Deciphering the role of *PRAC1* in castration resistant prostate cancer

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Introduction and objective
Resistance to androgen receptor (AR) targeting therapies is one of the key drivers of prostate cancer mortality. Although several molecular alterations involved in castration resistant prostate cancer (CRPC) have been catalogued, a deep mechanistic understanding of the diverse resistance pathways operative in CRPC is still lacking. Here, we investigate DNA methylation changes as potential drivers of castration resistance.

Methods
We aimed to specifically investigate CpG methylation changes that are associated with the acquisition of castration resistance. To this end, we applied a reductionist approach by performing whole genome methylation analyses using MBD-seq on paired androgen dependent and castration resistant cell lines to identify candidate gene loci with differential methylation in CRPC. Results from this screen were validated in metastatic CRPC (mCRPC) samples from rapid autopsy cohorts. *In vitro* and *in vivo* loss and gain of function experiments were used to delineate phenotypic and transcriptomic alterations.

Results
We identified *PRAC1* as a differentially expressed and hypermethylated gene locus in castration resistant models. In clinical mCRPC samples, *PRAC1* hypermethylation was found in 42% of cases, but not in primary hormone naïve tumors, suggesting that epigenetic silencing of *PRAC1* is induced by and/or selected for by AR targeted therapies. *PRAC1* knock down or knock out resulted in a conversion to castration resistance of multiple cell lines *in vitro* and *in vivo*. Conversely, overexpression of the protein coding open reading frame of *PRAC1* inhibited growth of CRPC models in the absence of androgens. Mechanistically, depletion of *PRAC1* resulted in widespread transcriptional changes affecting in particular androgen regulated genes and genes involved in cell cycle progression.

Conclusion
Our data suggests that *PRAC1* is epigenetically silenced and may regulate AR signaling in CRPC. We are committed to further investigate the impact of *PRAC1* alterations in mCRPC and delineate the role of *PRAC1* in physiological androgen receptor signaling and resistance to AR directed therapies.

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