Activity-associated Protein Target Profiling of the Androgen Receptor Antagonist EPI-002

Jian Tang¹, John C. Widen¹, Scott M. Dehm²,³, and Daniel A. Harki¹,²*

¹Department of Medicinal Chemistry and ²Masonic Cancer Center, ³Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN 55455

Constitutive activation of androgen receptor (AR) signaling in castration-resistant prostate cancer (CRPC) facilitates tumor growth in patients despite treatment with anti-androgen therapies that target AR C-terminal ligand-binding domain (LBD).¹ EPI-001/EPI-002 (2R, 20S isomer) have been reported as AR antagonists by binding covalently to the N-terminal domain (NTD) through its chlorohydrin moiety and blocking protein-protein interactions that are required for transcriptional activity.²,³ Therefore, AR NTD antagonists may function as viable therapies for CRPC. However, recent studies have shown multilevel inhibitory effects of EPI-002 in prostate cancer cells through non-AR interactions.⁴ We have used unbiased activity-associated protein target profiling to annotate those proteins covalently bound by EPI-002 that likely confer AR inhibitory activity. Alkyne probe EPI-054³ was synthesized and shown to have similar anti-proliferative activity compared to parent compound EPI-002. Using EPI-054 as a tool compound, our progress towards target profiling of this class of AR antagonists will be presented.

Reference: