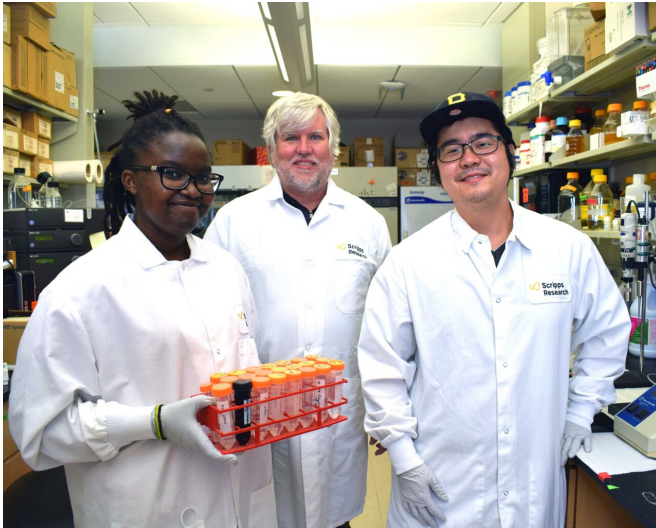


Dual-action breast cancer compounds aim to overcome common drug-resistance issues

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Kendall Nettles, Ph.D. (center) meets with two students in his lab, Jacqliene Njeri (left) and Charles Min (right). Nettles and colleagues designed drug-like molecules that appear to fight estrogen-sensitive breast cancer in two ways, in cell studies. Njeri and Min are co-authors on the paper, published August 27, 2021, in *PNAS*. Credit: Scripps Research, Florida

A set of compounds developed by scientists at Scripps Research in Florida target estrogen-sensitive breast cancer cells in new ways, potentially creating better options for patients with treatment-resistant cancers.

"Hormone therapies for [breast cancer](#) have been one of the greatest success stories of molecularly targeted medicines. But a significant fraction of patients don't respond to these therapies," says Kendall Nettles, Ph.D., associate professor of Integrative Structural and Computational Biology, and lead author on the study published August 27 in the journal *Proceedings of the National Academy of Sciences*.

"There's a continued unmet medical need for better hormone therapies. This represents the first change in approach in 20 years," Nettles says.

Drugs like tamoxifen, fulvestrant or anastrozole are frequently prescribed for estrogen-sensitive breast cancers. But over time, some breast cancers can develop resistance, through inflammatory processes identified by Nettles's group and others in 2017, and through expression of resistance genes including EGFR.

The compounds developed by Nettles and colleagues work by interfering with estrogen's ability to activate its [cellular receptor](#) in the traditional way, as seen with the hormone therapy tamoxifen, but also by a second inhibitory mechanism. Tests in cells showed greater efficacy in the presence of drug-resistance mechanisms, Nettles says.

Estrogen and cancer: Going up

Seven out of 10 breast cancers are sensitive to estrogen. The hormone promotes cancer growth by activating receptors on the cell surface which respond a bit like an elevator's up button. When touched, they send chemical signals into the cell nucleus that lead key growth and proliferation genes to march into action.

That's why doctors treat estrogen-sensitive cancers by either suppressing estrogen production or interfering with estrogen's ability to bind those receptors. If the cell can't receive the signal, the estrogen won't activate more tumor growth. However, shutting off all of estrogen's activity brings menopause-related side effects including osteoporosis and hot flashes.

Depending on a breast cancer patient's age, and

whether that patient is a woman who has passed menopause, doctors will prescribe either a group of medicines called selective estrogen receptor modulators (SERMs), such as tamoxifen, or ones called selective estrogen receptor down-regulators (SERDs) such as fulvestrant, Nettles says.

At a molecular, structural level, those drugs interact with the pocket where estrogen binds and use a single, carefully positioned side chain to block the receptor's growth promoting activity.

Structural studies drive design

Working with colleagues from Scripps Research and the University of Illinois at Urbana-Champaign, Nettles's team designed the set of compounds to interfere with estrogen binding, via distortion of the estrogen receptor binding pocket, and via binding with two different molecular side chains.

Their studies showed the compounds acted either as estrogen receptor down-regulators, or much like tamoxifen, as selective estrogen receptor modulators. Their two different side chains can be altered in a variety of ways to influence potency and manage side-effects, Nettles says.

Chemist John Katzenellenbogen, Ph.D., built the molecules in Illinois, while in Florida, at Scripps Research, Tina Izard, Ph.D., oversaw X-ray crystallography studies that revealed the molecules' structure, and Pat Griffin, Ph.D., oversaw hydrogen-deuterium mass spectrometry studies that enabled studies of the compounds' effect on [estrogen receptors](#). Those studies showed the compounds destabilized or repositioned the receptor shape, allowing for a different method of direct binding.

One-third of women with early-stage breast cancer treated with tamoxifen developed resistance to the drug within two to five years, a recent study found. The new compounds are urgently needed, Nettles says.

Next steps include testing the compounds in mouse models of breast cancer, and tweaking the molecules to enhance their drug-like properties, such as staying in the bloodstream for the appropriate length of time. Most investigational

drugs fail endpoints before reaching the clinic, but Nettles is optimistic about the compounds' path forward.

"We're hopeful this could be a breakthrough for treatment-resistant [breast cancer](#)," Nettles says. "With a new mechanism of action, the compounds do what you could expect from combining two different drugs, but in one molecule."

More information: Jian Min et al, Dual-mechanism estrogen receptor inhibitors, *Proceedings of the National Academy of Sciences* (2021). [DOI: 10.1073/pnas.2101657118](https://doi.org/10.1073/pnas.2101657118)

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