Award ID:
RP100421

Project Title:
Chemical Probes for Signal Transducer and Activator of Transcription (STAT) 3 that Selectively Target Leukemia-Initiating Cells

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

Improving cancer survival will require development of drugs that target a subset of the cancer cells that are responsible for cancer recurrences referred to as cancer stem cells (CSCs) while at the same time, sparing normal stem cells, particularly stem cells that give rise to the red cells, white cells and platelets that circulate in the blood. Blood stem cells share many features with CSCs; therefore, finding a way to target CSCs while sparing blood stem cells has been difficult. Recently, however, a protein called Stat3 has been shown by us and others to be an important contributor to CSC development and maintenance in many cancers. Notable among these cancers is a form of leukemia called acute myeloid leukemia (AML), in which recurrence following standard chemotherapy is frequent and survival is poor. Importantly, genetic removal of Stat3 within blood stem cells in mice does not impair blood cell development in these animals. This proposal will test the novel idea that Stat3 is essential for human CSCs, in particular, leukemia stem cells but is dispensable for the function of normal blood stem cells in humans. AML in humans consists of several distinct disease subsets each marked by specific genetic changes. In this proposal, we will perform studies to determine which specific genetic changes found in AML cells mediate leukemia development through Stat3 and secondly which are susceptible to Stat3 targeting by the small, drug-like molecules that we will develop in this proposal. These results will guide studies using AML patient samples and help us identify which AML patients may benefit from treatment using the drugs we develop. We anticipate that these drugs will be used in combination with current chemotherapy regimens to reduce AML relapse and improve patient survival.