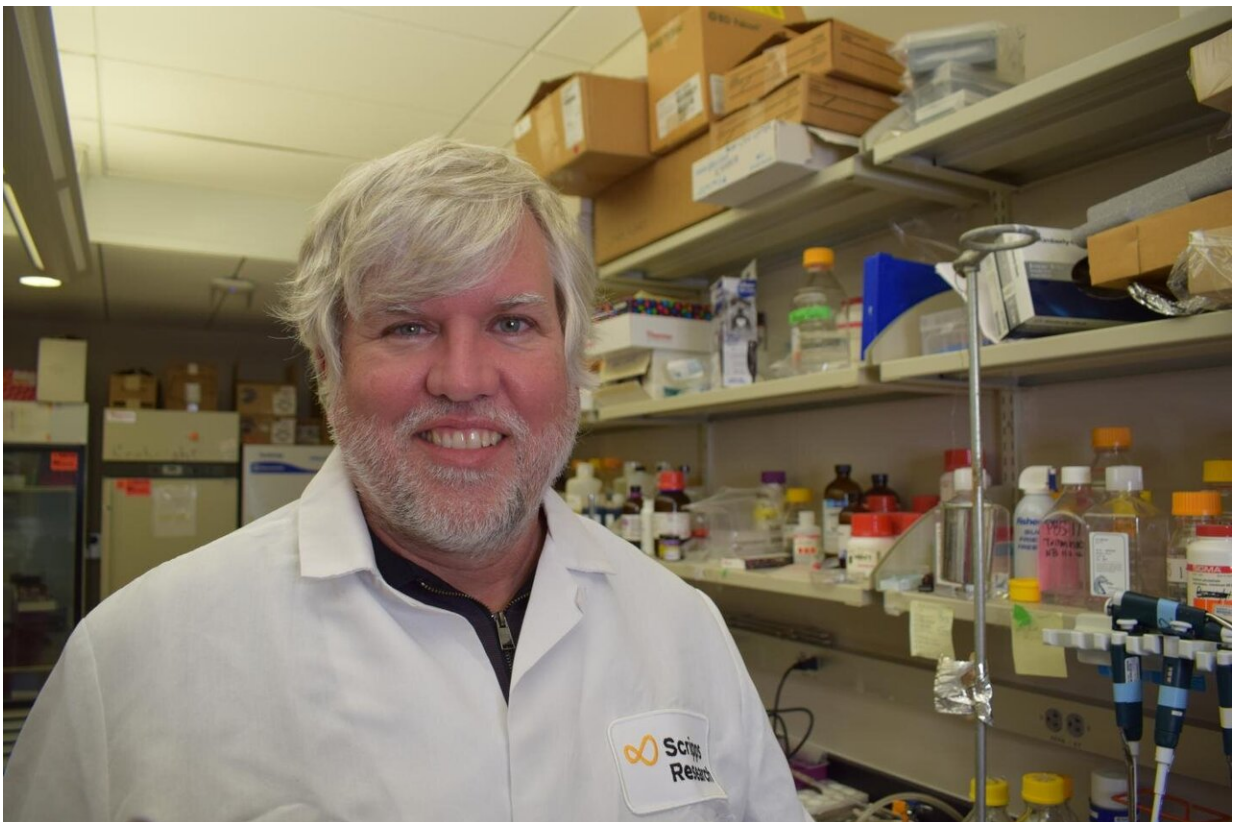


# Scientists devise method for improving safety of drug used to treat COVID-19, autoimmune disorders and more

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Kendall Nettles, Ph.D., a molecular biologist at Scripps Research, Florida, collaborated with experts in many disciplines to systematically improve the safety of glucocorticoids. Credit: Scripps Research

A collaboration led by Scripps Research has developed a way to separate the beneficial anti-inflammatory properties of a group of steroids called glucocorticoids from some of their unwanted side-effects, through an optimization process they named "ligand class analysis."

Their process enabled them to engineer two new, drug-like compounds that show steroidal anti-inflammatory action and other specific traits. One boosts muscle and energy supply, while the other reduces risk of muscle-wasting and bone loss typical of such drugs.

Their report, titled, "Chemical systems biology reveals mechanisms of [glucocorticoid](#) receptor signaling," appeared Jan. 28 in the journal *Nature Chemical Biology*.

