

## **Epigenetic regulation of the glucocorticoid receptor drives drug resistance in prostate cancer**

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### **Background:**

We have previously shown that the glucocorticoid receptor (GR) is an important mediator of enzalutamide (Enz) resistance in a pre-clinical model of prostate cancer. GR is necessary for resistance, and is able to bypass the androgen receptor (AR) blockade by binding to and driving the expression of a subset of AR target genes. However, the mechanism by which GR expression is induced and maintained in these resistant cells is unknown. Here, we propose an epigenetic basis by which GR is able to be induced upon AR-inhibition in prostate cancer cells.

### **Methods and Results:**

As previously described, LREX' resistant cells (GR-high) and LNAR' sensitive cells (GR-low) were derived from an in vivo mouse xenograft model. LREX' resistant cells have a distinct loss of the repressive H3K27me3 mark around the GR locus, thus allowing for robust GR expression upon AR-inhibition. This epigenetic regulation of GR expression is also seen in prostate organoid cultures, and primary prostate tissues.

Furthermore, we describe a prostate-tissue specific enhancer that is important in regulating GR expression in this model. Using BET bromodomain inhibitors, we are able to target GR expression via this putative enhancer, and re-sensitize these resistant tumours to Enz.

### **Conclusion:**

We propose an epigenetic basis for resistance to Enz which allows for robust GR expression, and a subsequent bypass of the AR blockade. These resistant tumours can be re-sensitized to Enz by treatment with a BET bromodomain inhibitor, which effectively inhibits GR expression by targeting a tissue-specific GR enhancer.

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