CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180309

Project Title:
Inhibiting Oxidative Phosphorylation: A Novel Strategy in Leukemia

Award Mechanism:
Individual Investigator

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

Lay Summary:

In adults, acute myeloid leukemia (AML) remains difficult to treat, and most patients are expected to die either of their disease or of treatment-related toxicities. The need for novel therapies is thus unquestioned.

Cancer cells utilize glycolysis, mitochondrial respiration or both to convert the chemical energy of food molecules into cellular energy and biosynthetic building blocks. AML cells predominantly utilize mitochondrial respiration, and unlike normal cells, are deficient in glycolytic capacity. Oxidative phosphorylation (OxPhos) is a series of reactions within mitochondrial matrix, whereby energized electrons are transferred from the donor molecules and drive synthesis of ATP and aspartate, a precursor in nucleic acid synthesis. In turn, inhibition of OxPhos results in arrest of cellular respiration and death of cancer cells that depend on this metabolic process.

We have identified a novel potent inhibitor of OxPhos IACS-010759 which induces death of AML blasts and stem cells, but not of the normal cells. Studies in the murine models of human leukemia demonstrated good tolerability at doses that extended survival. We have recently shown that resistant AML cells surviving chemotherapy selectively depend on OxPhos for survival, and have demonstrated synergy between IACS-010759 and cytarabine. IACS-010759 has recently entered Phase I clinical trial in relapsed/refractory AML patients at M.D. Anderson Cancer Center.

This proposal will evaluate combined efficacy of the standard chemotherapy agents and IACS-010759 and determine mechanisms of anti-leukemia cell death by analysis of gene expression and metabolic signatures. We will further identify most potent combinations of IACS-010759 and selected inhibitors, by testing lethality and metabolic wiring in high-throughput screening of AML and normal cells. These studies will provide rationale for the future combination clinical trials of IACS-10759, with the ultimate goal of improving outcomes in AML.