Abstract 3078: YIV-818-A enhanced apalutamide, darolutamide and enzalutamide action for prostate cancer treatment by down-regulating androgen receptor protein, inhibiting glucocorticoid receptor function and epigenetic regulation

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Abstract

Prostate cancer is the second leading cause of cancer death among men in the United States. Androgen or Androgen receptor (AR) targeted therapy is a strategy for the treatment of prostate cancer, however, long-term treatment with androgen deprivation therapy inevitably leads to the development of Castration-Resistant Prostate Cancer (CRPC). AR variants and glucocorticoid receptor (GR) (replacing AR function) are two key factors to promote resistance to AR-targeting therapies in CRPC patients. Developing a multi-targeted drug that can inhibit both the AR variant and GR action could help overcome drug resistance, increase durability, and improve the therapeutic outcome for prostate cancer patients. Through our STAR (Signal, Transduction, Activity, and Response) Drug Discovery Platform, we studied the effects of three hundred medicinal plant extracts across 25 signaling pathways to identify a drug candidate. YIV-
818-A was developed as a novel drug candidate based on optimized water extracts of Rubia cordifolia (R.C). R.C collected from different sources had different quantities of compound X. The amount of compound X of R.C could be correlated to the potency of AR inhibition. YIV-818-A was able to inhibit DHT or Dexamethasone (DEX) induced luciferase activity of 22RV1 cells which were harboring ARE luciferase reporter. Using activity guided purification of YIV-818-A, compound X was identified as the key active compound for inhibiting AR and GR activities. YIV-818-A and compound X could down regulate both AR (full length) and AR-V (splice variants) protein but not GR protein of 22RV1 cells. YIV-818-A and compound X could also inhibit KLK2, and PSA (AR target genes) mRNA expression induced by DHT or SGK (GR target gene) mRNA expression induced by DEX. YIV-818-A and compound X had the potential to affect epigenetics of 22RV1 cells by down-regulating Brd2 and Brd4 (BET: bromodomain and extra-terminal proteins which could serve as epigenetic readers to promote AR or GR-dependent gene transcription) and reduce histone 3 lysine 27 acetylation (H3K27Ac), which is required for BRDs binding, but not H3K9Ac or K14Ac. Most importantly, YIV-818-A and compound X showed synergies with apalutamide, darolutamide and enzalutamide to inhibit AR activity and growth of 22RV1 cells. In conclusion, YIV-818-A and compound X could overcome drug resistance caused by AR variants and GR by down-regulating AR protein, inhibiting GR function and epigenetic regulation. YIV-818-A and compound X could enhance anti-prostate cancer drug action against CRPC. R.C has a long history of safe, human usage in Asia as a dietary supplement for improving health. Given R.C.'s safety profile, YIV-818-A also could be developed as a chemoprevention agent and/or anti-cancer prostate cancer drug.


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