

Dual AR/AR-V7 Molecular Glue Degraders Overcomes Therapeutic Resistance in Advanced Prostate Cancer

CheukMan Cherie Au¹, Michelle Naidoo¹, Catrina Estrella¹, Kiran Kumari Sahu¹, Charles D. Warren², Prerna Vatsa¹, Xuanrong Chen³, David M. Nanus^{1,4}, Urko del Castillo¹, Jacob B. Geri^{2,5}, Paraskevi Giannakakou^{1,4}

¹ Department of Medicine, Weill Cornell Medical College, New York, United States

² Tri-Institutional PhD Program in Chemical Biology (TPCB), New York, NY, USA

³ Department of Urology, Weill Cornell Medicine, New York, NY, USA

⁴ Meyer Cancer Center, Weill Cornell Medical College, New York, United States

⁵ Department of Pharmacology, Weill Cornell Medicine, Cornell University, New York, NY, USA

Metastatic castration-resistant prostate cancer (mCRPC) remains a lethal malignancy, **driven by persistent androgen receptor (AR) signaling**. Most AR-directed therapies target the ligand-binding domain (LBD), yet selective pressure inevitably leads to treatment resistance through mechanisms including AR amplification, LBD mutations, and expression of constitutively active AR splice variants. AR-V7, the most prevalent AR splice variant, lacks the LBD, is detected in a substantial proportion of patients with mCRPC, and is associated with resistance to AR signaling inhibitors and taxane chemotherapy. Despite its clinical importance, no pharmacologic AR-V7 inhibitor is currently available, representing **a major unmet therapeutic need**.

To address this, we performed a high-throughput phenotypic screen of 170,000 compounds and identified **a novel chemotype that induces proteasome-dependent degradation of both full-length AR (AR-fl) and AR-V7**. Medicinal chemistry/SAR optimization generated potent lead compounds with favorable drug-like properties. The lead compounds induce degradation of AR-fl and AR-V7, suppress their downstream transcriptional activity, and retain potent activity in enzalutamide-resistant prostate cancer models expressing endogenous AR-fl, AR-V7, and clinically relevant AR-LBD mutations, while sparing AR-negative and normal prostate cells.

Mechanistic studies confirmed degradation through the ubiquitin-proteasome pathway, dependent on Cullin-RING ligase activity. A CRISPR-based E3 ligase screen identified DDB1 and RBX1 among candidate mediators of degradation, and DDB1 depletion partially rescued compound-mediated AR-fl/AR-V7 degradation, supporting a molecular glue mechanism. Domain mapping using AR truncation mutants, together with thermal shift studies, localized compound activity to the intrinsically disordered AR N-terminal domain (NTD), specifically the TAU1/AF-1 region, providing **the first evidence of small-molecule engagement of this “undruggable” domain** and establishing a novel strategy to bypass LBD-mediated resistance. Global proteomics, following 24 hr treatment of 22RV1 cells with lead compounds, demonstrated compound target selectivity with AR/AR-V7 ranking among the top 1% of downregulated proteins, across the entire detectable proteome (~10,000 proteins quantified), and differentiation from prior PROTAC-based AR degraders. RNA-seq further demonstrated robust suppression of AR signaling, including key AR-regulated genes KLK3, FKBP5, and TMPRSS2, as well as previously established AR- and AR-V7- specific gene signatures, identifying coordinated transcriptional and proteomic changes. In castrated mice bearing enzalutamide-resistant 22Rv1 xenografts, oral administration of the lead compounds significantly inhibited tumor growth, outperforming enzalutamide and AR PROTAC comparators. Tumor pharmacodynamic analyses confirmed simultaneous degradation of AR-fl and AR-V7, demonstrating on-target activity *in vivo*. The lead compounds were orally bioavailable and well tolerated at effective antitumor doses.

Taken together, these data establish our compounds as **first-in-class dual AR/AR-V7 molecular glue degraders** with a novel NTD-targeted mechanism and strong preclinical activity. By enabling dual degradation of both full-length AR, the central oncogenic driver of prostate cancer, and AR-V7, a key mediator of treatment-resistance, this strategy has the potential to provide a fundamentally new therapeutic approach for both hormone-sensitive and advanced prostate cancer.

Funding Acknowledgement: This work was supported by grants from the National Cancer Institute (NCI) Grant NIH T32 CA062948 (2020-2022) (C C Au), NIH-NCI Dual Fast Track phase I STTR/Phase II SBIR 1R42CA290913-01 (2024-2027) (C C Au), First place of 2020 eBiomedical Business Plan Challenge (C C Au and P Giannakakou), The Daedalus Fund for Innovation award (P Giannakakou), The SPORE DRP award (P Giannakakou), DOD Grant W81XWH-19-1-0666 (P Giannakakou).

I have the following relevant financial relationships to disclose: Co-founder of ARMA BIO, Corp