Targeting Androgen Receptor and ACK1 signaling with Novel Epigenetic Therapeutics in Castration-Resistant Prostate Cancer

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Background Onset of prostate cancer (PC) and its progression is critically dependent on androgen receptor (AR), which has led to development of therapeutic strategies that counteract AR activity, including, Enzalutamide, which has been approved for treatment of Castration-Resistant Prostate Cancer or CRPC. The overall survival advantage with Enzalutamide was found to be modest with most patients relapsing within 2 years. A significant increase in AR splice variant, AR-V7 that lacks the ligand binding domain was associated with increased Enzalutamide resistance.

Methods To address these setbacks, we opened a new line of investigation- ablation of AR protein and its variant AR-V7 using a suitable small molecule inhibitor. We developed a novel small molecule inhibitor (*R*)-9bMS that targets a non-receptor tyrosine kinase, ACK1. Further, we identified a new epigenetic modification in histone H4 in human CRPC samples by using mass spectrometry.

Results We observed that CRPCs upregulate ACK1 kinase expression upon androgen deprivation. ACK1 interacts with AR to regulate a distinct transcription program in androgen-deprived PC cells, including expression of AR itself. ACK1 (also known as TNK2) phosphorylated histone H4 at tyrosine 88 upstream of the AR transcription start site. The WDR5/MLL2 complex reads the H4-Y88-phosphorylation marks and deposited the transcriptionally activating H3K4-trimethyl marks promoting AR transcription. (*R*)-9bMS inhibited cell proliferation and works at nanomolar concentrations. Importantly, (*R*)-9bMS sensitized naive and enzalutamide-resistant PCs and reduced AR and AR-V7 levels to mitigate CRPC tumor growth.

Conclusions ACK1 is an important therapeutic target in CRPCs. It regulates AR expression upon androgen deprivation. (*R*)-9bMS and derivatives could be a new class of ACK1/AR pathway antagonists with a potential to inhibit CRPC growth in a subset of patients that either do not respond to enzalutamide or abiraterone, or have developed resistance to it.

Conflict of Interest N.P.M. and K.M. are named as inventors on a patent for antibodies specific for phosphorylated histones, and K.M., H.R.L., N.J.L., and N.P.M. are named as inventors on ACK1/TNK2 kinase inhibitors. Both the patents have been licensed by TechnoGenesys, Inc. K.M. and N.P.M. are co-founders of TechnoGenesys, Inc., own stock, and serve as consultants for TechnoGenesys, Inc.

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