ORIC-101 Overcomes Resistance to Diverse Chemotherapeutics Across Cancer Types

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BACKGROUND

Glucocorticoids circulate throughout the body and mediate multiple physiological processes including metabolism, cell growth, inflammation, apoptosis and differentiation (Azher et al, 2016).

Upon glucocorticoid binding, the glucocorticoid receptor (GR) translocates into the nucleus and regulates gene transcription.

Elevated GR expression and dysregulated cortisol levels are associated with poor prognosis, drug resistance, and metastasis (Pan et al, 2011; Tangen et al, 2017; Obradovic et al, 2019).

Our prior studies revealed that GR antagonist ORIC-101 enhanced taxane response in preclinical breast cancer models (Zhou et al, 2019).

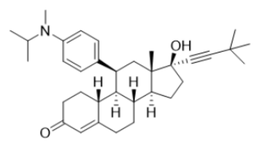
This preclinical study demonstrates the ability of ORIC-101 to overcome GR-mediated resistance to diverse chemotherapeutics across cancer types.

Phase 1b studies of ORIC-101 in combination with nab-paclitaxel in patients with advanced or metastatic solid tumors (NCT03928314) and in combination with enzalutamide in patients with metastatic prostate cancer progressing on enzalutamide (NCT04033328) are ongoing.

1. ORIC-101

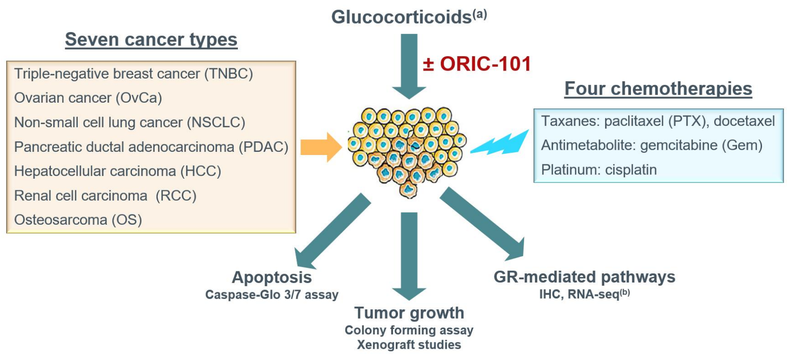
ORIC-101 is a potent, selective, orally bioavailable small molecule GR antagonist with a more favorable cytochrome P450 inhibition profile than other clinical compounds, making it particularly suitable for combination with taxanes.

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



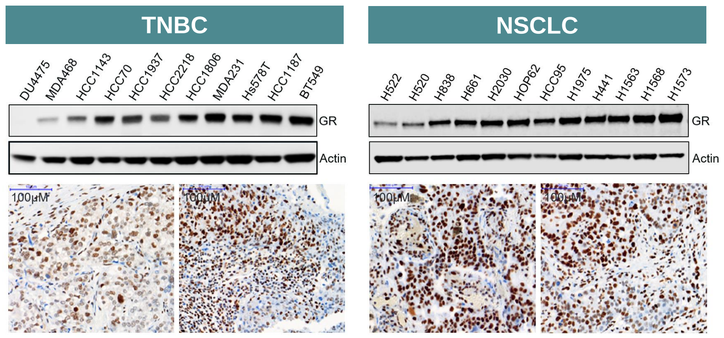
Rew et al., 2018

2. Experimental overview



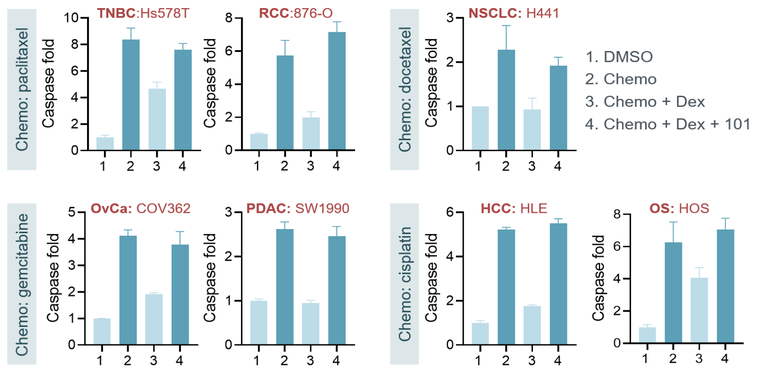
(a) Glucocorticoids (GCs): Dex, 30 nM dexamethasone for in vitro assays; Cort, 100 mg/L cortisol water for xenograft studies. (b) RNA-seq results are presented on AACR 2020 Poster #4120.
IHC: immunohistochemistry; 101: 0.5 µM ORIC-101 for in vitro assays, 75 mg/kg ORIC-101 BID × 21, PO for xenograft studies.

