**BACKGROUND**

Glucocorticoids circulate throughout the body and mediate multiple physiological processes including metabolism, cell growth, inflammation, apoptosis and differentiation (Asher 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 (NCT0433328) 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.

<table>
<thead>
<tr>
<th>ORIC-101 (Steroidal)</th>
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<tr>
<td>GR antagonism IC50 &gt; 5000 nM</td>
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<tr>
<td>PR antagonism IC50 &gt; 22 nM</td>
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<tr>
<td>CYP3A4 IC50 &gt; 1.6 µM</td>
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<tr>
<td>CYP2C8/CYP2C9 IC50 &gt; 10 µM</td>
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Row et al., 2018

2. Experimental overview

Glucocorticoids (a)

(a) Glucocorticoids (GCs): Dex, 30 nM dexamethasone for in vitro assays; Cort, 100 mg/L cortisol water for xenograft studies.

Non-small cell lung cancer (NSCLC)

Pancreatic ductal adenocarcinoma (PDAC)

Hepatocellular carcinoma (HCC)

Renal cell carcinoma (RCC)

Ovarian cancer (OvCa)

Triple-negative breast cancer (TNBC)

*Seven cancer types*

*Four chemotherapies*

*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 AACC 2020 Poster #4120.

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

4. ORIC-101 reverses GM-mediated antiapoptosis

5. ORIC-101 reverses GR-driven tumor growth

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

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

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

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