

BACKGROUND

Prostate cancer is the second leading cause of cancer-related death in men. Androgen deprivation and blockade are commonly used to treat prostate cancer. However, relapse occurs with subsequent progression to metastatic castration-resistant prostate cancer (mCRPC).

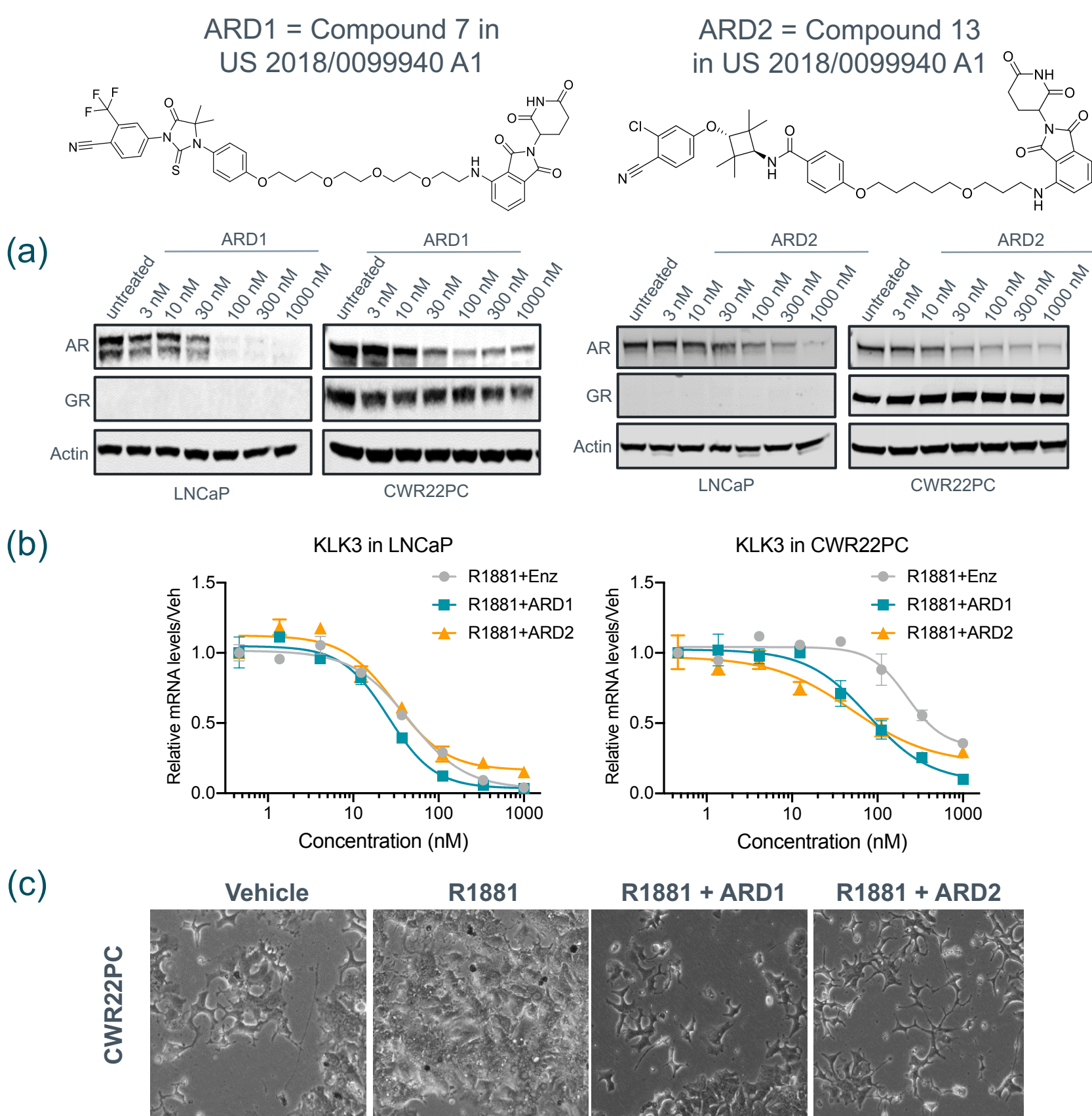
The glucocorticoid receptor (GR) has been implicated as a potential antiandrogen bypass mechanism to enzalutamide treatment in prostate cancer (Arora et al, 2013; Isikbay et al, 2014). We have shown that the GR antagonist ORIC-101 completely restores enzalutamide sensitivity in preclinical CRPC models (Zhou et al, EORTC-NCI-AACR 2019).

