Award ID:
RP140328

Project Title:
Synthetic Protein Degradation Agents To Clear Oncogenic Proteins From Cells

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
The University of Texas at Austin

Lay Summary:

A hallmark of cancer is the presence of proteins that inappropriately signal cells to grow and to divide. We are developing a strategy to purge such oncogenic proteins from cells by taking advantage of the cells' own protein removal system. Cancer cells can be addicted to oncogenic proteins and die when they no longer receive the growth stimulus from these proteins. For example, the drug Gleevec kills cancer cells by inhibiting the oncogenic protein Bcr-Abl from sending its growth signal. Thus, clearing oncogenic proteins from cells could be a novel strategy for molecularly targeted therapeutics. Cells constantly remove proteins that are unwanted and much of this protein removal occurs by the Ubiquitin Proteasome System (UPS). We are developing a method to shunt oncogenic proteins into the UPS by short-circuiting the cell's normal removal process. We will use artificial adaptor molecules tailored to recognize oncogneic proteins and the proteolytic machine at the core of the UPS, the proteasome, simultaneously. Thus, these adaptors would destroy toxic proteins by feeding them into the proteasome. We have begun to test these adaptors on two specific targets involved in chronic myelogenous leukemia (CML). CML is caused by the creation of Bcr-Abl. CML cells are addicted to Bcr-Abl and they die when its function is inhibited by Gleevec, which makes Gleevec one of the most successful cancer drugs. We will evaluate our therapeutic strategy by testing whether adaptors molecules can kill cells by shunting Bcr-Abl to the proteasome for destruction and comparing its effectiveness to Gleevec. Our proteasome adaptors are built on an antibody-like technology, which makes it possible, in principle, to destroy almost any protein. We will test the versatility of our strategy by aiming it at a second protein, called Shp2, which plays an important role in CML but also in a range of other cancers, including some solid tumors.