ORIC-101 Overcomes Glucocorticoid-Driven Resistance to Androgen Receptor Inhibition in CRPC

Haiying Zhou, Shravani Barkund, Aleksandr Pankov, Sharvani Sinha, Dena Sutimantanapi, Omar Kabbarah, Lori S. Friedman

ORIC Pharmaceuticals, South San Francisco, CA 94080

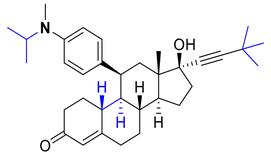
BACKGROUND

Prostate cancer is the second leading cause of cancer-related death in men. Second-generation antiandrogens such as enzalutamide and abiraterone benefit patients with castration-resistant prostate cancer (CRPC). However, relapse eventually occurs (Giacinti S et al, 2018).

The glucocorticoid receptor (GR) has been identified as a potential antiandrogen bypass mechanism, and thus GR inhibition may overcome this resistance to restore or prolong antiandrogen sensitivity (Arora V et al, 2013, Isikbay M et al, 2014).

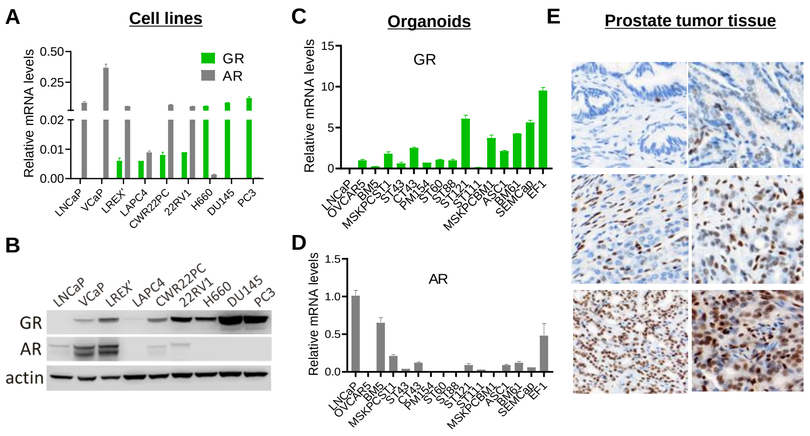
- **ORIC-101 is a selective and potent GR antagonist without androgen receptor (AR) agonism, making this compound particularly suitable for combination with enzalutamide (Rew Y et al, 2018).**
- **ORIC-101 showed good safety, pharmacokinetic properties, and target engagement in phase 1a healthy volunteer studies.**
- **A phase 1b study of ORIC-101 in combination with enzalutamide is planned in patients with metastatic prostate cancer.**

ORIC-101 is a selective and potent GR antagonist



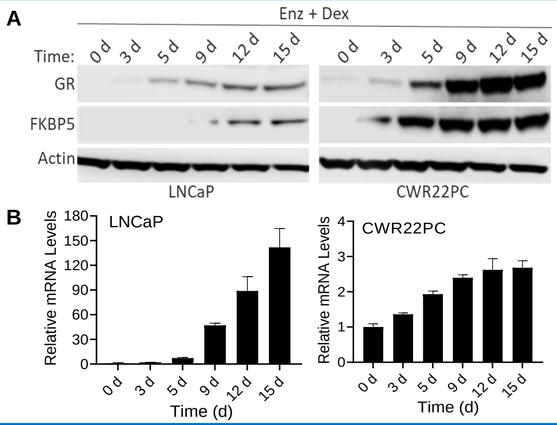
A. ORIC-101 chemical structure. **B.** ORIC-101 profile, a: IC_{50} in GR luciferase antagonist assay; b: EC_{50} (E_{max}) in AR luciferase agonist assay.

GR is widely expressed in prostate tumors



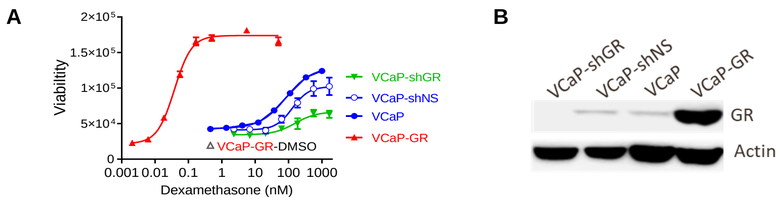
A and B. AR and GR mRNA (A) and protein (B) levels in prostate cancer cell lines. **C and D.** GR (relative to GR+ line OVCAR5) and AR (relative to AR+ line LNCaP) mRNA levels in prostate tumor organoids. **E.** GR immunohistochemistry detecting GR protein levels in human prostate tumor tissue.

AR inhibition upregulates GR levels in CRPC cells



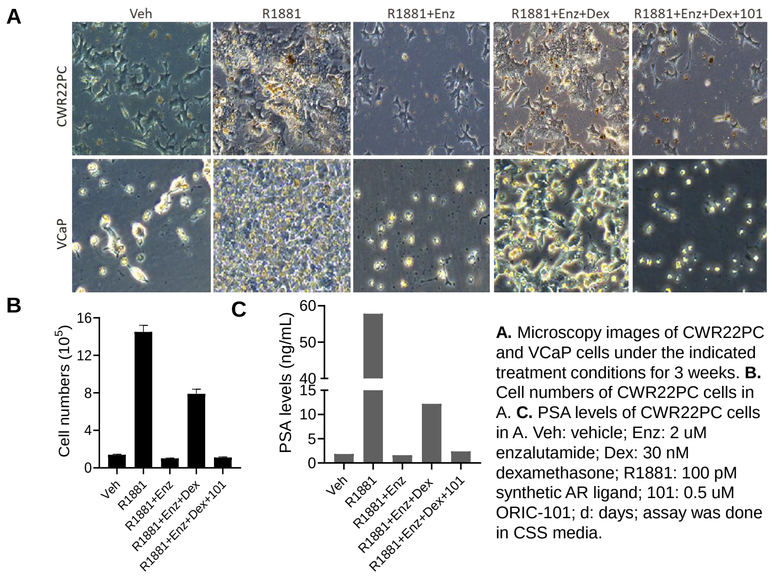
A. GR and FKBP5 protein levels in CRPC cells treated with 30 nM dexamethasone (Dex) and 1 uM enzalutamide (Enz) in a time-dependent manner. d: day. **B.** GR mRNA levels relative to untreated samples (0 d) in the indicated samples as shown in A.