Androgen receptor (AR) degraders are being evaluated as a new therapeutic modality for prostate cancer. ARV-110 is an AR PROTAC™ protein degrader in early clinical development (Petrylak et al, ASCO 2020).

Hypothesis: GR is a mechanism of resistance to AR degraders, and a GR antagonist reverses GR-mediated resistance to AR degradation in mCRPC.

1. AR degraders

Because the structure of ARV-110 has not been disclosed, we used two exemplary AR degrader (ARD) compounds, ARD1 and ARD2. We confirmed that both compounds (a) degrade AR protein in a dose-dependent manner (72hrs), (b) inhibit AR target gene expression (24hrs), and (c) blunt cell growth in CRPC cell lines.

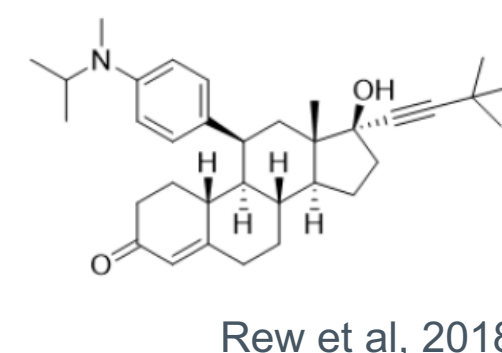


22-day proliferation assay, CSS media; 100pM synthetic androgen R1881, 1uM ARD1/2

2. ORIC-101 GR antagonist

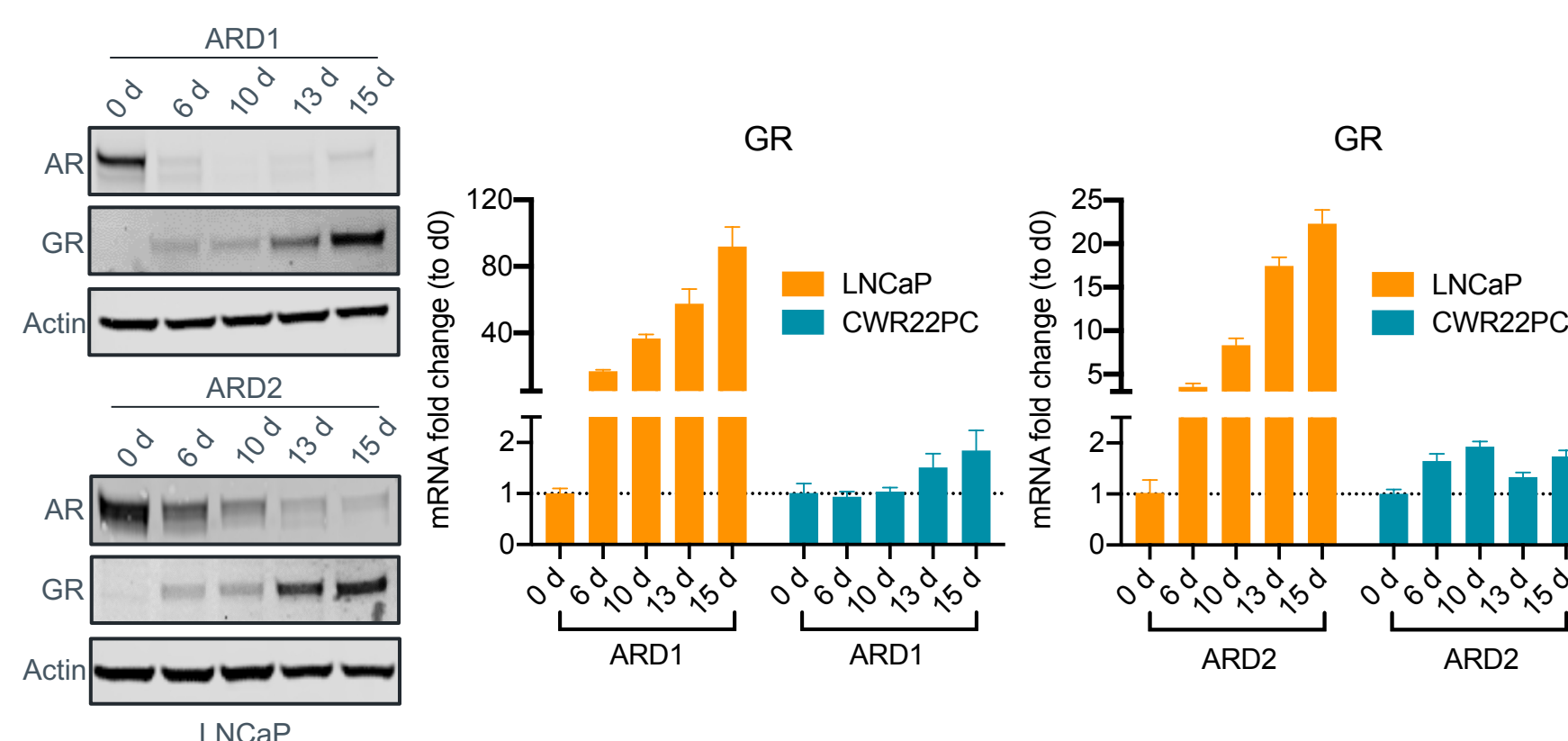
ORIC-101 is a potent, selective, orally bioavailable small molecule GR antagonist with a favorable cytochrome P450 inhibition profile and without AR agonism, making this compound particularly suitable for combination with antiandrogens such as enzalutamide.

