Cleveland Clinic Innovations

Inhibitors of Hexose-6-Phosphate Dehydrogenase as a Novel Therapeutic for Metastatic, Castration Resistant Prostate Cancer (CRPC)

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PRODUCT

Hexose-6-Phosphate Dehydrogenase (H6PD) Inhibitors

INDICATIONS

Therapeutic for Prostate Cancer

VALUE PROPOSITION

- H6PD inhibitors as stand-alone or synergistic therapy.
- Identification of metabolic mechanism that drives AR antagonist resistance.
- In-vivo POC established

INTELLECTUAL PROPERTY

Patent pending

DEVELOPMENTAL STAGE

Lead series of novel inhibitors active in animal models.

PUBLICATION

Li J, Berk M, Alyamani M, et al. Hexose-6-phosphate dehydrogenase blockade reverses prostate cancer drug resistance in xenograft models by glucocorticoid inactivation. Sci Transl Med. 2021;13(595): eabe8226.

CONTACT INFORMATION

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PROBLEM

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 11βHSD2, the bi-directional enzyme required to convert cortisol to cortisone. Therefore, Enzalutamide resistance can be reversed by re-establishing 11βHSD2 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 11β-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 shows efficacy in animal models.

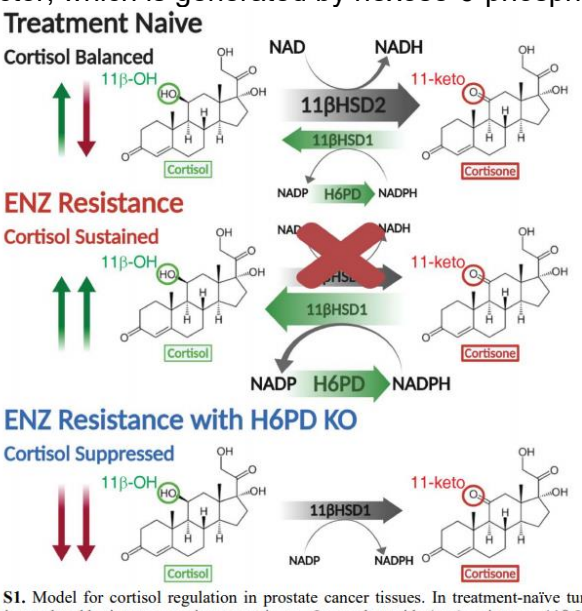

Figure S1. Model for cortisol regulation in prostate cancer tissues. In treatment-naïve tumors, cortisol is regulated by interconversion to cortisone. In enzalutamide (enz) resistance, 11β-HSD2 loss and H6PD upregulation impede cortisol inactivation, which sustains cortisol, resulting in enhanced GR activation. H6PD knockout (KO) or pharmacologic inhibition blocks NADPH, impeding the cortisone → cortisol directionality of 11β-HSD1, suppressing cortisol concentrations, inhibiting GR stimulation and reversing enz resistance.