CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP130660

Project Title:
Creating Novel Translation Inhibitors to Target Pro-survival Oncoproteins

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
Texas A&M University

Lay Summary:

Lymphoid malignancies, both leukemias and lymphomas, are prevalent in the general population. At the present time, responses to therapy are generally transient, and there is no established treatment that results in a cure. These diseases express proteins that are required for survival of the tumor, but are not directly affected by current first line therapies. Some of these survival proteins are degraded rapidly, and therefore continual synthesis is required to maintain lymphoid malignancies. Importantly, although tumor cells require these pro-survival proteins, the viability of normal cells is not dependent upon their continued presence. Therefore, we propose to test a strategy that is directed at decreasing levels of these critical pro-survival proteins as a means of selectively killing tumor cells. We propose a high risk approach involving protein synthesis inhibition to tackle a critical issue of first line chemotherapy resistance with concurrent potential for broad and high impact. We will use primary tumor cells from one such disease, chronic lymphocytic leukemia (CLL), to test this hypothesis. Our approach is the use of small molecule inhibitors that block the synthesis of such proteins for a relatively short time (6 to 12 hours), thereby depleting the CLL cells of these essential factors, and allowing normal cell death processes to be activated. Our earlier studies investigated this in the laboratory and demonstrated our lead drug candidate to be effective in killing CLL cells. We propose to investigate this further in CLL cells from patients whose disease is resistant to our most effective therapies. We will also modify our lead drug candidate to improve its solubility, to decrease binding to proteins in blood serum, and to increase its potency at blocking protein synthesis. Our ultimate goal is to identify the most successful drug candidate for evaluation in clinical trials with patients with these lymphoid malignancies.