CUDC-907, a dual PI3K and HDAC inhibitor, reduces AR-FL, AR-Vs, and Myc expression in prostate cancer

Nathan Lau[1], Bobby Tofig[2], Takuma Uo[3], Stephen R. Plymate[3], Robert Damoiseaux[2], Owen N. Witte[2], **John K. Lee[1]**

[1]Fred Hutchinson Cancer Research Center, [2]University of California at Los Angeles, [3]University of Washington

Background: Castration-resistant prostate cancer (CRPC) is a heterogeneous disease that constitutes multiple molecular and histologic subtypes. Most CRPCs remain dependent on active androgen receptor (AR) signaling and overcome castration through AR amplification, AR mutation, expression of constitutively active AR variants (AR-Vs), and aberrant AR activation. Myc amplification and overexpression are also common in CRPC. Myc is a direct transcriptional target of AR and is involved in a wide array of critical cellular functions that enable androgen-independent proliferation.

Methods: Cell-based fluorescent reporter assays of full-length AR (AR-FL) and AR splice variant 7 (AR-V7) abundance were established in HEK 293T cells. HEK 293T cells were co-transduced with 1) a lentivirus simultaneously expressing AR-FL or AR-V7 fused to a destabilized enhanced green fluorescent protein (dEGFP) and a destabilized red fluorescent protein (dRFP) and 2) a lentivirus expressing enhanced blue fluorescent protein fused to Histone H2B.

The HEK 293T AR-FL and AR-V7 cell lines were used to optimize a high-content, high-throughput screen to image and quantitate relative fluorescence as indicators of AR abundance and subcellular localization at the UCLA Molecular Shared Screening Resource. We evaluated a 430-compound kinase inhibitor library to identify agents at concentrations of 10 μM and 1 μM that may reduce AR-FL and AR-V7 protein abundance at 24 hours. Hits were filtered based on reduction in dEGFP/dRFP signal and a cell count threshold to exclude broad, non-specific cytotoxicity.

Screen hits were evaluated in the CWR22Rv1, LNCaP, LNCaP95, and VCaP cell lines to examine effects on AR-FL and AR-Vs protein levels by immunoblot analyses. Dose response curves were also generated using a larger panel of benign prostate epithelial and prostate cancer cell lines.

Results: CUDC-907 (Fimepinostat), a first-in-class dual PI3K and HDAC inhibitor, was identified as the top hit in both kinase inhibitor screens in the HEK 293T AR-FL and AR-V7 cell lines. On-target effects on PI3K and HDAC as well as the inhibition of AR-FL, AR-Vs, and Myc expression were identified in multiple human prostate cancer cell lines at sub-micromolar treatment doses of CUDC-907. Prostate cancer cell lines exhibited enhanced sensitivity to CUDC-907 relative to benign prostate epithelial cell lines.

Conclusions: CUDC-907 is a clinical therapeutic agent (currently in trials for B cell lymphomas) for which we provide preliminary evidence of activity across a diverse human prostate cancer cell line panel with potent inhibition of AR and Myc expression. Ongoing studies are aimed at evaluating the mechanisms of oncogenic disruption by CUDC-907 in prostate cancer and the anti-tumor activity of CUDC-907 in patient-derived xenograft models.

Conflict of Interest: None.

Funding Acknowledgements: JKL is funded by a PCF Young Investigator Award and a Department of Defense Prostate Cancer Research Program Physician Research Award. This work was also funded by a Pacific Northwest Prostate Cancer SPORE Career Enhancement Program Award to JKL.