CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180463

Project Title:
Compound heterozygous mutations in pediatric cancer predisposition

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

Principal Investigator:
Schlacher, Katharina

Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Understanding the underlying causes for pediatric cancer is instrumental in guiding prediction and treatment strategies to reduce the suffering of our children. Fanconi Anemia is a disease that affects children at a young age. Typically, it first presents itself as anemia, but also may include short stature and skin abnormalities. Most prominently, even after treatment of the anemia by bone marrow transplantation, these children develop cancer, in particular leukemia, head and neck and gynecological cancers.

Biologically, genes with mutations that lead to Fanconi Anemia are important for the repair of a specific type of DNA damage, a DNA interstrand cross link. However, we recently have identified an added biological function for these genes in protecting stalled DNA replication forks from DNA damage that is needed upon any DNA insult that halts the copying of the DNA. This includes conventional chemotherapy, which introduces DNA damage to destroy the duplicating tumor cells. Because all cells in Fanconi Anemia patients, not just the tumor cells, are ineffective in repairing and protecting their DNA, these patients are unusually sensitive to chemotherapy and suffer great side effects and cancer recurrence.

We have two copies of each given gene in our DNA. Current diagnostics for Fanconi Anemia are based on their classical DNA repair function, which requires both copies of a given Fanconi Anemia gene to be mutated to show a DNA repair defect. Our newly found fork protection function on the other hand shows defects also when only one of the two copies is mutated.

We here propose to test if single-copy mutations in multiple Fanconi Anemia genes could result in a fork protection defect that causes pediatric cancer. Such mutations are found in patients that clinically show Fanconi Anemia symptoms but currently are not diagnosed as such. Our results could change current diagnostics and change treatment to prevent unnecessary suffering in these patients.