Defining prostate cancer cells of origin through single cell profiling

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Abstract: Despite remarkable improvements in prostate cancer survival with next generation antiandrogen therapies, drug resistance remains a significant issue. Interestingly, the use of these more potent inhibitors has led to a shift to lineage plasticity as a new mechanism of resistance, where tumor cells transdifferentiate from androgen receptor (AR)-dependent luminal cells to AR- independent basal, mesenchymal or neuroendocrine cells. This shifting pattern of resistance is observed in other tumor types such as lung cancer and melanoma following treatment with increasingly potent kinase inhibitors. In collaboration with Orit Rosenblatt-Rosen and Aviv Regev at the Broad Institute, we have used single cell RNA-sequencing (scRNA-seq) to reveal heterogeneity in the molecular underpinnings of lineage plasticity. Specifically, we have identified several master regulator transcription factors (Sox2, Zeb 1, Slug) that drive different aspects of lineage plasticity in mouse prostate organoid culture. We have also found unappreciated cellular complexity in the normal mouse prostate gland *in vivo*, as well as changes in subpopulations of luminal cells in response to castration and prostate regeneration (following androgen addback) that provide clues to the identity of prostate stem cells. In this proposal we will expand our *in vivo* analysis to three genetically engineered mouse prostate cancer models, using scRNA-seq to characterize tumor progression and response to castration. We will also isolate subpopulations of luminal cells with stem-like features from normal prostate tissue and measure the ability of these cells to regenerate normal prostate tissue and to serve as cells of origin for initiating cancers from various prostate cancer driver genes.