CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180835

Project Title:
Targeted Proteolysis of Glucocorticoid Receptor as a Therapeutic Strategy in Antiandrogen Treatment-Resistant Prostate Cancer

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

While a majority of men with early stage prostate cancer have good overall outcome, advanced prostate cancer remains a devastating disease with grim outcome and limited treatment options. Recently, new treatments such as enzalutamide have been developed that primarily block the effects of male hormones (hence known as anti-androgens). Such anti-androgen treatments have been highly beneficial in improving the survival of advanced prostate cancer patients. Unfortunately, the cancer returns in many patients. Studies have shown that a major cause of the recurrence of prostate cancer is activation of a different type of hormone receptor called glucocorticoid receptor (GR). The glucocorticoid receptor shares similarities to the androgen receptor and prostate cancer hijacks GR to stimulate its growth when androgen receptor is blocked by enzalutamide. This suggests that GR could be an attractive therapeutic target.

Hence, we have developed drug-like molecules that induce the destruction of glucocorticoid receptor by utilizing a new technology that sends cancer-causing proteins to the cell's garbage disposal system. We call these molecules GR PROTACs (glucocorticoid receptor proteolysis targeting chimeras).

The major objective of the proposed study is to determine whether GR PROTACs have therapeutic benefit in anti-androgen treatment resistant models of prostate cancer. First we aim to perform in depth molecular studies to better understand the biological properties of GR PROTACs in cell culture systems. Next, we will study the anti-tumor efficacy of GR PROTACs in animal models of prostate cancer.
If successful, our study will provide a new therapeutic modality to anti-androgen treatment resistant prostate cancer patients. In summary, we will investigate first-in class drug-like molecules with a unique mode of action against a known cancer promoting protein and our proposal could have direct impact on prostate cancer patients by delivering much needed new therapeutics.