# CRPC Tumors Are Inhibited by High Testosterone Therapy: Can We Identify Responders?

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**Background:** Supraphysiological testosterone (SPT)-based therapy produces clinical responses with improved quality of life; however, not all patients respond and responding patients exhibit differential magnitude and duration of responses. The objective of this study was to investigate molecular phenotypes predictive of response to improve patient selection.

**Methods:** A patient-derived xenograft (PDX) preclinical trial was conducted to evaluate the therapeutic efficacy of SPT in vivo. RNASeq and ChIPSeq data were analyzed to interrogate differences between responders and non-responders.

**Results**: SPT-therapy inhibited growth of 4/13 PDX models while 9/13 models were refractory to treatment. AR ChIPSeq analysis of the 14 pre-treatment PDX tumors revealed that there are significant differences in AR chromatin binding between responders and non-responders. These differential AR binding sites (ARBS) were also associated with FOXA1 binding and K27 acetylation. Notably, our analysis indicated that the responder-specific ARBS were significantly associated with the terms prostate gland growth, prostate epithelium morphogenesis and prostate gland development. However, further analysis showed that the responders specific ARBS are not enriched for a previously defined set of normal epithelium ARBS (Pomerantz et al. Nat. Gen. 2016). An integrated analysis of ChIPSeq and RNASeq showed that the responder-specific ARBS were highly enriched in the neighborhood of genes that were more highly expressed in the responders. One of the more robustly upregulated genes (>100 fold) identified is *PCA3* that could potentially serve as a biomarker of SPT responsiveness. GSEA analysis

indicated that interferon alpha and gamma signaling and KRAS signaling are higher in responders vs non–responders.

**Conclusions**: The AR-regulated genes that we identified in this study could form the basis of a signature for identifying potential responders to SPT therapy. Moreover, PCA3 is intriguing as a potential biomarker since PCA3 commercial tests are already available.