Selective Androgen Receptor Degraders (SARDs) for the Treatment of Androgen Receptor-Positive, Triple-Negative Breast Cancer

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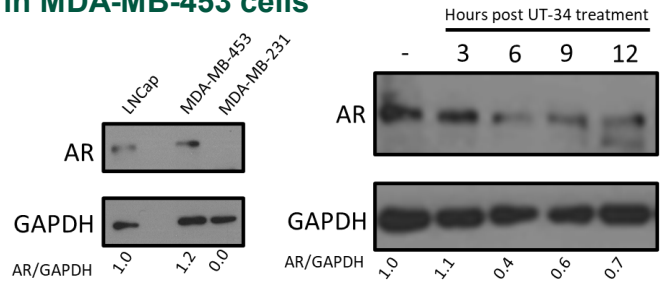
Introduction

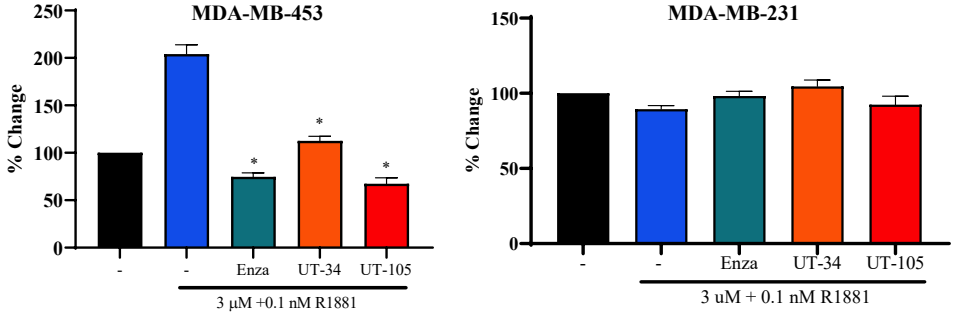
Triple-negative breast cancer (TNBC) is an aggressive breast cancer type with shorter overall survival compared to other breast cancer types. One of the six molecularly-classified TNBC subtypes is the luminal androgen receptor subtype (LAR), which expresses androgen receptor (AR) and is dependent on the AR for its growth. About 10-20% of TNBCs belong to the LAR subtype. Competitive AR antagonists, enzalutamide and bicalutamide, were effective in preclinical models of LAR TNBC and modestly effective in clinical trials. This led us to hypothesize that potent selective AR degraders (SARDs), due to their ability to inhibit and degrade the AR protein, could provide a novel therapeutic strategy for treatment of the LAR subtype of TNBC.

SARDs treatment decreases AR expression in MDA-MB-453 cells



Left: AR Western blot was performed in LNCaP, MDA-MB-453, and MDA-MB-231 cells. **Right**: MDA-MB-453 cells were maintained in csFBS-containing medium for two days. Cells were treated for 24 hours and Western blot for AR and GAPDH was performed.

SARDs Selectively inhibit MDA-MB-453 cell proliferation

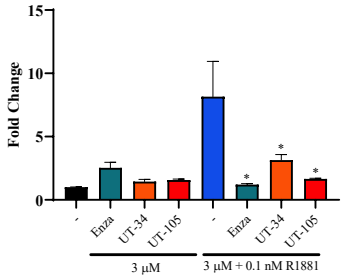


Left: MDA-MB-453 cells plated in csFBS-containing medium were treated as indicated in the figure for 14 days, with medium change and re-treatment after three days. Sulforhodamine Blue (SRB) assay was performed to measure cell viability (n=4/treatment). **Right:** MDA-MB-231 (AR-negative TNBC) is used as a negative control. * p<0.05 from R1881-treated.