ORIC-101 (Steroidal)	
GR antagonism	IC ₅₀ = 7.3 nM
AR agonism	IC ₅₀ > 5000 nM
PR antagonism	IC ₅₀ = 22 nM
CYP3A4	IC ₅₀ = 1.6 μM
CYP2C8/CYP2C9	IC ₅₀ > 10 μM



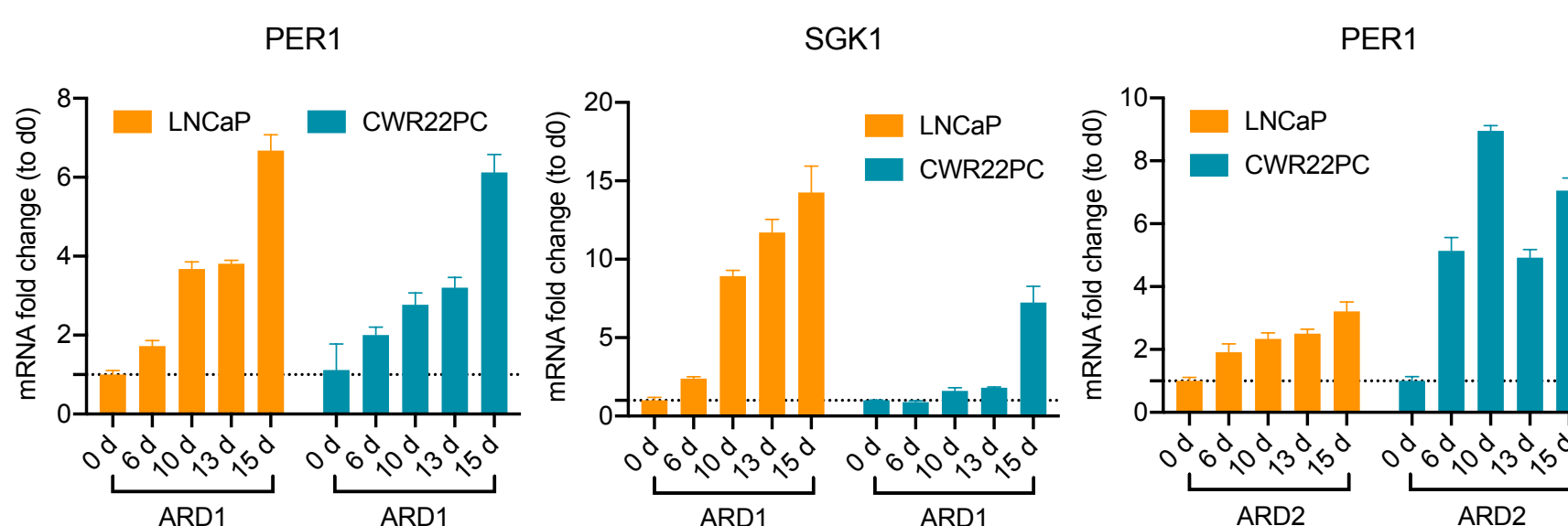
3. AR degradation upregulates GR expression

GR protein and mRNA levels are significantly upregulated in a time-dependent manner upon chronic ARD treatment, in GR-negative LNCaP cells and in CWR22PC cells with moderate GR expression pre-treatment.



