CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150559

Project Title:
Small Molecules to Perturb A Novel PPI Target For Chemotherapy

Award Mechanism:
High Impact/High Risk

Principal Investigator:
Burgess, Kevin

Entity:
Texas A&M University

Lay Summary:

Acute myeloid leukemia (AML) is a prevalent and aggressive form of blood cancer with a poor prognosis, particularly for older people. Most of the established drugs to treat AML are horribly toxic. However, some emerging treatments are likely to be better tolerated because they target a particular biochemical pathway that is switched on in cancer cells, making them more vulnerable to the drug than healthy ones. One such drug candidate in clinical trials, MLN4924, is unique insofar as it modifies a protein called NAE so that it is no longer able to bind to another one called NEDD8. Clinical data for MLN4924 is extremely promising, but cell studies indicate some forms of AML could be resistant. Consequently, it is highly desirable to explore compounds with the potential to prevent NAE interacting with NEDD8 in a different way, and that is the focus of the proposed study. Specifically, plans are presented to identify compounds that disrupt the NEDD8•NAE interaction not by attaching to NAE, but by inserting itself at the interface between the two proteins. Usually it is difficult to find molecules that do this type of thing; the standard approach is to screen millions of compounds, but even then a favorable outcome is often not obtained. However, we have a new method to sort protein-protein interactions that a carefully designed small molecule might interfere with. This method was applied before this collaboration was initiated, and, highly significantly, NEDD8•NAE "came to us" as a target. Funds are requested for the opportunity to make these molecules and test their potential for treatment of AML.