Cooperative actions of a novel ERβ ligand, WTIV012, and enzalutamide in advanced prostate cancer

Jaimie S. Gray, Moray J. Campbell

Background: Early successful therapies in prostate cancer (PCa) included the use of estrogens but were discontinued due to serious side effects. Given estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) appear to have opposing actions, it is unclear how estrogen actions control PCa growth. The OSU Drug Development Institute has developed a novel compound, WTIV012, that selectively targets ERβ, allowing for the possibility to study ERβ effects in androgen deprivation therapy (ADT) resistant or sensitive PCa.

Methods: A combination high-throughput drug viability screen was undertaken in ADT-sensitive and resistant PCa models that combined multiple concentrations of WTIV012 with 30 compounds including Enzalutamide (Enza), and epigenomic regulators. Quantitative PCR (qPCR) for key genes and RNA-Seq was undertaken for selected WTIV012 combinations.

Results: The 30 different WTIV012 multi-dose combinations were tested in one ADT-sensitive and four ADT-resistant PCa cell lines in duplicate; equivalent to 23,040 dose/drug combinations. Drug interaction delta values were calculated as observed percent inhibition of drug combination minus the expected additive percent inhibition of each drug. All cell lines were sensitive to high doses of WTIV012 alone (1-10μM) whereas each cell line displayed unique responses to WTIV012 drug interactions; 22RV1 cells responded with the greatest additive effects to combinations of WTIV012 with Enza and several histone deacetylase inhibitors (Istodax). We focused on WTIV012 plus Enza for pathway analyses. In the first instance, qPCR in cells treated with WTIV012 plus Enza revealed a significant decrease in transcription of AR target genes including *TMPRSS2* and reduced transcription of AR itself. Currently, we are undertaking RNA-Seq LNCaP, 22RV1 and LNCaP C4-2B in response to estrogen plus Enza or WTIV012 plus Enza to reveal the unique pathways regulated by WTIV012 plus Enza.

Conclusion: The possibility of targeting ERβ in the context of PCa is now becoming a reality with development of the novel, highly selective ERβ agonist, WTIV012. Specifically, this ligand is a powerful tool to understand the specific role of ERβ has on transcriptomic and epigenetic regulation. Our initial data suggest that there is a promising cooperative action between WTIV012 and the ADT drug Enza. Overall, using WTIV012 may prove to be a powerful tool to study estrogen anticancer functions in PCa.