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Identification of novel inhibitors for the most aggressive and lethal prostate cancer subtype 1

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Prostate cancer is a heterogeneous disease and the major clinical challenge has long been in recognition and targeting of the most aggressive disease. Recently, new classification method for prostate cancer described three novel subtypes, PCS1, PCS2 and PCS3 from which PCS1 was identified as the most aggressive and lethal subtype that correlated with poor survival. However, there are no specific molecular targets or therapeutics available for this subtype in the clinic.

To investigate whether our recently generated castration and Enzalutamide (ENZ) resistant prostate cancer cell line models display any of the newly characterized prostate cancer subtypes, we performed gene expression analyses and analysed the expression of the subset specific genes in our cells. Surprisingly, the results showed that 'androgen receptor (AR)-indifferent' $42D^{ENZR}$ and $42F^{ENZR}$ cells displayed PCS1 signature whereas the AR-driven, ENZ resistant $49B^{ENZR}$, $49D^{ENZR}$ and $49F^{ENZR}$ cells were categorized as PCR2 subtype. The results were also confirmed by gene set enrichment analyses. These results indicate thatmolecular features in PCS1-like $42D^{ENZR}$ and $42F^{ENZR}$ cells can be utilized to study novel targets and therapeutics for PCS1.Next, we utilized the gene expression data from thePCS1 subtype and PCS1-like cells and identified forkhead box M1 inhibitor Thiostrepton as the most enriched compound reversing all three signatures. These results suggest Thiostrepton as a novel PCS1 targeting agent. Moreover, the results reveal that targeting forkhead box M1 is a potential novel strategy to target the most lethal subtype of prostate cancer.

In conclusion, the results revealed that our AR-indifferent Enzalutamide resistant prostate cancer cells model the most aggressive and lethal prostate cancer subtype PCS1. These results also indicate that elucidating the molecular mechanisms that govern aggressive cell phenotypes, and establishing their importance in prostate disease progression, may guide clinical evaluation of compounds targeting PCS1 subtype associated with ENZ and castration resistant prostate cancer to improve current standard of care.

Biography:

US Department of Defense and Prostate Cancer Canada Fellow Kirsi Ketola, PhD, is a molecular biochemist and prostate cancer researcher at the University of British Columbia and Vancouver Prostate Centre. She has expertise in cancer systems biology, precision medicine and drug discovery and her current research interests include utilizing the 'knowledge of the omics' in designing novel treatment options for cancer and to repurpose drugs for personalized cancer treatment. Her projects specially focus on the mechanisms of castration and Enzalutamide resistance and development of novel targeted agents for adaptive response to therapy in advanced and lethal prostate cancer. She has published several peer-reviewed publications related to these areas.