**OVPR REVISE AND RESUBMIT SEED GRANT PROGRAM**

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**Title:** *Investigating targetable mechanisms of altered cell states in castration-resistant prostate cancer*

## Project Summary:

The mechanisms driving phenotypic cellular diversification in tumors remain understudied, posing a major barrier to effective therapeutic strategies. Recent scRNAseq studies, including ours, have highlighted the diversity of altered cell states diverging from normal transcriptomic states. Drug-resistant subtypes often activate unique survival and growth pathways and may establish early during tumor development, undermining current treatments. Identifying specific markers/pathways driving the fitness of resistant subtypes is essential for understanding their development and informing strategies toward potentially curative treatments.

Our project aims to dissect and exploit mechanisms driving the emergence of specific cellular subtypes in early prostate cancer capable of proliferating under androgen-deprivation therapy (ADT). Preliminary studies indicate that a rare subpopulation in ADT-naïve tumors expresses follistatin (Fst) and expands in castration-resistant prostate cancer (CRPC), with increased Fst levels. We **hypothesize** that Fst overexpression marks a subpopulation with intrinsic castration resistance. We will address the role of Fst in three specific aims: 1) **functional analysis of follistatin modulation in castration resistance**, 2) **elucidate Fst's pro-survival mechanisms in CRPC,** and 3) **characterize and target Fst+ cell states in CRPC.**

This research will advance understanding of Fst-dependent mechanisms in CRPC progression, potentially leading to new therapies to control advanced disease and improve patient outcomes.