CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP160237

Project Title:
A novel epigenetic reader as therapeutic target in MLL-translocated pediatric leukemias

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:

Cancer is the leading cause of disease-related death among children and adolescents in the United States. Leukemias, cancers of the bone marrow and blood, are the most common childhood cancers, that account for ~30% of all cancers in children versus ~2% in adult. The most prevalent leukemia types in children are acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Despite remarkable improvement in the treatment outcomes over the past decades, a high-risk subgroup of ALL patients that bear translocations involving the MLL (mixed-lineage leukemia) gene are particularly associated with poor response to standard treatments and dismal prognosis. The MLL gene is located on chromosome 11q23. Rearrangements of the MLL gene are associated with aggressive acute leukemias, both lymphoblastic and myeloid. Up to 80% of infant ALL and 35-50% of infant AML are characterized by MLL rearrangement. However, the development of effective therapies for this subtype of aggressive fatal disease is still in urgent need. In leukemias, MLL is found to fuse with >70 partners, among which the most frequent fusion partners are components of two protein complexes: the super elongation complex and the DOT1L complex. These fusions are believed to share a common pathway by “hijacking” these protein complexes to promote aberrant activation of MLL-fusion target genes. Nevertheless, detailed regulation of the MLL-fusions and the associated proteins and their roles in leukemogenesis are still not clear. Our preliminary discovery of the ENL and AF9 YEATS domains in the recognition of histone acetylation suggest that ENL and AF9 may function as epigenetic readers within these complexes. In this study, we will determine whether the recognition of histone acetylation by the YEATS domain is essential for the growth, survival, and tumorigenesis of the MLL rearranged leukemias. The proposed study will likely provide the YEATS domain as a potential therapeutic target.