CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP120016

Project Title:
Small molecule inhibitors of proteasome assembly: a new strategy for cancer therapy

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Many cancers result from abnormal levels of proteins that control cell growth. Levels of proteins that control cell growth are determined in an important way by their rate of destruction, a process that is highly regulated in normal states but is altered in cancer and other diseases. The destruction of many cellular proteins is carried out by a large enzyme complex called the proteasome. The proteasome exists in multiple forms that consist of a common element called the 20S proteasome, and any one of at least six variable elements. Different proteasome forms likely have different cellular roles, but little is known about how cells determine relative proportions of proteasome forms or how they are directed to their specific roles. This project will attempt to identify small drug-like molecules that selectively disrupt assembly of the 26S proteasome, a specific proteasome form that seems particularly important for destruction of proteins involved in cell growth. We will use a simple biochemical assay to rapidly test thousands of existing compounds for this effect. We hypothesize that blocking formation of the 26S proteasome will selectively inhibit rapidly growing cancer cells, but not affect other important proteasome-dependent processes on which normal cells rely. Molecules with this property will be used to study the role of the proteasome in basic processes involved in normal cellular growth and function, and how changes in these processes lead to abnormal cellular growth characteristic of cancer. The long-term goal of this work is to develop compounds that work in this manner into drugs for treatment of cancer.