Small molecule inhibitors targeting AR/AR, AR/ARV and ARV/ARV dimerization interfaces as potential therapies for CRPC.

Kush Dalal[1], Fuqiang Ban[1], Huifang Li[1], Helene Morin[1], Mani Roshan-Moniri[1], Kevin J. Tam[1], Ashley Shepherd[1], Aishwariya Sharma[1], James Peacock[1], Mike. L. Carelson[2], Eric LeBlanc[1], Carl Perez[1], Franck Duong[2], Christopher J. Ong[1], Paul S. Rennie[1] and **Artem Cherkasov[1]**

[1]Vancouver Prostate Centre (VPC), 2660 Oak Street, Vancouver, British Columbia, V6H3Z6, Canada

[2]Department of Biochemistry and Molecular Biology, University of British Columbia, 2350, Health Sciences Mall, Vancouver, British Columbia, V6T 1Z3, Canada

The currently used anti-androgens that interfere with steroid recruitment to human androgen receptor (AR) temporarily prevents AR-driven tumor growth, but are rendered ineffective by the emergence of mutations in the ligand binding domain (LBD) of the receptor or by expression of its constitutively active splice variants, such as ARV7, that lack the LBD altogether. Both of these drug-resistance mechanisms have confounded attempts to treat this 'castration resistant' stage of PCa (CRPC), characterized by the return of AR signalling and lethal outcomes.

We have utilized a computer-aided drug design platform to develop small molecules that block the dimerization of the AR – a critical step for activation of all forms of the receptor. In particular, by conducting a virtual screening on the AR DNA binding domain (DBD) dimerization interface, several prototypical protein-protein interaction inhibitors have been developed and further verified to block homo- and hetero dimerization of full length and truncated forms of the AR. The developed compounds effectively supressed transcriptional activity of AR and ARV7 through a novel and LBD-independent mechanism of action.

Such AR dimerization inhibitors therefore have a potential to circumvent all AR-dependent resistance mechanisms, thereby presenting an opportunity to directly target CRPC tumor growth.

Conflict of Interest

We have a license agreement with *Hoffmann* la Roche.

Funding Acknowledgements

This work is supported by the Canadian Institutes of Health Research grant (PJT-156094) and US Department of Defense / Prostate Cancer Idea Development Award (W81XWH1810584 ; PC170905P2)