

“Functional Validation of Somatic Mutations in Prostate Cancer”

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Abstract: Despite the fact that prostate cancer remains the second most common cause of cancer death in men, knowledge of its genetic underpinnings remains incomplete. Indeed, obtaining sufficient prostate tumor tissue for large-scale genome characterization efforts has proved challenging. Our overarching goal is to impact prostate cancer clinical care by identifying key driving mechanisms enacted by somatic genetic alterations. Having successfully procured a large cohort of high-quality tumor tissues from aggressive prostate cancer, we are performing matched whole genome DNA sequencing (>30X coverage) and RNA sequencing (> 10 million reads) on multiple prostate tumor/normal pairs. The goal of this proposal is to develop novel computational approaches to integrate DNA and RNA alterations and use these methods to guide experimental validation studies. In Aim 1, we will develop an integrative analysis of the complete genome (DNA) and transcriptomic (RNA) sequencing data from at least 10 prostate cancers. All samples are high-grade primary tumors (Gleason grade 7 to 9) and include cases with and without known ETS family gene fusions. Candidate mutations and translocations will be validated with RNA-seq data from an additional 50 cases and from a biobank of over 1500 prostate cancer samples (frozen tissue and tissue microarrays). For validation we will also use a combination of PCR, pooling/sequencing, immunohistochemistry, and FISH. We will correlate findings with clinicopathologic parameters to prioritize key molecular lesions. In Aim 2, we will functionally characterize high-priority candidate genes using *in vitro* cell line experiments to parse out those lesions most likely to drive prostate cancer. As a result of this work, we anticipate nominating multiple novel genetic alterations associated with prostate cancer progression that may ultimately inform new therapeutic avenues in this malignancy.