

**Curebound Discovery Spring 2022**

**Pre-clinical development of new autophagy targeting drugs for bone metastatic prostate cancer**



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**Scientific Abstract:**

The primary target for treating advanced prostate cancer (PCa) is inhibition of the androgen receptor (AR) using androgen pathway directed therapy (APDT). However, patients invariably progress to castrate-resistant prostate cancer (CRPC), which metastasizes most often to bone for which there is no cure. Treatment with APDTs upregulates autophagy (ATG), a survival and resistance pathway, and promotes cancer cell dormancy. Our preliminary data indicate that ATG modulation through inhibition of the ULK1/2 kinase blocks APDT-induced autophagy and kills resistant cells. Bone metastasis of PCa are not often surgically resected, resulting in few bone metastatic PCa models. In collaboration with UCSD surgeons, we have collected patient PCa bone metastasis specimens, established patient derived xenografts (PDX), and created 2D and 3D cellular models of bone metastatic PCa for use in therapeutic development. We find that treatment of these models with APDTs promotes cell dormancy thus fostering therapeutic resistance. Our Aims are to: 1) Evaluate ATG flux and dormancy in 2D and 3D cell culture models of patient-derived castrate-resistant bone metastatic PCa, 2) Evaluate ULK1/2 inhibitors in 2D and 3D cell culture models of patient-derived castrate-resistant bone metastatic PCa models for cell death and dormancy, and 3) Evaluate ULK1/2 inhibitors in vivo in patient derived xenograft (PDX) models of castrate-resistant bone metastatic PCa. These aims will allow us to achieve our overall objective of identifying ULK1/2 inhibition as a novel treatment mechanism for APDT treatment resistant metastatic prostate cancer.

**Lay Abstract:**

One in six men will be diagnosed with prostate cancer (PCa), making it one of the leading health problems affecting men in today's society. Patients diagnosed during the earlier stages are surviving longer due to improved therapies and the prevalence of prostate-specific antigen (PSA) testing. A growing number of these patients, however, go on to develop advanced PCa. The main treatment for advanced prostate cancer (PCa) is androgen pathway directed therapy (APDT). Unfortunately, patients invariably become resistant to APDT, and their cancer metastasizes - most often to bone - for which there is no cure. Autophagy (ATG) plays a role as a survival pathway that contributes to cancer growth, resistance, and cell dormancy. Therefore, inhibiting ATG is a novel mechanism to reduce survival of PCa resistant to APDT. While cellular models of bone metastatic PCa have been difficult to generate, we have recently established patient derived cellular 2D and 3D models allowing us to evaluate treatments for this fatal disease. In our proposal we will examine a class of specific ATG inhibitors in patient bone metastatic PCa cells and evaluate their ability to reduce PCa tumor burden in mouse models alone and in combination with APDT. This will allow the development of a new drug therapy for the treatment of this deadly cancer and enhance patient outcomes.