Summary

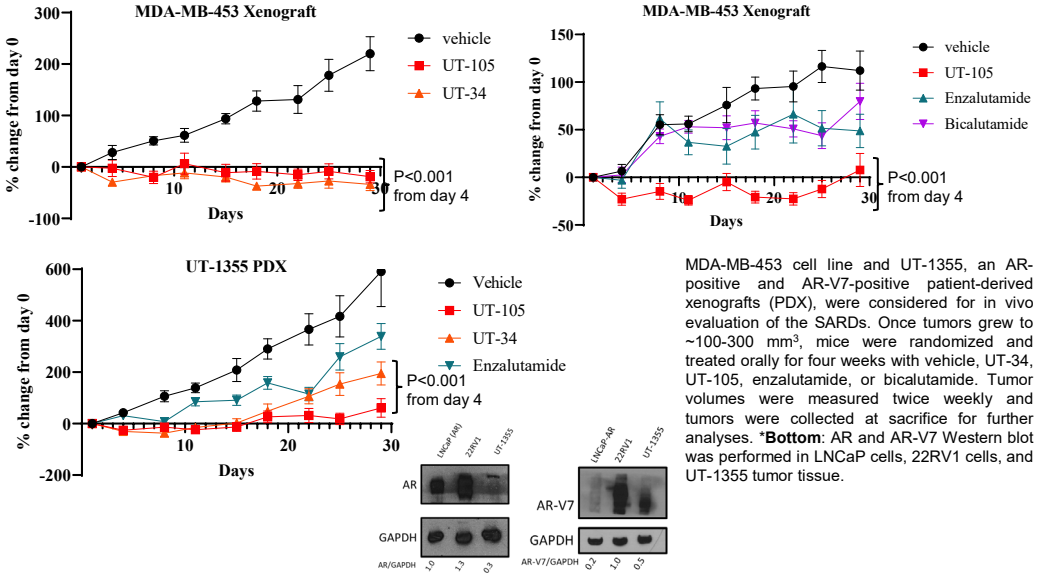
SARDs bind to the N-terminus of the AR and have been characterized in preclinical advanced prostate cancer models. In this study, the SARDs UT-34 and UT-105 were evaluated in preclinical models of LAR TNBC. Western blot for AR in LAR MDA-MB-453 cells demonstrated degradation of the AR protein by SARDs at low micromolar doses. Gene expression studies showed a complete inhibition of androgen-induced AR-target gene expression by SARDs. Androgen-induced proliferation of MDA-MB-453 cells in vitro was inhibited by SARDs. MDA-MB-453 cells and UT-1355 TNBC PDX implanted subcutaneously in NOD SCID Gamma female mice grew robustly to 100-300 mm^3 in 15-20 days. Treatment of the tumor-bearing animals with the SARDs completely inhibited or regressed the tumors, including UT-1355 PDX tumors expressing an AR splice variant (AR-SV).

SARDs treatment inhibits AR-target gene expression in MDA-MB-453 cells



MDA-MB-453 cells were maintained in csFBS-containing medium for two days. Cells were treated for 24 hours and expression of FKBP5 was measured by real time PCR and normalized to GAPDH (n=4/treatment). * p<0.05 from R1881-treated.

SARDs inhibit MDA-MB-453 cell line and UT-1355 PDX models



MDA-MB-453 cell line and UT-1355, an AR-positive and AR-V7-positive patient-derived xenografts (PDX), were considered for in vivo evaluation of the SARDs. Once tumors grew to ~100-300 mm^3, mice were randomized and treated orally for four weeks with vehicle, UT-34, UT-105, enzalutamide, or bicalutamide. Tumor volumes were measured twice weekly and tumors were collected at sacrifice for further analyses. ***Bottom**: AR and AR-V7 Western blot was performed in LNCaP cells, 22RV1 cells, and UT-1355 tumor tissue.

Conclusions

- These results support the conclusion that AR-dependent TNBC cell and tumor growth can be inhibited by SARDs via their unique mechanism of action.
- SARDs might be an effective new therapeutic option to women affected by the LAR subtype of TNBC.

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