



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP110291

Project Title:
Targeting Oncoprotein Folding Intermediates to Treat Cancer

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

Cancer is caused by the actions of abnormally regulated proteins called oncoproteins, which transform normal cells into cancer cells. One of the greatest advances in cancer treatment in the past 20 years has emerged from our ability to solve the atomic structure of the mature forms of some oncoproteins and to use these structures to design drugs that regulate or inactivate them. Unfortunately, to date, only a few structures of mature oncoproteins have revealed points of weakness vulnerable to attack by a drug. In this grant application, we are proposing a completely novel approach to drug targeting of oncoproteins. This approach involves obtaining their structures while they are being assisted to fold into their mature shape by a protein-folding machine within cells known as TRiC. Many proteins important for cell growth require assistance from TRiC and when this assistance is reduced, the immature protein, which is unstable, accumulates within the cell and is eliminated by the cell's protein degradation system. The long-term goal of this proposal is to design drugs that block the interaction of immature oncoproteins with TRiC resulting in their elimination by the cell. Our group has solved the structure of TRiC to the atomic level using a visualization technique called cryo-electron microscopy (cryo-EM). We also have preliminary cryo-EM structures of an oncoprotein called Stat3 bound to TRiC. Stat3 is involved in up to 70% of cancers. In this two-year proposal, we will use cryo-EM to obtain atomic resolution structures of Stat3 and three other oncoproteins bound to TRiC. We will use these structures in subsequent proposals to design drugs that will block the ability of the oncoproteins to interact with TRiC leading to their elimination within cancer cells and reversal of transformation.