Conference Abstracts

Overcoming Therapeutic Resistance in High-Risk Prostate Cancer: A dTAG-AR 22Rv1 Model to Advance Equity in Precision Oncology

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Keywords: Treatment Resistance, Resource-limited population, CRPC, Health Equity, Affordable cancer care

https://doi.org/10.53876/001aa.129714

International Journal of Cancer Care and Delivery

Vol. 6, Issue Supplement 1, 2026

Background

Androgen receptor (AR)–targeted therapies remain central to prostate cancer treatment; however, therapeutic resistance and limited access to advanced molecular profiling disproportionately affect patients from underserved and resource-limited populations. A major driver of this survival gap is resistance to Androgen Deprivation Therapy (ADT), often mediated by AR splice variants, mutations and amplification. To advance equitable and affordable care, we must develop precision tools to dissect these resistance mechanisms common in aggressive prostate cancer phenotypes. To address this, we established a dTAG (degron TAG)-based AR-degradation model in the 22Rv1 cell line, a model of aggressive castration-resistant prostate cancer (CRPC), to facilitate the development of novel therapeutics for difficult-to-treat populations.

Methods

We established a dTAG-based conditional AR degradation system in 22Rv1 prostate cancer cells using a dual-guide, single-vector CRISPR/Cas9 approach to generate AR-knockout (ARKO) clones, confirmed by targeted amplicon sequencing. We reintroduced an HA-tagged AR-dTAG fusion construct, enabling rapid and reversible AR protein degradation with precise temporal control. We validated temporal and dose-dependent AR loss via immunoblotting, assessed canonical AR downstream target gene suppression at mRNA and protein levels, and performed RNA-seq profiling at 1-, 2-, 6-, and 15-days post-treatment to comprehensively map transcriptional dynamics and compensatory AR-bypass signaling pathways.

Results

dTAG treatment achieved superior AR degradation compared to existing clinical degraders, with significant reductions in proliferation, cell viability, and distinct growth-curve phenotypes indicative of G1 cell-cycle arrest, as analyzed by western blot, immunofluorescence, flow cytometry, etc. RNA-seq analyses revealed dynamic remodeling of AR-driven gene networks and identified emerging resistance mechanisms, providing actionable therapeutic targets.

Conclusion

This validated, tunable platform can accelerates preclinical evaluation of next-generation AR degraders and elucidate novel targetable resistance-overcoming strategies. By shortening drug development timelines, this model supports the creation of more effective and potentially more affordable therapies that could advance equitable cancer care and favorable outcomes for

underserved prostate cancer populations experiencing the greatest disease burden.