4. AR degradation enhances GR signaling

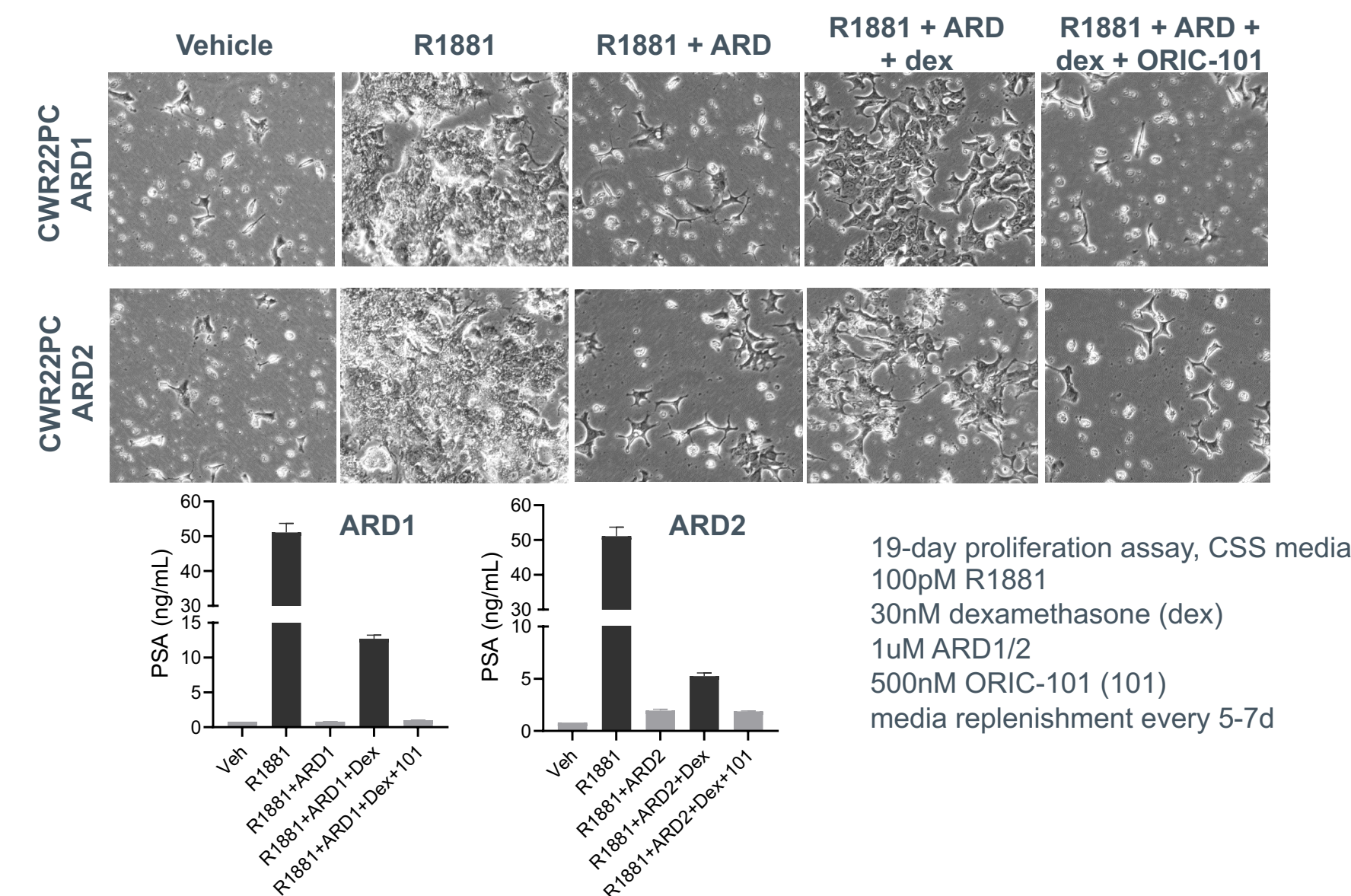
GR target gene expression is also increased with both compounds, indicative of activated GR signaling.



