CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP110050

Project Title:
Novel Epigenetic Modulators Targeting Leukemia Initiating Cells

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

Leukemia with MLL (mixed-lineage leukemia) gene translocations accounts for ~75% of infant and ~10% child/adult acute leukemia with a particularly poor prognosis. While the survival for children with acute lymphocytic leukemia (ALL) now exceeds 80%, that for infants with MLL-rearranged ALL is only about 40%. Even more serious is that the survival for infants <3 months old at diagnosis is less than 20%. Intensified chemotherapy has led to increased toxicity without significantly improved survival. New drugs for treating MLL-rearranged leukemia are desperately needed. After initial chemotherapies, most cases of this type of leukemia will relapse, due to a small population of leukemic stem cells (LSC) that are resistant to conventional chemotherapeutic agents. The objective of this research is to discover and develop novel agents that selectively target LSCs with MLL gene translocations, but do not affect the functions of normal bone marrow cells. Recent studies have shown that DOT1L, a protein which can modify histone (a key protein of chromosome) and thereby affect gene transcriptions, is essential for the survival and proliferation of MLL-associated LSCs. DOT1L inhibitors (agents that can block the function of DOT1L) should represent novel anticancer agents for the leukemia. However, there have been no DOT1L inhibitors identified to date. We propose to use rational drug design and medicinal chemistry to find such inhibitors and investigate their anti-leukemia activity on MLL-associated LSCs as well as primary leukemia cells from patients with MLL translocations. As a first step towards this goal, we have obtained, for the first time, several potent DOT1L inhibitors that can selectively block the growth of the LSCs, but have no toxicity to bone marrow cells. Success of this work would open up a new approach to the treatment of acute leukemia with MLL translocations.