CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170510

Project Title:
Telomere Maintenance Mechanisms in Neuroblastoma

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

Principal Investigator:
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Entity:
Texas Tech University Health Sciences Center

Lay Summary:

Neuroblastoma is childhood cancer that can spontaneously regress without therapy or relentlessly progress in spite of intensive chemotherapy. For continual cell growth cancer cells must maintain the ends of chromosomes (called telomeres) which erode if not maintained by telomere maintenance mechanisms (TMM). The most common TMM uses an enzyme in cells called telomerase which is capable of adding DNA to the ends of chromosomes. Some cancers use a non-telomerase mechanism known as alternate lengthening of telomeres (ALT). Low-risk wide-spread neuroblastomas (known as stage 4S) can spontaneously regress without therapy; some stage 4S neuroblastomas progress and kill the patient. In collaboration with the nationwide Children's Oncology Group (COG) we will study TMM in tumors from stage 4S neuroblastoma patients, seeking to identify high telomerase as a marker for stage 4S neuroblastomas that will progress so therapy can be instituted rapidly. Conversely, we seek to demonstrate in high-risk stage 4 neuroblastomas that low telomerase is associated with ALT and with a poor clinical outcome. Our preliminary data suggest that ALT neuroblastomas express high levels of DNA repair genes, which may be why ALT cancers are resistant to therapy. We have shown that the enzyme ATM kinase is a driver of ALT, and that it also enhances gene expression of DNA repair genes, leading to resistance to chemotherapy and radiation. Our proposed studies will enable classifying neuroblastomas based on TMM, thus helping to categorize children with neuroblastoma into risk groups that are used to determine the intensity of therapy. We will also define the role of ATM kinase as a driver of ALT and show that ALT neuroblastomas, via ATM kinase, increase expression of DNA repair genes causing therapy resistance, while at the same time being an "Achilles heel" for ALT cancers. We will exploit this by identifying ATM kinase as a novel therapeutic target for ALT neuroblastomas.