CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180319

Project Title:
Rhabdomyosarcoma vulnerabilities: Prioritizing and extending to the clinic

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:

Survival for children with certain types of cancer remains dismal despite many years of research. This is particularly true for children with rhabdomyosarcoma, the most common soft tissue sarcoma in children. Only about 1 in 5 children with metastatic or recurrent disease survive for three years, and this poor outlook has not improved despite many attempts to intensify chemotherapy and use new agents.

Many experts feel that new insight into rhabdomyosarcoma biology is needed to light a path toward better therapy. Toward this goal, advances in DNA sequencing and computational analysis tools have enabled detailed studies of DNA within rhabdomyosarcoma, and much of that work has focused on identifying mutations in individual genes. Potentially “actionable” mutations in rhabdomyosarcoma are rare, though, and those analyses have not substantially improved outcomes.

Recognizing this problem, my team shifted our focus from mutation detection toward integrated analyses of gains or losses in the copies of individual genes, particularly when those copy number changes correlated with increased or decreased expression of that gene. We reasoned that cancer-causing “driver” genes would accumulate and so-called “tumor suppressors” would be lost in the tumor. We used our new iExCN analysis pipeline to study over 20,000 genes in rhabdomyosarcoma, and we identified 33 as candidate drivers or tumor suppressors. A number of them are already implicated in the disease, but most have not previously been considered.

The current proposal carries this work forward toward three major goals: a) to validate the importance of the 33 iExCN-defined genes in a series of rhabdomyosarcoma models; b) to uncover the mechanisms by which iExCN genes enhance or block rhabdomyosarcoma formation or progression; and c) to use the 33 iExCN-identified genes as the foundation for a new biomarker to better define prognosis and to guide the use of therapy targeting individual iExCN-defined drivers.