CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180694

Project Title:
TREX2 Inhibitors to Treat BCR-ABL-Cancers

Award Mechanism:
High Impact/High Risk

Principal Investigator:
Hasty, E. Paul

Entity:
The University of Texas Health Science Center at San Antonio

Lay Summary:

BCR-ABL is generated from the improper fusion of two genes. This protein has unregulated activity that can increase genomic mutations and the risk to cancers like leukemia. Tyrosine kinase inhibitors (TKIs) are drugs that effectively treat BCR-ABL-expressing cancers. However, BCR-ABL has a negative influence on DNA repair that leads to genomic mutations and these mutations can cause resistance to TKIs. I propose to test a novel approach to fight TKI resistance that combines the use of TKIs with TREX2 inhibitors (TX2Is), a new class of drugs developed in my lab. I hypothesize that BCR-ABL induces genomic mutations by reducing the capacity of two DNA repair pathways called homologous recombination (HR) and mismatch repair (MMR). Then a third pathway, DNA damage tolerance (DDT) takes over, but this substitute pathway causes mutations that result in TKI resistance. Our preliminary results show that deletion of TREX2, a member of the DDT pathway, reduces mutations in cells defective for HR and MMR and improves the effectiveness of chemotherapeutics. My lab has developed drugs that inhibit TREX2. Therefore, I propose that TX2Is will be an efficacious addition to TKIs to fight cancers that express BCR-ABL.