CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180410

Project Title:
Mechanisms of Nuclear Export in Cancer

Award Mechanism:
Individual Investigator

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

Lay Summary:

CRM1 transports about 1000 different protein cargos, including many tumor suppressors, out of the cell nucleus. In cancer, many tumor suppressor cargos are inappropriately transported by CRM1, thus preventing cancer cell death and causing resistance to therapy. Anti-CRM1 drug Selinexor reverts cargo misplacement and causes cancer cell death. Selinexor is in more than 30 Phase 1, 2, and 3 clinical trials for various cancers. 2nd generation drug KPT-8602 is also in a Phase 1/2 study for multiple myeloma. Selinexor and KPT-8602 are well tolerated, unlike an older toxic CRM1 blocker named Leptomycin B (LMB) because of a key difference (discovered by our laboratory) in how they block CRM1. Selinexor blocks in a reversible or temporary manner while LMB blocks CRM1 permanently. KPT-8602, designed to be more reversible, is even better tolerated, can be dosed more frequently and therefore is better at killing cancer cells. The different effects of KPT-8602, Selinexor and LMB in animals and patients underscore the importance of understanding how they work on CRM1 differently. Aim 1 of this proposal focuses on learning how to control the reversibility/permanence of anti-CRM1 drugs' action on the CRM1 protein as a strategy to improve drug tolerability in patients. The goal of Aim 2 is to understand how Selinexor and LMB act differently in cells - Selinexor targets CRM1 to be destroyed and but this effect is absent with LMB. We will identify the molecules in Selinexor-treated cells that recognize Selinexor-bound CRM1 and send it to be destroyed. Aim 3 focuses on understanding how CRM1 mutants in several cancers function differently from normal CRM1. We have determined how these mutations change arrangement of atoms in CRM1 and change how CRM1 contacts cargos and drugs. This atomic information about the CRM1 cancer mutants will guide biochemical studies to understand how the tightness and speed at which mutant CRM1 binds cargos and drugs are different compared to normal CRM1.