

New path to overcoming drug resistance in HER2-positive breast cancer

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A rendering of the PEPD protein, a version of which Roswell Park is studying as an anticancer agent. Credit: Wikimedia Commons

The HER2 protein, which encourages the growth of cancer cells, is present in about 20% of all breast cancers. While HER2-positive breast cancers tend to be very aggressive, today the prognosis is generally very good, thanks to the introduction of HER2 inhibitors such as trastuzumab (brand name Herceptin). However, not all HER2-positive breast cancers respond to existing HER2 inhibitors.

Now, in a study titled "A recombinant human protein targeting HER2 overcomes drug resistance in HER2-positive [breast cancer](#)," published recently in *Science Translational Medicine*, Roswell Park researchers report that a new anticancer agent, PEPD-G278D, has the potential to overcome that drug resistance. It is a novel HER2 inhibitor that operates on several different fronts.

The Roswell Park team, led by Yuesheng Zhang, MD, Ph.D., Professor of Oncology in the Departments of Pharmacology & Therapeutics and Cancer Prevention & Control, concluded based on results of a preclinical study that PEPD-G278D, a

modified human protein—specifically, a recombinant enzymatically-inactive mutant of human peptidase D—binds to HER2 and strongly inhibits its activity in [cancer cells](#). At the same time, the team observed that PEPD-G278D shows additional mechanisms of action not seen with other HER2 inhibitors:

- It improves the efficacy of the chemotherapy drug paclitaxel (brand names Taxol and Onxal).
- It prevents HER2 from being protected by the protein mucin 4, making the cancer cells more vulnerable to treatment.
- It prevents HER2 from interacting with other receptor tyrosine kinases ([cell surface receptors](#)), which contribute to the growth of cancer cells.
- It decreases production of epidermal growth factor receptor, which strengthens drug resistance in HER2-positive breast cancer.

"Our results show that HER2 remains a critical target in drug-resistant HER2-positive breast cancer and that PEPD-G278D is a promising agent for overcoming [drug resistance](#) in this disease," says first author Lu Yang, Ph.D., a Research Associate in Dr. Zhang's lab.

Based on these and earlier results from laboratory research, the team plans to pursue clinical studies with this agent, which has not yet been given to humans.

More information: Lu Yang et al. A recombinant human protein targeting HER2 overcomes drug resistance in HER2-positive breast cancer, *Science Translational Medicine* (2019). [DOI: 10.1126/scitranslmed.aav1620](#)

Provided by Roswell Park Cancer Institute

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