# Compounds found that alter cell signaling, could lead to new breast cancer treatments

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Using a broad spectrum of analytical tools, scientists from the Florida campus of The Scripps Research Institute (TSRI) have uncovered a class of novel compounds that can alter cell signaling activity, resulting in a variety of responses including a strong anti-inflammatory effect. These findings could lead to new strategies for treating diseases such as breast cancer.

The study, published this week in the journal *Nature Chemical Biology*, focuses on compounds that interact with the estrogen receptor-α, a therapeutic target in breast cancer that causes widely varied effects, including cell proliferation, inflammatory activity and immune cell changes. The receptor, which binds to estrogens or similar molecules, is over-expressed in nearly three-quarters of breast cancer cases.

In the study, the scientists used a unique "structure class analysis" approach, making it far easier to identify broad structural patterns underlying how estrogen receptors bind to other molecules. In general, ligands—molecules that bind to a larger complex and trigger a reaction—bind in two distinct ways, either through a dynamic, changeable orientation or a single, constrained orientation. In the study, TSRI scientists compared a set of estrogen receptor ligands with dynamic binding orientation with those that bind in a single orientation.

"When you design a drug, you want a combination of effects that are beneficial," said Kendall Nettles, a TSRI associate professor who led the study. "We discovered a new class of compounds that can bind to the

receptor protein in two different orientations, flipping back and forth between the two. That shift can be used to give us specific signaling outcomes—anti-inflammatory, for example—far different from a ligand that binds in a single orientation."

In this new analysis, estrogen receptor activity reflects an integration of a number of factors, any of which can alter the nuclear receptor's signaling activity. In fact, the study establishes a novel principle in biology—that ligand dynamics can be exploited to control signaling specificity, a concept that could be applied more broadly in drug development.

The study also offers insight into environmental estrogens—such as Bisphenol A (BPA), an organic compound that has been in commercial use since 1957 to produce things like water bottles and sports equipment; BPA's hormone-like properties have caused concern among consumers. The new study suggests a potential explanation as to why various environmental estrogens behave differently. "They all have different activity profiles and this mechanism could be one of the reasons," Nettles said.

**More information:** "Ligand Binding Dynamics Rewire Cellular Signaling via Estrogen Receptor-α" www.nature.com/nchembio/journa … s/nchembio.1214.html

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