CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP110189

Project Title:
Discovery of Small Molecule Activators of NR4A Orphan Nuclear Receptors for Treatment of Acute myeloid Leukemia.

Award Mechanism:
Individual Investigator

Principal Investigator:
Conneely, Orla M

Entity:
Baylor College of Medicine

Lay Summary:

The overall goal of this project is to develop new therapies for treatment of acute myeloid leukemias (AML). AMLs represent a group of blood cancers that develop as a result of defective production of infection fighting myeloid blood cells and are a leading cause of death from leukemias in the U.S. with overall patient survival of <25%. AMLs vary widely among patients in terms of their genetic and molecular causes, course of development and response to chemotherapy. This considerable variability presents a major challenge toward development of much needed new therapies to treat AML patients. Nuclear receptors represent a large family of related proteins that interact with DNA to control its ability to produce new proteins required to control normal cell behavior. Disruption of nuclear receptor function occurs in a wide variety of diseases and these proteins have been extensively validated as key targets for therapeutic intervention in the treatment of a variety of cancers. We recently discovered that loss of function of two novel nuclear receptors, NR4A1 and NR4A3, is a primary cause of extremely aggressive spontaneous AML development in mice leading to early death. Further, we found that widespread loss of function of both NR4A1 and NR4A3 occurs in human AML patients regardless of the genetic cause of their disease. Our findings indicate that loss of NR4A function is a common step in human AML development and that strategies directed toward reactivation of these proteins may be of great therapeutic benefit in treatment of AML. The goals of this proposal are to validate NR4As as new therapeutic targets for treatment of AML patients, identify novel drugs that restore NR4A function in AML cells and test their ability to treat and block AML disease development using mouse models of human AML disease. We anticipate that these studies will identify new drugs for treatment of AML that can be rapidly transferred to cancer clinics and made available to AML patients.