will serve as a platform for the development of truncated APC CRC targeted non-toxic drugs as a novel strategy for prevention/treatment of colon cancer. This proposal is a new paradigm in an under explored area, challenges existing approaches to treating CRC patients, and if successful will lead to substantial advances in the field