Functional genetic and genomic characterization of androgen receptor signaling in castration-resistant prostate cancer

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Background: There is currently no curative therapy for castration-resistant prostate cancer (CRPC), the terminal phase of prostate cancer that develops when the disease progresses on maximal androgen deprivation therapy. A defining molecular feature of CRPC is the reactivation of androgen receptor (AR) signaling, indicating that the AR remains central to prostate cancer pathogenesis across disease states. Several diverse mechanisms have been reported to contribute to persistent AR signaling in CRPC, and many more likely remain to be discovered. Elucidating the mechanisms by which some prostate cancers fail to respond to second-generation antiandrogens is critical to designing future therapies.

Methods: To identify *cis*- and *trans*- molecular factors that control *AR* expression and signaling in CRPC, we have used a combination of genomic and functional genetic technologies. With respect to the former, we have performed linked-read whole genome sequencing (WGS) on mCRPC biopsy specimens, patient-derived xenografts, and cell lines, including those collected both before and after progression on next-generation androgen pathway inhibitors. With respect to the latter, we have used genome-scale functional genetic screening to define the factors that control *AR* expression and splicing in CRPC.

Results: Our sequencing analysis has helped to define the structural variant landscape of CRPC, including most notably highly recurrent alterations involving a long-range enhancer of the *AR* that contribute to sustained AR signaling in the face of potent androgen pathway blockade. In addition, our functional genetic approach has identified several candidate genes responsible for regulating *AR* expression in CRPC. Preliminary mechanistic studies are ongoing to determine how these genes/pathways regulate AR signaling and to determine whether combining inhibition of these genes with direct targeting of AR may help to overcome castration resistance in preclinical models.

Conclusions: Complementary functional genetic and genomic sequencing approaches may be useful in identifying the complex landscape of features contributing to castration resistance in advanced prostate cancer.