CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140179

Project Title:
Targeting Self-Renewal in Leukemic Stem Cells Through the Inactivation of KLF4

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

Chronic myeloid leukemia (CML) is originated by transformation of a primitive hematopoietic progenitor in bone marrow hematopoietic stem cells into leukemic stem cells (LSCs) that sustain the bulk of leukemia while self-renewing for unlimited time. Even though standard chemotherapy keeps patients in complete remission, treatment must be continued and many relapse by acquisition of LSC chemoresistance. The Holy Grail in the cure of leukemia is to identify genes involved in LSC self-renewal and discover cell-permeable compounds that can modulate such genes and cause the demise of disease initiating LSCs. CML is the first cancer associated to a specific genetic translocation, BCR-ABL oncogene, and the first target of molecular therapy with specific inhibitors. However, LSC chemoresistance is driven by acquisition of survival and self-renewal pathways that are not targeted by BCR-ABL inhibitors. The discovery of new drugs that cripple LSCs without affecting normal blood formation will allow combination therapy with current drugs. We discovered that the transcription factor KLF4 promotes maintenance of LSCs and therefore inhibition of KLF4 expression or function can lead to their complete eradication. Our hypothesis is that KLF4 promotes LSC self-renewal by BCR-ABL independent mechanisms that can be targeted to ‘cure’ CML patients without inducing immunosuppression. We propose to study the effect of genetic inactivation of KLF4 in LSC self-renewal using a mouse model of human CML (new paradigm), to investigate the role of genes involved in cell division and survival of LSCs (new targets), and to identify small molecules that inhibit KLF4 expression or function selectively in leukemia cells as a first step towards targeted therapy (new drugs). The growing population of CML survivors will need alternative drugs to reach complete cure and cessation of drug therapy. This proposal will identify the targets and bullets to “cure” CML patients.