Glucocorticoids are steroid hormones, a group that includes cortisone, prednisone and dexamethasone. Among the most frequently prescribed of medications, their anti-inflammatory properties make them useful in an array of forms and doses.

Glucocorticoids are used as injections for hip or back pain, tablets for autoimmune disease, nasal spray for sinus congestion, anti-itch cremes for soothing rashes or insect bites, and more.

Most recently, the glucocorticoid drug dexamethasone has become the standard of care for COVID-19 treatment later in illness, as it can help quiet overaggressive immune attacks in delicate lung tissue and blood vessels.

But glucocorticoids are also among the more problematic of medicines, as prolonged use or high doses can lead to adverse events including high blood pressure, muscle wasting, bone loss, vulnerability to infections, vision problems, anxiety, swelling, weight gain, high blood sugar, [insulin resistance](#), diabetes, and more, while naturally occurring glucocorticoids

in the body can contribute to prostate cancer progression.

## **Pursuing safety**

A key goal of the team was to engineer more precise glucocorticoids able to act in tissue-specific or activity-specific way, while limiting specific adverse events, says the study's lead author, Kendall Nettles, Ph.D., associate professor of Integrative and Structural Biology at the Scripps Research, Florida campus.

"There is a great unmet need to improve glucocorticoids," Nettles says. "We asked, 'Can we develop glucocorticoids that have more selective effects on inflammation and the immune system, instead of hitting the body with a hammer?' This method is showing that we can do that now."

The project pooled the expertise of many collaborators, in areas including chemistry, bioinformatics, structural biology, proteomics, genomics, cell metabolism and more. Contributors included Scripps Research, Florida-based faculty and their scientific staff and students; a researcher from the institute's California-based drug discovery division, Calibr, and scientists from Weill Cornell Medicine, Emory University School of Medicine, the National Cancer Institute and others.

Nettles says their "ligand class analysis" process began with selection of a known corticosteroid compound. Scripps Research chemist Theodore Kamenecka, Ph.D., modified the compound in many ways to build a collection of new molecules.

One substitution at a time, the scientists created 22 new compounds that showed an ability to actively bind with cell receptors for steroids. They then devised an experimental platform for testing precisely how these compounds affected muscle, bone and lung cells, to indicate each one's risk of causing muscle loss or bone loss, while keeping anti-

inflammatory activity.

One of the greatest challenges they encountered was devising a way to accurately test the molecules in cultured cells, Nettles says. At first, they seemed to require 1,000 times more compound than expected to measure impact.

### **Stress produces results**

First author Nelson Bruno had the breakthrough idea of testing only after stress, specifically, fasting followed by brief insulin challenge. That's because stress is the trigger for release of endogenous steroid hormones in real life, Nettles explains.

"It took us two years just to develop the experimental assays to reproduce the effects of what glucocorticoids do in people," Nettles says. "We found we needed realistic physiology."

They also used a machine learning approach to predict how the compounds would affect insulin receptor signaling, gene transcription, protein balance and glucose disposal in the cells, depending on chemical structure.

Through repeated challenges and tests in the cells and in mice, they settled on two compounds, SR11466 and SR16024, as ones with medically useful traits including inflammation control, plus muscle-sparing ability, or mitochondria-building potential. Mitochondria convert cellular nutrients into energy.

The process they developed to refine the compounds has implications well beyond the improvement of glucocorticoids, Nettles adds. It can power more-selective drug-discovery for any number of medicines that work via the cell surface and nuclear receptors to impact signaling and

gene transcription in cells, he says.

This project started long before the COVID-19 pandemic began, Nettles says, but it has potential to benefit people sickened with COVID-19. In the context of an infectious disease, the ideal anti-inflammatory would be one that suppressed overly aggressive immune attack without impairing ability to fight off infection, so that's the next goal, he says. More work is needed to address [bone loss](#) risk as well, he says.

"These drugs could be used more widely if we could reduce the side-effects profile," Nettles says. "We brought together many recent scientific advances to address a significant problem that affects huge numbers of people. Our findings show that using ligand class analysis, we can potentially improve the safety and specificity of steroids and other needed medicines."

**More information:** Nelson E. Bruno et al, Chemical systems biology reveals mechanisms of glucocorticoid receptor signaling, *Nature Chemical Biology* (2021). [DOI: 10.1038/s41589-020-00719-w](https://doi.org/10.1038/s41589-020-00719-w)

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