Resistance to standard-of-care anti-androgen therapy (ADT) is the primary reason patients with metastatic prostate cancer die. The primary mechanism of ADT-resistance, also known as castration resistant prostate cancer (CRPC), is reactivation of the androgen receptor (AR), through mutation, amplification, or splicing variants, such that its dependence on androgen is lost or severely reduced. Under these conditions, AR becomes constitutively activated and remains the major oncogenic driver. To overcome CRPC, it will be crucial to devise a different way to target AR other than through suppression of its ligand. An ideal approach is to find ways to inhibit AR expression rather than just its activity. Promoter analysis of the AR gene reveals the presence of a G-quadruplex structure ~120 bp upstream of the transcriptional start site. A drug screen using a newly developed library of G-quadruplex stabilizing agents (GSA) identified 3 top candidates with the selective ability to inhibit AR mRNA and protein expression in 4 different AR+ prostate cancer cell lines, including the ARv7 splice variant commonly found in CRPC. The ability of the GSA compounds to suppress AR was found to be dependent on their ability to recruit the nuclear scaffold protein, Nucleolin, to the AR G-quadruplex and to stabilize the structure. The most stable structure produces an 11-13 base loop, which is the likely target of the GSA/Nucleolin complex. Initial results suggest that the complete sequence of the 11-13 base loop is required for drug-induced stabilization. A similar extended loop structure is also formed in the G-quadruplex in front of the MYC gene, and its ability to be stabilized also requires Nucleolin. MYC, another major driver of prostate cancer, is overexpressed or amplified in over 80% of CRPC. The top 3 drug candidates that suppress AR, were also very efficient at suppressing Myc expression. Preliminary MTD studies indicate the GSA0932 drug is well tolerated by mice. It is stable in PBS but is rapidly degraded in microsomes. In IP injections, its half-life in serum is XX. Studies are ongoing to determine the effectiveness of GSA0932 at suppressing the growth of CRPC in vivo. Given that Myc is also a major driver of prostate cancer, these new compounds offer the potential for dual targeting of Myc and AR in CRPC.

Funding: UA Accelerate for Success; UACC; TLA 19-015