Curebound Targeted Grant Fall 2022

Clinical Strategizing of PARP Inhibitors in Castration Resistant Prostate Cancer

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Scientific Abstract:

The management of castration resistant prostate cancer (CRPC) is an unmet clinical need. Metastatic CRPC (mCRPC) heralds a lethal disease resulting in the death of over 27,000 men per year in the United States alone. Though approved therapeutic agents have prolonged survival of men with this disease, most patients develop resistance. Emerging data demonstrate that defects in homologous recombination genes are enriched in mCRPC. This finding is highly relevant given the susceptibility of HR-deficient (HRD) tumors to PARP inhibition and to platinum therapy. Currently, however, commercially available tests to determine HRD rely primarily on assessing mutation status of common DNA repair genes, thus overlooking patients that may harbor HRD as a result of alternative defects. In this project, we will utilize Dr. Rana McKay's expertise in biomarkers and clinical management of prostate cancer and combine this with the computational and AI capabilities of Dr. Ludmil Alexandrov's lab. Specifically, we will generate genomic and transcriptomic profiles from 300 advanced prostate cancer patients with robust clinical annotation, including samples from two large phase 2 studies of PARP inhibitors in men with advanced mCRPC (NCT02893917, NCT03317392). These genomics and transcriptomics data will be examined using previously established state-of-the-art computational methods for assessing HRD by utilizing patterns of somatic mutations, known as mutational signatures. Overall, we propose to extend the two PIs' past research in prostate cancer and HRD in order to develop a comprehensive and high-fidelity diagnostic test to identify men with HRD which will likely respond to PARP inhibition and platinum therapy.

Lay Abstract:

Prostate cancer is the most common cancer diagnosis made in men with more than 160,000 new cases each year in the United States. Although it often has an indolent course, prostate cancer remains the second-leading cause of male cancer death in the US. Additionally, while the mainstay therapy for patients with advanced disease is androgen deprivation, a subset of patients develop cancer progression, termed "castration resistance", which is universally lethal. Additional novel therapeutic strategies are needed to improve survival for patients with metastatic castration resistant prostate cancer. Previous genetic profiles of metastatic castration resistant prostate cancers have shown that a subset of these cancers have a deficiency in a DNA repair pathway, known as homologous recombination deficiency (HRD). Importantly, prior studies have revealed that tumors with alterations in homologues recombination (HR) genes can be successfully treated with specific drugs including PARP inhibitors and platinum therapies. Historically, however, classification of tumors as HRD has been largely dependent on mutations in select HR genes and, thus, responses to PARP inhibitors have been vastly heterogeneous and dependent on the underlying gene alteration. In this project, we propose to utilize the expertise of the two PIs to deliver a high-fidelity diagnostic tool to identify prostate cancer patients that will benefit from PARP inhibition and platinum therapy. Given the expertise of our team, our future goal is to utilize this tool as an integral biomarker in a phase 2 trial of PARP inhibitor therapy in men with advanced metastatic castration resistant prostate cancer.