CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180851

Project Title:
Targeting MYCN-Driven Metabolism in Neuroblastoma

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

Neuroblastoma (NB) accounts for 15% of all pediatric cancer deaths. The majority of patients which present with amplification of the oncogene MYCN die due to drug-resistant disease relapse. Thus, strategies that disrupt MYCN oncogenic programming are critically needed for NB therapy.

Cell metabolism, or the way in which cells use nutrients, is a key aspect of tumor biology. Tumors frequently have alterations, or undergo rewiring, in the specific type of nutrients they require for growth. In particular, MYCN is capable of driving defined changes in tumor metabolism. We have recently discovered a novel approach to oppose these metabolic changes driven by MYCN in NB. Our approach relies on restoring the retinoic acid-related orphan receptor (RORa) signaling in NB tumors in order to block tumor growth and enhance their sensitivity to therapy. Interestingly, RORa is both an important player of numerous metabolic functions and a key regulator of the circadian rhythm. We have found that RORa and other genes that control the circadian rhythm are profoundly dysregulated in aggressive NBs. Thus, we hypothesize that restoring the aberrant expression of these clock genes will oppose MYCN metabolic reprogramming and block NB tumor growth. We propose to: 1) characterize this dysregulation of the circadian clock and cell metabolism, and 2) therapeutically target it with novel RORa synthetic ligands, which are very promising compounds under clinical development.

We have recently discovered novel intriguing connections between MYCN, the circadian clock, and tumor metabolism that can be exploited for therapeutic intervention in NB with new metabolic inhibitors. These studies will enable us to identify genes and metabolic vulnerabilities that will offer new avenues for treating this aggressive and deadly disease.