Cross-resistance among next generation anti-androgen drugs through the AKR1C3/AR-V7 axis in advanced prostate cancer

*Jinge Zhao, Shu Ning, Wei Lou, Joy C. Yang, Cameron M. Armstrong, Alan P. Lombard, Leandro S D'Abronzo, Christopher P. Evans, Allen C. Gao, Chengfei Liu**

Department of Urologic Surgery, UC Davis Comprehensive Cancer Center, University of California at Davis, Sacramento, CA, USA

INTRODUCTION AND OBJECTIVES: The next generation anti-androgen drugs, XTANDI® (Enzalutamide), ZYTIGA® (Abiraterone acetate), ERLEADA™ (Apalutamide) and NUBEQA (Darolutamide) extend survival times and improve quality of life in advanced prostate cancer patients. Despite these advances, resistance occurs frequently and there is currently no definitive cure for Castration-Resistant Prostate Cancer (CRPC). Our previous studies identified that similar mechanisms of resistance to enzalutamide or abiraterone occur following treatment and cross-resistance exists between these therapies in advanced prostate cancer. In this study, we will investigate the role of the AKR1C3/AR-V7 axis in apalutamide and darolutamide resistance.

METHODS: C4-2B cells were chronically exposed to increasing concentrations of apalutamide (5 μM ~ 40 μM) by passage in media containing apalutamide for >12 months in complete FBS and stored for further analysis. Cells resistant to apalutamide were referred to as C4-2B APALR. The effects of AKR1C3 expression and activation were examined by knock down of AKR1C3 expression using lenti-shRNA or inhibition of AKR1C3 enzymatic activity by indomethacin. AR and AR-V7 activity were determined by luciferase reporter assay. The effects of AKR1C3 activation on anti-androgen sensitivity were examined by growth assay and clonogenic assay.

RESULTS: Enzalutamide and abiraterone resistant prostate cancer cells are further cross-resistant to apalutamide and darolutamide. Mechanistically, we have determined that the AKR1C3/AR-V7 axis confers this cross-resistance. Knockdown of AR-V7 in enzalutamide resistant cells re-sensitize cells to apalutamide and darolutamide treatment. Furthermore, targeting AKR1C3 re-sensitizes resistant cells to apalutamide and darolutamide treatment through AR-V7 inhibition. Chronic apalutamide treatment in C4-2B cells activates the steroid hormone biosynthesis pathway and increases AKR1C3 expression which confers resistance to enzalutamide, abiraterone and darolutamide.

CONCLUSION: Apalutamide and darolutamide share similar resistant mechanisms with enzalutamide and abiraterone. The AKR1C3/AR-V7 complex confers cross-resistance to second generation AR-targeted therapies in advanced prostate cancer.