[L7] A Cheminformatics Story Behind 141,000,000$ Molecule

Artem Cherkasov

Vancouver Prostate Centre, University of British Columbia, 2660 Oak Street, Vancouver, British Columbia V6H3Z6, Canada

The human androgen receptor (AR) is considered as a master regulator in the development and progression of prostate cancer (PCa) and its prime drug target. As resistance to current clinically used anti-AR drugs remains a major challenge for the treatment of advanced PCa, there is a continuing need to pursue new anti-AR therapeutic avenues. In this study, we applied an array of cheminformatics techniques including docking, pharmacophore search, fingerprint and shape-based similarity search, a variety of 3D and 4D QSAR models to identify an initial set of virtual hits that target the DNA binding domain (DBD) of the AR – a target site that has never been previously explored for nuclear receptors. Through further exploration of a related chemical space around the most active hit - compound VPC 1 (IC50 = 3.27 μM), its active analogue VPC 6 was identified demonstrating 10-fold improved anti-AR potency (IC50 = 0.33 μM). Further computer-aided optimization of the initial AR DBD binders resulted in the creation of more than 500 synthetic analogues of compound VPC 6. One of the developed molecules exhibited anti-AR potency (IC50 = 0.05 μM) that is comparable to a newly approved anti-AR drug Enzalutamide (IC50 = 0.11 μM).

The following site-directed mutagenesis experiment demonstrated that the developed inhibitors do interact with the intended target site on the AR DBD. Importantly, it has also been demonstrated that the developed AR DBD binders effectively inhibit the growth of cells which already developed resistance to Enzalutamide as well as can block the transcription activity of constitutively active AR splice variants, such as V7 and V567 implicated in castration-resistant PCa. The compounds also demonstrated significant efficacy in animal castration-resistant PCa models and exhibited to cross-reactivity toward other nuclear receptors.

As the result of the conducted cheminformatics-driven discovery efforts, the University of British Columbia licensed the compound VPC6 and its analogues to Hoffmann-Roche Company for a 141M dollars.