Accepted Manuscript

Selectively targeting the dimerization interface of human androgen receptor with small-molecules to treat castration-resistant prostate cancer

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PII: S0304-3835(18)30528-7

DOI: 10.1016/j.canlet.2018.08.016

Reference: CAN 14030

To appear in: *Cancer Letters*

Received Date: 3 April 2018

Revised Date: 14 August 2018

Accepted Date: 16 August 2018

Please cite this article as: K. Dalal, F. Ban, H. Li, H. Morin, M. Roshan-Moniri, K.J. Tam, A. Shepherd, A. Sharma, J. Peacock, M.L. Carlson, E. LeBlanc, C. Perez, F. Duong, C.J. Ong, P.S. Rennie, A. Cherkasov, Selectively targeting the dimerization interface of human androgen receptor with small-molecules to treat castration-resistant prostate cancer, *Cancer Letters* (2018), doi: 10.1016/j.canlet.2018.08.016.

Abstract

Prostate cancer (PCa) is a leading cause of death for men in North America. The androgen receptor (AR) - a hormone inducible transcription factor - drives expression of tumor promoting genes and represents an important therapeutic target in PCa. The AR is activated by steroid recruitment to its ligand binding domain (LBD), followed by receptor nuclear translocation and dimerization via the DNA binding domain (DBD). Clinically used small molecules interfere with steroid recruitment and prevent AR-driven tumor growth, but are rendered ineffective by emergence of LBD mutations or expression of constitutively active variants, such as ARV7, that lack the LBD. Both drug-resistance mechanisms confound treatment of this 'castration resistant' stage of PCa (CRPC), characterized by return of AR signalling. Here, we employ computer-aided drug-design to develop small molecules that block the AR-DBD dimerization interface, an attractive target given its role in AR activation and independence from the LBD. Virtual screening on the AR-DBD structure led to development of prototypical compounds that block AR dimerization, inhibiting AR-transcriptional activity through a LBD-independent mechanism. Such inhibitors may potentially circumvent AR-dependent resistance mechanisms and directly target CRPC tumor growth.