

PROBLEM STATEMENT

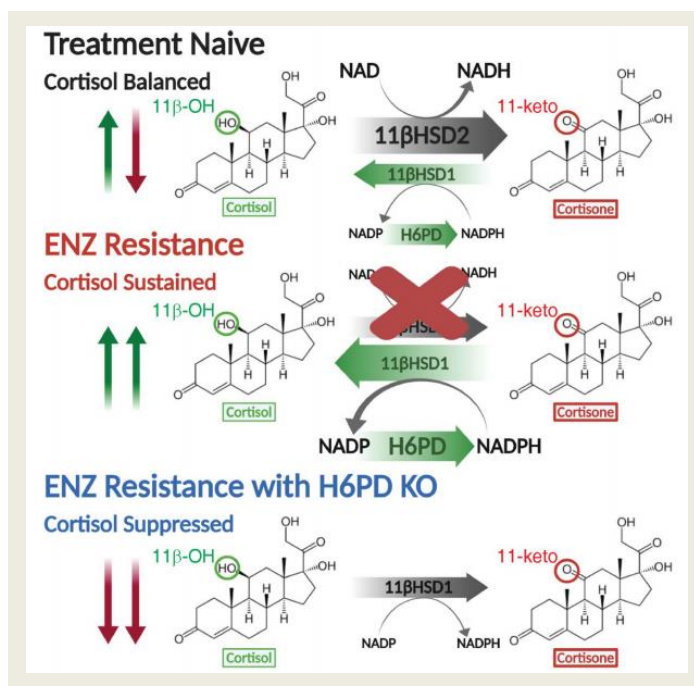
There are approximately 120,000 castration resistant prostate cancer patients in the U.S. Of all CRPC drugs 85% of them are next generation antiandrogen therapies (AR antagonists), such as Enzalutamide and Apalutamide. Responders eventually face resistance and it's estimated that half of all men experience recurrence associated with significant up-regulation of glucocorticoid signaling. Overcoming resistance to next generation antiandrogens remains an unmet need and novel therapeutics are needed to address these concerns

SOLUTION

At Cleveland Clinic we hypothesize that glucocorticoid metabolism in tumor tissues regulates GR activity in CRPC. In our working model, Enzalutamide treatment permits sustained local cortisol concentrations in prostate cancer by loss of 11 β HSD2, the bi-directional enzyme required to convert cortisol to cortisone. Therefore, Enzalutamide resistance can be reversed by re-establishing 11 β HSD2 enzymatic activity. This reductive reaction requires NADPH as a cofactor, which is generated by hexose-6-phosphate dehydrogenase (H6PD). Inhibition of H6PD will reduce local production of NADPH, thereby promoting the bi-directional enzyme 11 β -HSD1 to suppress biologically active glucocorticoids in prostate cancer cells leading to reversal of enzalutamide resistance. A lead series of novel small molecule inhibitors has been generated and demonstrated preliminary efficacy in animal models.

VALUE PROPOSITION

- Leverages fundamental metabolic mechanism that drives AR antagonist resistance.
- Novel inhibitors may be utilized as stand-alone or part of synergistic therapy.
- In-vivo proof-of-concept established by experienced drug discovery and development team.



OPPORTUNITY

Cleveland Clinic is seeking prospective development, commercialization, or investment partners to advance this program to clinical studies and beyond to advance patient care.

DEVELOPMENT STAGE

- Lead inhibitor series developed
- Undergoing in vitro and in vivo preclinical testing

INTELLECTUAL PROPERTY & PUBLICATIONS

- Provisional Patent Application filed
- Li J, Berk M, et al. *Sci Transl Med*. 2021;13(595) PMID: [34039740](https://pubmed.ncbi.nlm.nih.gov/34039740/)

LEARN MORE

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