CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150129

Project Title:
Drug Discovery and Mechanistic Studies of Protein Methylation Targeting Leukemia

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

Principal Investigator:
Song, Yongcheng

Entity:
Baylor College of Medicine

Lay Summary:

Acute leukemia is the most common cancer in children and adolescents. Although several subtypes of childhood leukemia have achieved high cure rates, the survivals for a subtype of acute leukemia that has mixed lineage leukemia (MLL) gene translocations are still low. MLL-rearranged leukemia accounts for ~75% of leukemia in infants as well as ~10% in children/adults, with 5-year survival rates being less than 40% (or 20% for patients aged less than 3 months). Current treatments are chemodrugs, which kill all rapidly proliferating cells including normal stem cells in bone marrow and other organs. This causes severe toxicities, side effects and limits the efficacy of these drugs. Due to mutagenesis, chemotherapy may cause secondary cancers for these patients after cure of leukemia. There is therefore a pressing need to find less toxic drugs targeting an oncoprotein that drives leukemia. Advantage for targeted therapies is the potential to be non-toxic, since the oncoprotein is essential for leukemia but may be dispensable in normal cells. This project aims to find targeted therapeutics for MLL and RUNX1-ETO oncogene driven acute leukemia. RUNX1-ETO is found in ~10% pediatric leukemia patients. Moreover, this research may benefit older patients, since MLL and RUNX1-ETO oncogenes cause ~10% and 15% adult leukemia, respectively, with poor prognosis. We found lysine specific demethylase 1 (LSD1), a protein able to remove methyl groups from its client proteins, is a drug target for these two subtypes of leukemia. Our preliminary studies showed LSD1 inhibition can significantly prolong the lifespan of mice transplanted with MLL leukemia without overt toxicities. We also identified a novel class of drug-like inhibitors for further drug development. The overall goals are to develop potent and selective inhibitors of LSD1 as potential drug candidates for leukemia treatment and to perform mechanistic studies to find LSD1's role in RUNX1-ETO leukemia.