CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP160739

Project Title:
Targeting Histone Acetylation Readers in MLL-translocated Leukemias

Award Mechanism:
High Impact/High Risk

Principal Investigator:
Shi, Xiaobing

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

Lay Summary:

Leukemias are cancers of the bone marrow and blood, mostly while blood cells. In children, leukemias are the most common cancers that account for almost 1 out of 3 cancers. The most prevalent childhood leukemia types 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. Rearrangements of the MLL gene account for about 80% of infant ALL and up to 50% of infant AML. In leukemias, MLL is found to fuse with more than 70 partners. A common mechanism of these MLL-fusion proteins is to promote aberrant expression of MLL-target genes, which leads to uncontrolled growth of white blood cells. On the basis of this knowledge, a common theme of developing personalized medicine for leukemia patients carrying MLL rearrangements is to block the recruitment of MLL and its fusion proteins to target genes, thus inhibiting aberrant gene expression. Recently, we identify a novel function of AF9 and ENL, two proteins that associate with most MLL-fusions in leukemias. These two proteins specifically interact with modified histones, and these interactions are critical for the recruitment of MLL-fusion proteins onto target genes. These exciting discovery opens a window for developing drugs that can specific interfere the interaction between AF9/ENL and histones, thus to inhibit aberrant expression of MLL-target genes and the growth and survival of MLL rearranged leukemias. This proposal aims to identify such inhibitors by high-throughput screening and validate their chemical and biological activities using both in vitro biochemical and in vivo cell-based assays. Our proposed study will provide lead compounds for further drug development for targeted therapy of MLL-translocated leukemias.