



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP160841

Project Title:
Targeting EWS-FLI-1 for degradation

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
The University of Texas Health Science Center at San Antonio

Lay Summary:

Ewing sarcoma is the second most common cancer of bone and soft tissues in children and young adults and is characterized by the chromosomal translocation generating a fusion oncogene between EWS and an Ets family transcription factor, most commonly FLI-1. EWS-FLI-1 fusion accounts for 85% of Ewing sarcoma cases. Ewing sarcoma is an aggressive cancer with relatively poor long-term outcome. Overall survival is approximately 50% and the five-year survival of recurrent cases is less than 10%. Considering that current cytotoxic chemotherapies used for Ewing sarcoma are not improving the survival of metastatic or recurrent disease, a new approach for targeted therapy needs to be developed.

The growth and survival of Ewing sarcoma cells critically depend on the EWS-FLI-1 fusion oncoprotein. Therefore targeting EWS-FLI-1 is a promising approach to treat Ewing sarcoma. Despite many attempts, however, EWS-FLI-1-targeted therapy has not materialized to date and EWS-FLI-1 continues to be "the perfect target without a therapeutic agent." Previous efforts to target EWS-FLI-1 were focused on inhibiting the gene regulatory activity of EWS-FLI-1. In this project, we will pursue an entirely different approach to target EWS-FLI-1: proteolytic degradation of the EWS-FLI-1 protein.

We have discovered that EWS-FLI-1 is selectively degraded by the lysosome (unlike most cellular proteins that are degraded by the proteasome) and demonstrated that EWS-FLI-1 can be targeted for degradation by a compound that stimulates lysosome biogenesis. In this application, we propose to delineate the mechanism of EWS-FLI-1 lysosomal degradation and identify the compounds that efficiently degrade EWS-FLI-1. The successful completion of this project will provide a basis for a novel therapeutic approach to Ewing sarcoma and develop new drugs to treat this cancer.