CSS media + 30nM synthetic glucocorticoid dexamethasone, 100nM ARD1/2

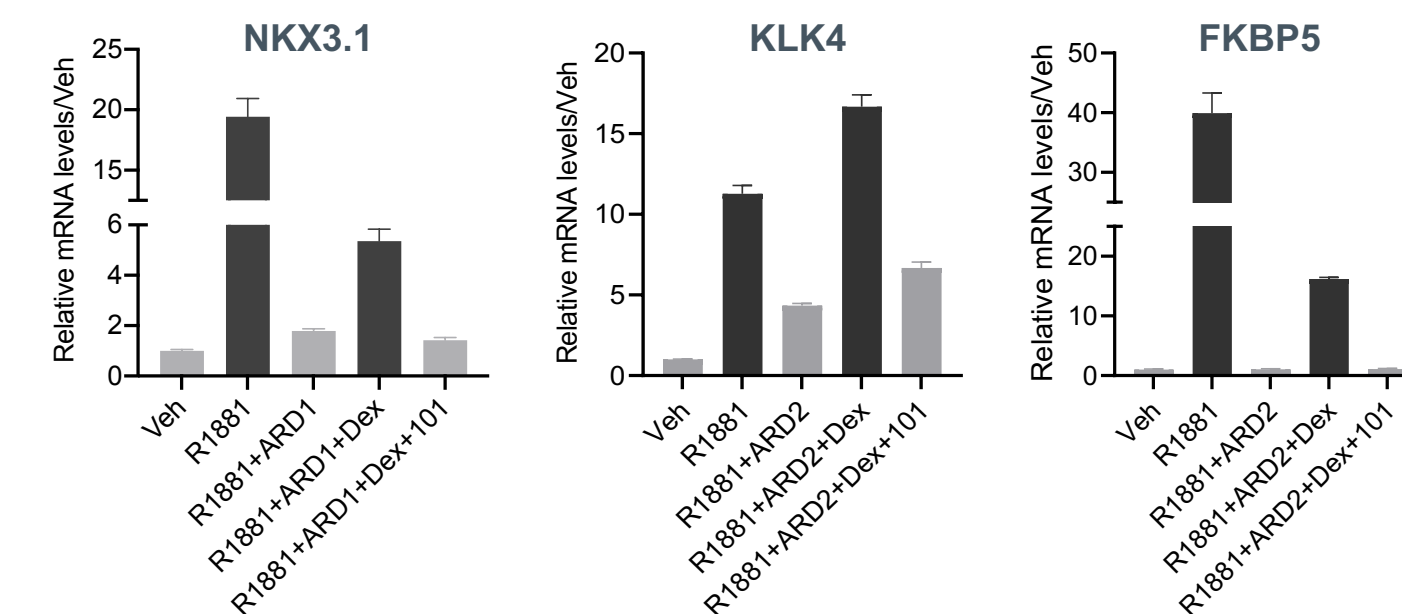
5. ORIC-101 reverses GR-driven resistance to AR degraders in prostate cancer cells

AR degrader treatment blunts androgen-induced cell growth and PSA secretion. GR activation with glucocorticoids partially restores cell growth and PSA secretion in the presence of ARD treatment. This resistance is completely reversed by ORIC-101.



6. ORIC-101 inhibits glucocorticoid-induced AR and GR target gene expression

Glucocorticoids stimulate and ORIC-101 fully inhibits androgen-regulated gene expression in the end-of-study CWR22PC cells.



CONCLUSIONS

- GR may be a mechanism of resistance to AR degraders.
- GR antagonist ORIC-101 overcomes GR-driven resistance to AR degradation in preclinical prostate cancer models.
- More broadly, targeting GR may help overcome resistance to various modalities of antiandrogen therapy.
- The combination of enzalutamide with GR antagonist ORIC-101 is being studied in patients with metastatic CRPC (phase 1b, NCT04033328).