GR levels correlate with Dex-driven CRPC viability



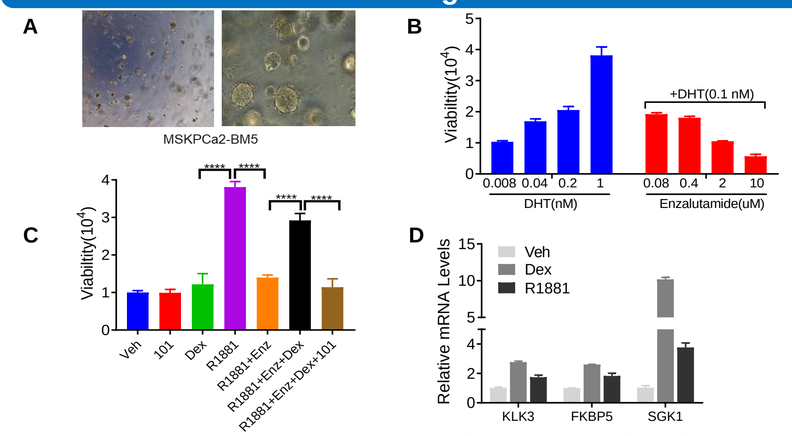
A. Viability of VCaP, GR knockdown (VCaP-shGR), non-specific control (VCaP-shNS), and GR overexpressed (VCaP-GR) cells in charcoal-striped serum (CSS) supplemented media in response to glucocorticoids (Dex) in a dose-dependent manner at day 7. **B.** GR protein levels in VCaP cell lines used in A as indicated.

ORIC-101 reverses GR-driven resistance to enzalutamide in CRPC cells



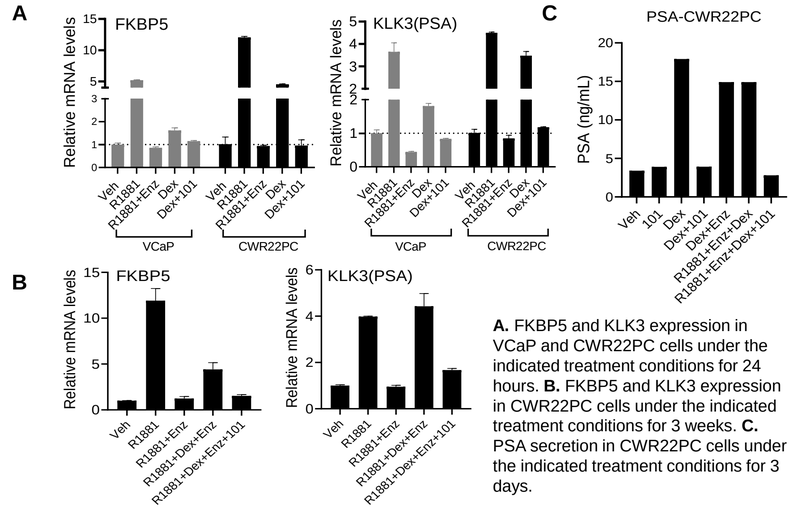
A. Microscopy images of CWR22PC and VCaP cells under the indicated treatment conditions for 3 weeks. **B.** Cell numbers of CWR22PC cells in A. **C.** PSA levels of CWR22PC cells in A. Veh: vehicle; Enz: 2 uM enzalutamide; Dex: 30 nM dexamethasone; R1881: 100 pM synthetic AR ligand; 101: 0.5 uM ORIC-101; d: days; assay was done in CSS media.

ORIC-101 reverses GR-driven resistance to enzalutamide in CRPC organoids



A. Morphology of MSKPCa2 (BM5) organoids at 5X (left panel) and 20X (right panel) magnification. **B.** DHT promotes, while enzalutamide inhibits, BM5 organoid viability (measured at day 7) in dose-dependent manner. DHT: dihydrotestosterone. **C.** BM5 viability under the indicated treatment conditions for 7 days. **D.** KLK3, FKBP5, and SGK1 mRNA levels in BM5 organoids under the indicated treatment conditions for 24 hours.

FKBP5 and KLK3 are biomarkers for ORIC-101 in CRPC



A. FKBP5 and KLK3 expression in VCaP and CWR22PC cells under the indicated treatment conditions for 24 hours. **B.** FKBP5 and KLK3 expression in CWR22PC cells under the indicated treatment conditions for 3 weeks. **C.** PSA secretion in CWR22PC cells under the indicated treatment conditions for 3 days.

CONCLUSIONS

- GR is widely expressed in prostate tumor cell lines, organoids, and tissue.
- AR inhibition leads to enhanced GR levels at mRNA and protein levels.
- GR levels correlate with glucocorticoid-driven CRPC viability.
- ORIC-101 reverses GR-driven resistance to enzalutamide in CRPC cells and organoids.
- FKBP5 and KLK3 are rational pharmacodynamic biomarkers that may be evaluated in clinical studies of ORIC-101 in CRPC.

Abstract LB-A10

ORIC
Overcoming Resistance in Cancer

AACR-NCI-EORTC, 27 October 2019, Boston