

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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## Recent Advances in Understanding Glucocorticoid Receptor Function in Cancer



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### **H&O** Are there any new insights into the role of glucocorticoids and/or glucocorticoid receptors?

**SC** There are several new insights into the role of glucocorticoids, particularly regarding how the glucocorticoid receptor functions in both normal and cancer cells. The glucocorticoid receptor is the body's stress hormone receptor. When the glucocorticoid receptor interacts with endogenous stress hormones (eg, cortisol), it becomes a very potent transcription factor that can turn gene expression on or off. For decades, glucocorticoids have been used to dampen the immune system and kill lymphocytes. It is now understood that glucocorticoids exert different effects in other cell types, such as epithelial cells.

Much of the recent data we have are from using relatively new laboratory techniques that allow evaluation of genome-wide gene expression in response to receptor activation. We also now use techniques that provide global information on how and where the glucocorticoid receptor interacts with DNA.

### **H&O** How does glucocorticoid signaling impact tumor progression?

**SC** Research is just beginning to explore this question. For many years, laboratory studies have shown that glucocorticoids and glucocorticoid receptor activation appear to slow the proliferation of breast cancer cells in patients with estrogen receptor (ER)-positive disease. Therefore, a surprising finding is that in breast cancers that lack ER expression, glucocorticoid receptor activation appears to prevent death of cancer cells and therefore may promote

tumor cell viability. Thus, glucocorticoid receptor functional activity appears to be highly context-dependent.

### **H&O** Does the role of glucocorticoids differ among different cancers?

**SC** Yes, the role of glucocorticoids and glucocorticoid receptor activation differs among cancer types. For example, synthetic glucocorticoids play a prominent therapeutic role in acute lymphocytic leukemia and lymphoma, where they cause apoptosis. Glucocorticoid

The glucocorticoid receptor plays a role in preventing apoptosis in mammary epithelial cells.

receptors may also have a very potent role in hormone-dependent solid tumors, where they interact with other hormone receptors.

The role appears to differ even within a certain type of cancer. As I mentioned, in laboratory studies of breast cancer, glucocorticoids slow cancer cell proliferation in ER-positive models, but in triple-negative breast cancer, glucocorticoid receptor activation inhibits chemotherapy-induced cytotoxicity, allowing the tumor to grow bigger by preventing apoptosis. In prostate cancer, before the tumor has become resistant to androgen deprivation,

glucocorticoids appear to slow proliferation of tumor cells, much like in ER-positive breast cancer. In preclinical models, however, as the prostate tumor is exposed to androgen deprivation and later to androgen receptor antagonists, it appears that glucocorticoid receptor activity becomes quite different, and if overexpressed in this context, can contribute to tumor progression.

### **H&O** Can glucocorticoid receptor expression be used to predict risk?

**SC** Preliminary data, albeit retrospective, suggest that glucocorticoid receptor expression in the primary tumor of an early-stage patient can be used to predict risk. In breast cancer, for example, we have published retrospective data suggesting that glucocorticoid receptor expression in ER-negative disease is highly associated with a poor prognosis. What is fascinating, however, is that the same is not true in ER-positive breast cancer, in which high glucocorticoid receptor expression and activity seem to slow cell proliferation. Thus, in patients with early-stage, ER-positive breast cancer, it appears that glucocorticoid receptor overexpression does not indicate a poor prognosis, and may even be associated with relative indolence.

At the 2016 meeting of the American Society of Clinical Oncology, a postdoctoral trainee from my institution, Dr Jennifer Veneris, presented data on glucocorticoid receptor expression in a retrospective cohort of patients with ovarian cancer. Tumors with high glucocorticoid receptor expression were associated with a higher relapse risk compared with tumors showing low receptor expression. Therefore, breast, prostate, and ovarian cancer may all be influenced by glucocorticoid receptor activity.