3. GR is widely expressed in cancer cell lines and human tumors



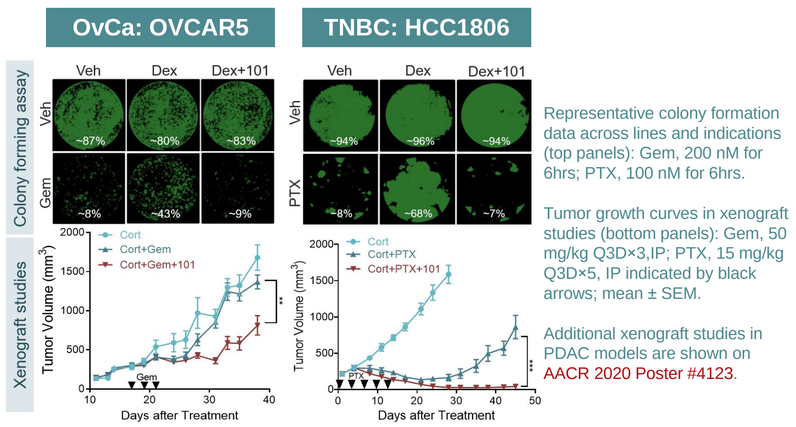
GR protein levels in TNBC and NSCLC cell lines (WB, top panels).
GR protein levels in representative human TNBC and NSCLC tumor tissues (IHC, bottom panels).

4. ORIC-101 reverses GR-mediated antiapoptosis



Representative examples from 8-12 tested lines per indication.
GR-mediated chemoprotection and ORIC-101 reversal was only observed in GR-positive lines.

5. ORIC-101 reverses GR-driven tumor growth

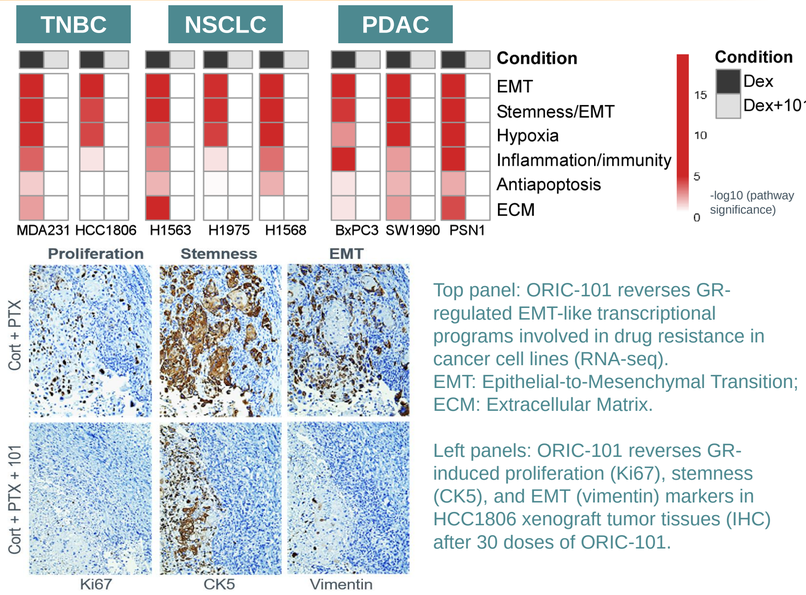


Representative colony formation data across lines and indications (top panels): Gem, 200 nM for 6hrs; PTX, 100 nM for 6hrs.

Tumor growth curves in xenograft studies (bottom panels): Gem, 50 mg/kg Q3D×3,IP; PTX, 15 mg/kg Q3D×5, IP indicated by black arrows; mean ± SEM.

Additional xenograft studies in PDAC models are shown on AACR 2020 Poster #4123.

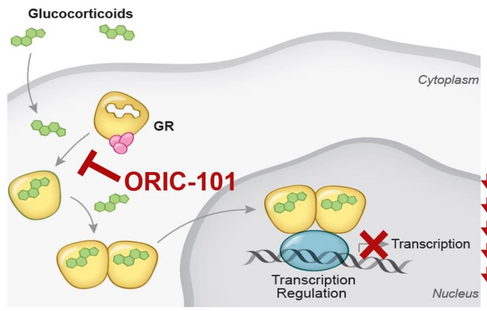
6. ORIC-101 reverses EMT-like phenotype in vitro and in vivo



Top panel: ORIC-101 reverses GR-regulated EMT-like transcriptional programs involved in drug resistance in cancer cell lines (RNA-seq).
EMT: Epithelial-to-Mesenchymal Transition; ECM: Extracellular Matrix.

Left panels: ORIC-101 reverses GR-induced proliferation (Ki67), stemness (CK5), and EMT (vimentin) markers in HCC1806 xenograft tumor tissues (IHC) after 30 doses of ORIC-101.

7. ORIC-101 overcomes resistance to chemotherapy by blocking GR-regulated transcription



Working model of GR in the absence (green) or presence (red) of ORIC-101 in response to glucocorticoids.

GR-regulated resistance pathways:
- Hypoxia
- EMT (vimentin, FN1)
- Stemness (ALDH1A1, CK5)
- Inflammation
- Antiapoptosis (BIRC3, survivin)

CONCLUSIONS

GR is widely expressed in cancer cell lines and tumor tissues functioning as a common resistance mechanism.

ORIC-101 is a potent, selective, orally bioavailable GR antagonist that:

- overcomes GR-mediated antiapoptosis to chemotherapeutics in vitro in multiple cancer types
- reverses GR-driven tumor growth in vitro and in vivo across indications
- inhibits GR-regulated transcriptional pathways such as EMT, stemness, and antiapoptosis

Acknowledgements: Melissa R Junttila, Edna Chow Maneval, Pratik S Multani, and Jacob Chacko

AACR Virtual Annual Meeting II, June 22-24, 2020, Poster #4121