**TARGETING NONO-PSPC1 IN METASTATIC PROSTATE CANCER**

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**Background:** Prostate cancer growth relies the androgen receptor (AR) pathway, and blocking this pathway through androgen deprivation and AR antagonists is used to treat prostate cancer. However, CaP patients who receive androgen deprivation therapy (ADT) often relapse and develop castration-resistant prostate cancer (CRPC), which still relies on the AR pathway for growth. Tumors at this advanced stage are highly proliferative and metastatic, leading to fatality. Neither the mechanism underlying CRPC progression nor the factors regulating AR under ADT conditions is fully understood. Our proposal addresses the urgent need to identify new therapeutic targets and develop new agents to combat metastatic castration-resistant prostate cancer. The AR function in CRPC is regulated through a network of signaling pathways that are altered upon ADT, thereby promoting metastasis and cancer progression.

**Method and Result**: Using an innovative target identification strategy that incorporates a functional genomic screen for AR coactivators with advanced bioinformatic analyses of gene expression changes between primary and metastatic prostate cancers from multiple patient cohorts, we identified the NONO-PSPC1 complex as a putative AR coregulator in CRPC. Our preliminary data indicate that NONO-PSPC1 functions as a dimer and behaves as a molecular scaffold that binds AR and regulates AR transcriptional activity. NONO-PSPC1 are overexpressed in metastatic compared with localized prostate cancer. NONO or PSCP1 depletion by siRNA decreased AR-mediated transcription and reduced the viability of therapy-resistant of prostate cancer cells. NONO or PSPC1 also induced apoptosis and accumulation of DNA damage in drug-resistant prostate cancer cells. The structure of the NONO-PSPC1 complex has been elucidated and a druggable pocket at the interface between NONO and PSPC1 has been identified. Our compound screen identified two small molecules that disrupted NONO-PSPC1 interactions, blocked AR biding to NONO-PSPC1, and suppressed AR transcriptional activity. These two NONO-PSPC1 inhibitors decreased the viability of CRPC cells while showing no effect in non-cancer cells.

**Conclusion**: Our high throughput target selection/therapeutics screen platform is fast and efficient compared to current method in drug discovery. From this premise, we showed that the NONO-PSPC1 complex is a novel AR coactivator and facilitator of therapy resistant metastatic prostate cancer. Inhibition of the NONO-PSPC1 complex represents an attractive therapeutic strategy for blocking AR activity.

Conflict: D.T. and K.F are employed by GeneCentrix.
This project does not have funding.