

Abstract title: Decoding the Molecular Landscape of BRCA1/2-Associated Prostate Cancer

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Background: Prostate cancer (PCa) remains a major cause of cancer-related mortality among men, and germline *BRCA1/2* mutation carriers face an elevated risk of aggressive, early-onset disease with poorer survival outcomes. African American men experience disproportionately high rates of aggressive PCa, likely reflecting a combination of genetic and social factors that remain incompletely understood. Because PCa is highly heterogeneous at both the clinical and cellular level, resolving tumor-associated cellular phenotypes is essential for understanding disease progression and identifying therapeutic targets.

Methods: This project uses single-cell and spatial transcriptomics, together with genomic and histologic approaches, to characterize how *BRCA1/2* loss shapes cellular heterogeneity in PCa, with particular attention to African American patients.

Results: Over the past year, we assembled a single-cell RNA sequencing cohort of prostate biopsy and prostatectomy tissue from age-matched *BRCA2* carriers and non-carriers, drawn from a broader collection of 78 normal prostate specimens and yielding a final cohort of 18 samples spanning normal and tumor tissue. Bulk RNA sequencing and targeted DNA sequencing (Twist panel) of an additional cohort of 80 tumor samples are underway to assess genomic instability markers. Differential expression (DESeq2) and gene set enrichment analysis (fgsea, Hallmark pathways) were used to compare *BRCA2* carriers and non-carriers. In parallel, we constructed tissue microarrays from 67 cases (201 cores) spanning benign and tumor, *BRCA*-carrier and non-carrier tissue, and performed immunohistochemistry for NKX3.1, p53, PIN4, and PSA ahead of spatial transcriptomic profiling.

Single-cell sequencing has been completed for the entire cohort, and we have established a working pipeline for quality control, batch integration, and cell-type annotation across samples. Cell sorting by deconvolution (CIBERSORT) is being applied to validate the single-cell annotations. Preliminary differential expression and pathway analyses are underway to compare *BRCA2*-mutant and wild-type samples across normal and tumor states, and our tissue microarrays have passed quality control (DV200) and are ready for spatial profiling. These efforts provide the cellular framework needed to resolve *BRCA2*-associated transcriptional changes. Next, we will finalize cell-type annotations and proportions, complete differential expression and gene set enrichment comparisons between *BRCA2* and wild-type samples in normal and tumor tissue, and extend pathway analysis using single-sample GSEA and transcription factor activity inference (decoupleR).

Conclusion: Together, these findings will clarify how *BRCA1/2* loss drives cellular heterogeneity and progression in prostate cancer, informing targeted prevention and treatment strategies aimed at reducing disparities in prostate cancer outcomes.

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Conflicts of Interest: No

