CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140218

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. Recent data indicate that 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 pass through channels in the inner mitochondrial membrane that will drive synthesis of ATP. In turn, inhibition of OXPHOS results in arrest of cellular respiration and death of cancer cells that depend on this metabolic process. Currently, there are no FDA-approved drugs that act as effective and safe OXPHOS inhibitors. We have identified a novel potent inhibitor of OXPHOS IACS-1131, selected from the series of more than 1,000 compounds across distinct structural classes. Our preliminary data strongly indicate that this agent induces profound death of AML blasts, but not of the normal bone marrow cells, at nanomolar concentrations. Studies in the murine models of human leukemia demonstrated good tolerability at doses that extended survival 5-fold compared with untreated mice that succumbed from leukemia in less than 20 days. This proposal will determine mechanisms of the leukemia cell death; elucidate genetic and metabolic signatures of sensitivity or resistance to OXPHOS inhibition; and characterize biomarkers of response to IACS-1131, including novel metabolic imaging techniques. Most importantly, these studies will provide justification for the planned clinical trials testing this novel therapy for patients with leukemia, with the ultimate goal of improving outcomes.