Targeting oncogenic transcription in prostate cancer with a novel, oral bioavailable, and ultra-selective CDK9 inhibitor

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Abstract

Castration resistant prostate cancers (CRPCs) lose sensitivity to androgen deprivation therapies but frequently remain dependent on oncogenic transcription driven by androgen receptor (AR) and its splice variants. To discover novel modulators of AR isoform activity, we identified binders of AR variants and their interactome members using a lysate-based small molecule microarray (SMM) screening assay and defined Ki-ARv-03 as a putative binder that reduces AR levels and proliferation in prostate cancer cells. We deduce Ki-ARv-03 to be a potent, selective inhibitor of CDK9, an important cofactor for AR, MYC, and other oncogenic transcription factors. Further optimization resulted in KB-00130742, an orally bioavailable, selective CDK9 inhibitor with potent anti-tumor activity in CRPC models. In 22Rv1 cells, KB-00130742 significantly reduced tumor growth in CRPC, supporting CDK9 inhibition as a promising therapeutic strategy to target AR dependence in CRPC.

I. ARv SMM screen funnel

A) SMM screen to identify binders of ARv complex

B) Screen funnel to identify modulators of ARv dependency

IV. Selective CDK9 inhibition blocks oncogenic nascent transcription

A) CDK9 inhibition globally downregulates nascent transcription

B) CDK9 inhibition downregulates AR-dependent oncogenic transcription

VI. In vitro activity of CDK9 inhibition

A) Selective CDK9 inhibition reduces tumor growth in vivo
