Molecular Glue Degraders of AR/AR-V7: A Paradigm Shift in the Treatment of Advanced Prostate Cancer

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Metastatic castration-resistant prostate cancer (mCRPC) remains a uniformly lethal malignancy, **driven by persistent dependence on androgen receptor (AR) signaling**. Over 90% of therapies target the AR ligand-binding domain (LBD). However, selective pressure from these agents inevitably leads to progression and resistance. Expression of AR splice variants, most notably AR-V7, which lack the LBD and are constitutively active, is a key resistance mechanism. Clinically, AR-V7 is strongly associated with resistance to enzalutamide and abiraterone and is detected in >75% of advanced mCRPC cases, yet no inhibitors exist—**underscoring a profound unmet need**.

To address this, we conducted a high-throughput screen of 170,000 compounds and identified **a first-in-class dual degrader of AR-V7 and AR with a novel chemotype**. Medicinal chemistry/SAR optimization yielded potent leads (IC50 <10 nM) with favorable drug-like properties. Mechanistic studies confirmed rapid degradation of AR-V7/AR via the ubiquitin-proteasome pathway, dependent on Cullin-RING ligase activity. A CRISPR-based E3 ligase screen implicated the DDB1–RBX1–Cullin-RING complex, consistent with a molecular glue mechanism. Global proteomics demonstrated excellent depth (entire proteome of ~10,000 proteins) and strong selectivity: AR/AR-V7 ranked among the top 1% of downregulated proteins, while sparing all nuclear receptors and avoiding liabilities of prior PROTAC-based AR degraders—highlighting excellent specificity and clinical developability.

Using thermal shift assays, AR truncation mutants, and Cryo-EM, we mapped compound binding to the N-terminal domain (NTD), specifically the TAU1/AF-1 subdomain—**the first demonstration of small-molecule engagement of this "undruggable" region**. Lead compounds reversed enzalutamide resistance and inhibited all clinically validated drug-resistant AR isoforms, including LBD-domain mutations. In vivo, PK-optimized leads suppressed tumor growth in enzalutamide-resistant xenografts, outperformed ARV-110, the only AR-PROTAC degrader in clinical trials, by >10-fold, and showed excellent tolerability.

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. Unlike all existing AR-directed therapies that target the LBD, this approach degrades AR and AR-V7 simultaneously, directly addressing the clinical challenge of treatment resistance. By enabling dual degradation of AR (the initiating oncogenic driver) and AR-V7 (the lethal, resistant variant), this strategy has the potential to transform outcomes in 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