CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150301

Project Title:
Epigenetics in Medulloblastoma Development and Therapeutics

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

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

Lay Summary:

Medulloblastoma (MB) is a highly malignant pediatric brain tumor. Although significant improvements have been made in 5-year survival rates in the past decade, survivors continue to be at substantial risk for recurrence and metastasis. Unfortunately the outcome for these patients is dismal as there are no therapeutic options available at this time. An incomplete knowledge of tumor biology and molecules that drive tumorigenesis has significantly hampered efforts to develop new treatments. The current focus on tumor genetics by many groups has yielded only a few druggable targets. In contrast, abnormalities in the tumor cell chromatin architecture or epigenome can be reversed pharmacologically and are therefore more amenable to clinical translation. We have taken the approach of studying tumor epigenetics. In the current application, we will focus on a chromatin remodeler called RE1 Silencing Transcription Factor (REST) and its role in MB development. Our preliminary data show that REST protein levels are abnormally high in MB tumor samples, particularly in recurrent/refractory tumors. Our goal therefore is to understand REST's contribution to MB development and to assess its druggable potential. To this end, we will leverage our novel genetically engineered REST knock-in mouse model to perform an innovative context-specific high throughput screen to identify other epigenes that cooperate with REST in MB genesis. We will also carry out the first chemical screen to discover novel inhibitors of REST activity in human MB cell lines and mouse orthotopic models of MB. Our studies have the potential to impact long-term survival in patients with recurrent/refractory disease who currently lack alternative treatment options and eventually succumb to their disease.