Prostate cancer non-neuroendocrine lineage plasticity: detection using multimodal integration and immunotherapeutic targeting

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Abstract**:** Untreated prostate cancers rely on androgen receptor (AR) forming the basis for the initial efficacy of androgen deprivation therapy (ADT). Yet the disease can relapse and progress to castration-resistant prostate cancer (CRPC). Reactivation of AR signaling represents the most common driver of CRPC, and AR signaling inhibitors (ARSIs) are used in combination with ADT. However, ARSIs can result in selective pressure generating AR independent tumors. Khurana and Chen labs created a map of the chromatin accessibility and transcriptomic landscape of CRPC1, which revealed four subtypes: CRPC-AR (AR dependent), CRPC-NE (neuroendocrine), CRPC-SCL (stem-cell-like) and CRPC-WNT (Wnt pathway dependent). CRPC-SCL was a novel subtype identified in our work in which oncogenic growth is driven by AP-1 and YAP/TAZ transcription factors. Analysis of transcriptomic data revealed ~30% patients exhibit CRPC-SCL, making it the most common subtype after CRPC-AR. In the past few years, we have worked towards its clinical identification using cell-free DNA and targeted therapy by inhibition of TEAD/AP-1 pathway. In this proposal we will embark on novel approaches to address the challenges of clinical identification of CRPC-SCL using hematoxylin and eosin (H&E) whole slide images (WSIs) with artificial intelligence (AI) (w/ Co-PI Sanchez-Vega) (Aim 1) and immunotherapeutic targeting (w/ Co-PI Zappasodi) (Aim 2). Based on published literature, we hypothesize that CRPC-SCL tumors have an actionable immunosuppressive microenvironment, which we will test in Aim 2. This proposal will lead to identification of CRPC-SCL in patients using routine clinical information and reveal strategies for their immunotherapeutic targeting, potentially redefining the practice of care.