CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP160249

Project Title:
DIS3L2 in Childhood Wilms Tumor: Mechanism to Medicines

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

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Wilms tumor is the most common kidney cancer in children and one of the most common childhood cancers overall. While most children with Wilms tumors can be treated successfully with combinations of surgery, radiation and chemotherapy, there are some with more aggressive tumors who unfortunately cannot be cured with current treatments. Furthermore, survivors of Wilms tumor therapy often later develop significant health problems, including hearing loss, kidney dysfunction, heart failure and secondary cancers. A better approach would be to devise treatments that are targeted to the specific abnormalities in the cancer cells that cause them to grow out of control. Such treatments have the potential to be both more effective and less toxic than current therapies. A few Wilms tumor mutations (i.e., changes in the tumor DNA sequence) are known, including mutations that occur in a gene called DIS3L2. This gene is frequently mutated in sporadic Wilms tumors, and children that inherit mutations in DIS3L2 develop a disease called Perlman syndrome, which is associated with overgrowth, kidney abnormalities including Wilms tumors, and early death. Nevertheless, how mutation of DIS3L2 causes Perlman syndrome and Wilms tumors is unknown. Using genetically engineered mice, we have discovered that DIS3L2 regulates a major growth-promoting pathway within kidney cells, which likely explains how mutations in this gene give rise to Perlman syndrome and Wilms tumors. In this application, we propose to apply cutting-edge genetic engineering technology to build upon this important discovery to determine precisely how mutations in DIS3L2 promote Wilms tumor growth. We will also exploit our new knowledge to test a novel targeted therapeutic strategy for Wilms tumors in mouse models. Successful completion of these experiments will lead to a new understanding of the causes of Wilms tumor, and will lead directly to new strategies for improved treatment of this disease.