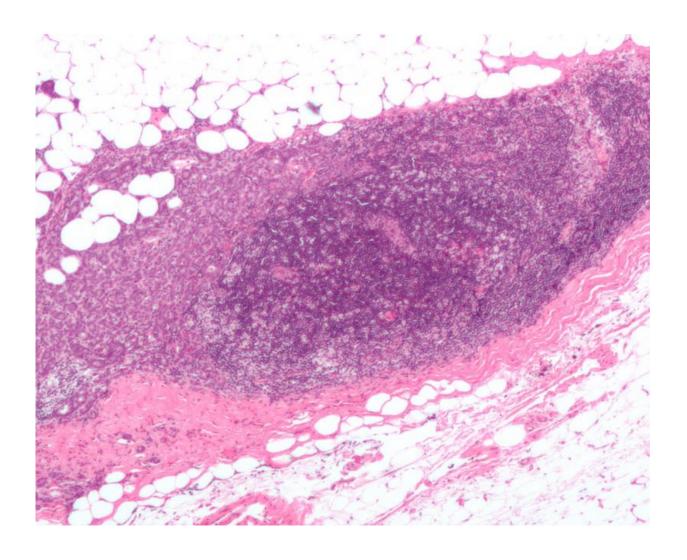


Scientists create innovative drug design strategy to improve breast cancer treatment

November 21 2016



Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia



While there have been advances in the treatment of hormone-driven breast cancer, resistance to these therapies remains a significant problem. Side effects, including an increased risk of uterine cancer among postmenopausal women, also severely curtail their use for prevention.

However, a new study by scientists from the Florida campus of The Scripps Research Institute (TSRI) offers a novel structure-based drug design strategy aimed at altering the basic landscape of this type of breast cancer treatment.

The findings show that the current approach is not the only, or even the best way, to block the <u>estrogen receptor</u>.

"We have created a different approach that gives us a mechanism to produce new types of therapeutic molecules," said TSRI Associate Professor Kendall Nettles. "There are a lot of ways to avoid resistance and other cancer risks, and this gives us a tool box full of alternative approaches that could limit or eliminate those effects."

"With the standard method, no one understands the structural basis," he continued. "With our approach we know exactly how we did it. If you can see the shape of the receptor protein and see how the drug works on it, that makes the development process that much faster."

The findings were published November 21, 2016, by the journal *Nature Chemical Biology*.

Seeing Is Believing

The current method of creating this class of drugs, which includes tamoxifen, involves attaching a bulky cluster of atoms with a chainlike structure (called, appropriately, a side chain) to molecules that disrupt



the estrogen receptor binding site.

The team's strategy taps a technique called x-ray crystallography to visualize the drug candidate as it binds to the receptor. This image is used to guide the production of estrogen receptor degraders that also lack the side chain, helping to reduce the risk of resistance and the development of other cancers.

"Our structure-trapping approach to X-ray crystallography provides a molecular snapshot of how subtle changes to a compound series generate a range of graded activity profiles," said Research Associate Jerome C. Nwachukwu, who was co-first author with Research Associate Sathish Srinivasan. "This structurally distinct mechanism, acting indirectly rather than involvement of the typical side chain, provides a new way to design biologically distinct molecules for breast cancer prevention and treatment."

The new method also makes it possible to identify structural rules for how the molecules interact.

"This is the first example of a structure-based design strategy targeting the estrogen receptor where there is a clear correlation between the chemistry, crystal structure and activity, which is another big advance that will be of broad interest to the cancer community," Srinivasan said. "We show that indirect antagonism can result in inhibition of proliferation in a predictive fashion."

More information: Full antagonism of the estrogen receptor without a prototypical ligand side chain, *Nature Chemical Biology*, nature.com/articles/doi:10.1038/nchembio.2236



Provided by The Scripps Research Institute

Citation: Scientists create innovative drug design strategy to improve breast cancer treatment (2016, November 21) retrieved 20 April 2024 from https://phys.org/news/2016-11-scientists-drug-strategy-breast-cancer.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.