

Combination overcomes breast cancer resistance to herceptin

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Breast cancer tumors take numerous paths to resist the targeted drug Herceptin, but a single roadblock at a crucial crossroads may restore a tumor's vulnerability to treatment, scientists at The University of Texas MD Anderson Cancer Center report on line at *Nature Medicine*.

Adding the drug saracatinib to [Herceptin](#) treatment shrinks previously resistant tumors by cutting off at least five different [molecular pathways](#), each of which can resist, said senior author Dihua Yu, M.D., Ph.D., professor in MD Anderson's Department of Molecular and Cellular Oncology.

"Scientists have identified so many ways by which a tumor resists Herceptin that it raises an important issue for treatment," Yu said. "Will we have to give patients six drugs or 10 drugs to block them all? The side effects would be awful. Two pills are better. This combination is a promising therapy for those with Herceptin-resistant [breast cancer](#)."

Working in cell lines, mouse models of breast cancer and checking their work in human tumor samples, Yu and colleagues identified SRC, a known cancer-promoting protein, as the crucial common downstream component of multiple resistance pathways.

Saracatinib is an SRC inhibitor, thwarting that protein and allowing Herceptin to work again in tumors that have a high amount of the [HER2 protein](#).

Only about 26 percent of women with HER2-positive breast cancer respond to Herceptin as single therapy. Between 40 and 60 percent respond to the drug when combined with other chemotherapy.

Combination is ready for clinical trials

Yu said saracatinib has been tested in phase I and phase II clinical trials as a single treatment against late-stage cancers. It has a favorable side effects profile.

"It didn't work as a single agent, but very few drugs work by themselves against late stage disease," Yu said. "Our experiments confirmed its lack of efficacy as a sole treatment. But combined with Herceptin, it's beautiful."

Another SRC inhibitor, dasatinib, has been approved by the U.S. Food and Drug Administration as an anti-cancer drug, but it has harsher side effects, said Siyuan Zhang, Ph.D., a postdoctoral fellow in Yu's lab and the paper's first author.

A tumor-suppressor's job

In 2004, Yu's lab discovered that loss of the tumor-suppressing gene known as PTEN led to Herceptin-resistant tumors. PTEN is a phosphatase - a protein whose function is to strip phosphate chemical groups off of other molecules.

PTEN has two components, one to remove phosphate groups from lipids, and another to remove them from proteins. PTEN's target protein however, was unknown.

Zhang discovered that SRC is a PTEN target. With its phosphate groups, SRC is active. PTEN stifles SRC by peeling away the phosphates.

If PTEN loss leads to Herceptin resistance, and PTEN targets SRC, would that make SRC the culprit?

On the trail of SRC

In a series of experiments the researchers found:

- SRC is active in breast cancer cells once vulnerable but now resistant to Herceptin and in cells that are resistant from the start.
- Activation of SRC drives resistance to Herceptin. Tumors with low SRC levels treated by Herceptin shrunk to 20 percent of their original volume in 21 days while SRC-heavy tumors increased by nearly 400 percent over the same time in mouse experiments.
- SRC activity correlates with patient response to Herceptin. Assessing SRC activation in samples of 57 human breast cancer tumors, the team found that more than 90 percent of tumors with low SRC responded compared with 40 percent of tumors with active SRC.
- Patients with little active SRC had a median survival of 57.9 months compared with 34.2 months in those with high SRC activity.
- SRC is activated by a number of receptor tyrosine kinases that cause resistance, including IGF-1R, EGFR, ERBB2, HER3, and Met, separate pathways that work through SRC. "Block SRC, and you reverse them all," Zhang said.

Crushing resistance

Combining Herceptin and saracatinib to treat resistant tumors in mice reduced tumor volume by 90 percent in 25 days. Herceptin alone kept tumor volume about the same during the same period, while control and saracatinib alone permitted growth of more than 200 percent.

The difference was more striking in tumors deficient in SRC's enemy, the PTEN tumor-suppressor. The combination reduced tumor volume by more than 90 percent while the two drugs alone allowed growth of between 200 and 400 percent.

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