CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140435

Project Title:
SHH/GLI3 Signaling Axis as a Therapeutic Target in Castration Resistant Prostate Cancer

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:

Prostate cancer is the most common malignancy and the second leading cause of cancer-associated deaths among US men. Although most prostate cancer patients initially respond to androgen deprivation therapy, they eventually progress to castration resistant prostate cancer (CRPC) characterized by androgen receptor-dependent tumor growth despite castrate levels of circulating androgens. Once patients have reached this stage, treatment options are frustratingly limited and average survival times range from 2-3 years only. Therefore, one of the overarching challenges in the field is to develop effective treatments and address mechanisms of CRPC. This innovative proposal conforms precisely to this challenge as it suggests a rational basis to explain the development of CRPC in a subtype that approaches 11-20% of prostate cancers, and further offers proof of concept in a preclinical model for treatment in this genetic setting. Recently, mutations in the genes encoding MED12 and SPOP were found in prostate tumors lacking hallmark chromosomal rearrangements previously linked to the disease, suggesting that MED12 and SPOP mutations may define a new molecular subtype of prostate cancer. We hypothesize that SPOP and MED12 are prostate tumor suppressors whose mutational inactivation drives CRPC by disrupting constraints on the Sonic hedgehog (SHH) signaling pathway responsible for reactivation of androgen receptor function following androgen deprivation. We further propose that vismodegib (GDC-0449), an FDA-approved SHH pathway inhibitor currently used to treat other cancers, will block CRPC in this genetic subtype. Thus, we aim to examine the relationship between androgen ablation therapy and SHH signaling in MED12/SPOP mutant prostate tumors and investigate the impact of vismodegib on the development of castration resistant MED12/SPOP mutant tumors in a preclinical model. We expect these studies to have important implications for precision treatment of prostate cancer patients.