ORIC-101 Comprehensively Inhibits Glucocorticoid Pathways to Overcome Therapeutic Resistance in Pan-Cancer Models

Aleksandr Pankov, Haiying Zhou, Shravani Barkund, Ganapati Hegde, Padmini Narayanan, Omar Kabbarah, Lori S. Friedman, Anneleen Daemen
ORIC Pharmaceuticals, South San Francisco, CA 94080

**BACKGROUND**

The Glucocorticoid Receptor (GR) is a member of the nuclear receptor superfamily of ligand-activated transcription factors. GR can be activated both by endogenous glucocorticoid ligands, including cortisol and corticosterone, and by synthetic glucocorticoid drugs, such as dexamethasone (Dex).

Preclinical studies have established a role for GR in mediating resistance to both anti-hormonal therapies and conventional chemotherapies in epithelial cancers (Zhang et al., 2006; Arora et al., 2013; Isikbay et al., 2014; Stringer-Reasor et al., 2015).

Studies in breast cancer models have established that the chemoprotective effect afforded by GR activation is facilitated, at least partially, through upregulation of genes involved in antiapoptosis, epithelial/mesenchymal transition (EMT), and metastasis – thus suggesting that GR inhibition may enhance therapeutic responses (Skor et al., 2013; Obradović et al., 2019; Shi et al., 2019).

**Opportunity:** Understand molecular consequences of GR signaling and identify a patient subgroup more likely to benefit from GR inhibition.

1. **ORIC-101: a potent small molecule GR antagonist**

   - ORIC-101 overcomes resistance to diverse chemotherapeutics across cancer types AACR 2020 Poster #4121
   - ORIC-101 overcomes GR-mediated chemoresistance in pancreatic cancer models AACR 2020 Poster #4123

2. **ORIC-101 shows modulation of common GR targets in surrogate tissues of healthy volunteers**

   - ORIC-101 blocks GR activity in PBMCs of healthy volunteers with once-daily ORIC-101

3. **Precision medicine strategy focuses on identifying patients with activated GR signaling**

   - Patients with activated GR signaling and GR-driven chemoresistance may benefit from ORIC-101

4. **GR Activation Signature derived from 8 TNBC, 12 PDAC, and 12 NSCLC cell lines**

   - Pathways associated with the GR Activation Signature in cell lines are recapitulated in human tumors from TCGA

5. **Cell lines show common and specific pathways modulated by GR activation**

6. **Association of the GR Activation Signature with pathways in human TCGA tumors**

   - GR Activation Signature score
   - Pathways

7. **GR activation captures the same biological processes in human tumors**

**CONCLUSIONS**

- ORIC-101 reverses GR-activated transcriptional programs at both the gene and pathway level in preclinical models.
- GR Activation Signature translates from cell lines to human tumors.
- The GR Activation Signature allows for monitoring target engagement of ORIC-101 and patient selection based on activated GR signaling.
- ORIC-101 is in early clinical development in combination with nab-paclitaxel in solid tumors (NCT03928314) and in combination with enzalutamide in metastatic prostate cancer (NCT04033328) where the GR activation signature is being evaluated.

Acknowledgments: Jessica D Sun, Melissa R Junttila, Ryan Athearn, Edna Chow Maneval, Pratik S Multani, and Jacob Chacko