CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150445

Project Title:
Ewing's sarcoma, a homologous recombination defective disease

Award Mechanism:
Individual Investigator Research Awards for Cancer in Children and Adolescents

Principal Investigator:
Bishop, Alexander

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

Lay Summary:

Ewing's sarcoma occurs in children and young adults. The standard treatment, that effective 70% of the time, is a mixture of toxic chemotherapeutics and surgery. The toxicity in children is a concern since any damaging effects last a lifetime. Further, no successful alternatives exist beyond this first line treatment. Targeted therapy with less toxicity would be a major benefit, but requires a better understanding of Ewing's sarcoma. We discovered that Ewing's sarcoma has a defect in a DNA repair pathway called homologous recombination. This is the same kind of defect found in BRCA1 deficient breast cancer. Those cancers are sensitive to PARP1 inhibitors and so is Ewing's sarcoma. We believe that this opens an opportunity to develop more targeted therapy strategies based on understanding how homologous recombination has been compromised. We examined the genes altered in Ewing's sarcoma, particularly the EWSR1 gene, and found that this gene is also necessary for homologous recombination. Interestingly, the protein made by this gene is involved in RNA transcription, the process of translating the DNA code into RNA, which is then used to make proteins in the cell. If this process is broken in some way, it can cause problems for the machinery that is involved in duplicating the DNA as cell grow and divide. We therefore propose to examine these processes in Ewing's sarcoma and in cells where we deplete EWSR1. If we are correct, then these studies will provide novel insight into Ewing's sarcoma and provide novel therapeutic strategies that are potentially less toxic to the cell. Further, since we know from BRCA1 studies some of the mechanisms that can circumvent a homologous recombination defect we can test if the same are altered in chemoresistant Ewing's sarcoma. Based on this we will test whether there are second line targeted therapies that can take advantage of these secondary changes and make otherwise resistant Ewing's sarcoma sensitive to treatments again.