### **H&O** What has recent research shown about glucocorticoid receptor antagonists?

**SC** Initially, the idea of using a glucocorticoid receptor antagonist to block glucocorticoid receptor signaling in tumors—and thereby enhance sensitivity to chemotherapy—was met with significant skepticism. For decades, oncologists have done the opposite: We have used synthetic glucocorticoid receptor agonists, such as dexamethasone, to prevent adverse side effects from chemotherapy. My colleagues Drs Gini Fleming, Rita Nanda, and Mark Ratain and I initiated a phase 1 clinical trial in triple-negative breast cancer evaluating nab-paclitaxel (Abraxane, Celgene) plus the addition of mifepristone (Korlym, Corcept), a nonspecific glucocorticoid receptor antagonist that also has some mixed agonist/antagonistic properties against the progesterone receptor and the androgen receptor. Mifepristone was administered on the day before and the morning of treatment

with nab-paclitaxel, and this combination was given 3 weeks out of 4. Most importantly, the trial showed that this combination appears to be safe. Mifepristone did not increase rates of nausea, vomiting, allergic reactions, or other adverse events that we use glucocorticoids to prevent. We have now initiated a randomized, phase 2 trial in triple-negative breast cancer with mifepristone

The addition of a glucocorticoid receptor blocker resulted in more tumor cell apoptosis and shrinkage than chemotherapy alone in our preclinical studies.

and weekly nab-paclitaxel. Enrolled patients will have a primary tumor shown to be glucocorticoid receptor-positive (10% positive cells by immunohistochemistry).

### **H&O** How are these antagonists being used in novel ways?

**SC** Mifepristone, which is approved by the US Food and Drug Administration for the treatment of Cushing syndrome, is currently being used with the intention of inhibiting signaling in the tumor cell itself, with the goal of preventing the expression of genes that encode antiapoptotic proteins. The aim is to antagonize the expression of these proteins before administration of chemotherapy. In mouse xenograft studies, this approach resulted in more cell kill in the tumor and greater tumor shrinkage than chemotherapy alone.

Another novel use of glucocorticoid receptor antagonists is to combine them with androgen receptor antagonists in patients with castration-resistant prostate cancer. Preclinical data from retrospective tumor samples have shown that glucocorticoid receptor activity is upregulated following androgen deprivation. Castration-resistant tumors may acquire this mechanism following androgen deprivation. The goal is to prolong time to progression through concurrent administration of a glucocorticoid receptor antagonist and an androgen receptor antagonist. Currently, a randomized phase 2 trial is evaluating the addition of mifepristone to enzalutamide (Xtandi, Astellas/Medivation) in patients with prostate cancer.

## H&O Are there any other new glucocorticoid receptor antagonists?

**SC** Pharmaceutical companies have been working to develop glucocorticoid receptor modulators (mixed agonist/antagonist) and more pure antagonists for many years. The distinction between a modulator and an antagonist in a steroid hormone receptor most likely depends on the cell type, as well as cooperating transcription factors, coactivators, and corepressors. Therefore, it is likely that for each cancer type, it will be necessary to determine the antagonistic or agonistic properties of a selective glucocorticoid receptor modulator.

## H&O What has your research into the molecular pathways in mammary epithelial cells shown?

**SC** The glucocorticoid receptor plays a role in preventing apoptosis in mammary epithelial cells. We made this discovery while screening for different hormones and growth factors that might prevent apoptosis caused by environmental stressors, such as low-growth-factor media and chemotherapy. In these experiments, one of the controls was to add glucocorticoid, which has been a component of the media used in mammary epithelial cells for decades. When we removed the glucocorticoid, we observed that the mammary epithelial cells were much more sensitive to classic apoptosis. This observation was confirmed by in vivo xenograft models in ER-negative breast cancer tumors. Use of a glucocorticoid also decreased apoptosis in response to chemotherapy. The addition of a glucocorticoid receptor blocker resulted in more tumor cell apoptosis and shrinkage than chemotherapy alone in our preclinical studies. The research has focused on identifying the pathways that protect triple-negative breast cancer cells from dying in response to therapy. We have identified several different pathways involved with cell survival. We are also beginning to look at how the glucocorticoid receptor may affect cell cycle and metabolic pathways in different tumor types. All 3 of these pathways—cell

death, cell cycle, and metabolism—will be important in understanding why mammary epithelial cells and triple-negative breast cancer cells are resistant to the effects of chemotherapy in the presence of high glucocorticoid receptor expression. We are also beginning to investigate how cells in the primary breast and metastatic cancer microenvironments, such as activated tumor macrophages, fat cells, and T and B lymphocytes, are affected by glucocorticoid receptor antagonists.

### Disclosure

*Corcept Therapeutics has licensed 2 patents related to the use of glucocorticoid receptor modulators in cancer from the University of Chicago. Dr Conzen is a coinventor on these patents.*

### Suggested Readings

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