

# Synthetic biology used to target cancer cells while sparing healthy tissue, study reports

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Synthetic proteins engineered to recognize overly active biological pathways can kill cancer cells while sparing their healthy peers, according to a study by researchers at the Stanford University School of

Medicine.

The customizable approach, which the researchers call RASER, relies on just two proteins: The first is activated in the presence of an "always on" growth signal often found in cancer cells, and the second carries out a researcher-programmed response, such as triggering the expression of genes involved in [cell death](#).

Although the experiments were confined to cells grown in the laboratory, the researchers believe the results could lead to a new type of cancer therapy in which [synthetic proteins](#) deliver highly targeted and customizable treatments to sidestep the sometimes devastating side effects of current options.

"We're effectively rewiring the cancer cells to bring about an outcome of our choosing," said Michael Lin, MD, Ph.D., associate professor of neurobiology and of bioengineering. "We've always searched for a way to kill cancer cells but not [normal cells](#). Cancer cells arise from faulty signals that allow them to grow inappropriately, so we've hacked into cancer cells to redirect these faulty signals to something useful."

A paper describing the work will be published May 2 in *Science*. Lin is the senior author. Former graduate student Hokyung Chung, Ph.D., is the lead author.

## Signals from receptors

Many cancers rely on a series of signals that originate from proteins called receptors that span the membrane of the cell. These signaling cascades, or pathways, are used by healthy cells to grow in response to external cues, for example during development or recovery from injury. Often, however, these [receptor proteins](#) are mutated or overexpressed in cancer cells in ways that render the receptor [protein](#) "always on,"

providing the cell with constant, unwarranted signals for growth. The researchers focused on two receptors, EGFR and HER2—members of a family of receptors called the ErbB receptors—that often drive the growth of brain, lung and breast cancers. HER2, for example, is targeted by Herceptin in [breast cancer](#).

Many common anti-cancer drugs, including Herceptin, work by blocking the cascade of signals triggered by receptor activation. Unfortunately, however, these drugs have no way to discriminate between cancerous cells, in which the pathway is always activated, and healthy cells going about their business as usual. That's where Lin and his team come in.

"We haven't had a drug that can tell the difference between a pathway signaling normally and one that is abnormally active," Lin said. "We knew we needed a better strategy, a more rational way of treating cancer. But we've not had a way to do it until recently."

## **Designing a synthetic protein**

Chung and her colleagues designed a synthetic protein consisting of two natural proteins fused together—one that binds to active ErbB receptors and another that cleaves a specific amino acid sequence. They then engineered a second protein that binds to the inner surface of the cell membrane and contains a customizable "cargo" sequence that can carry out specific actions in the cell. When the first protein binds to an active ErbB receptor, it cuts the second protein and releases the cargo into the interior of the cell.

"When the receptor protein is always on, as it is in cancer cells, the released cargo protein accumulates over time," Chung said. "Eventually enough accumulates to have an effect on the cell. In this way, the system produces an effect only in cancer cells, and we can convert the always-on state of the receptor into different outcomes through the choice of cargo

protein."

After several rounds of tinkering, the team saw that their RASER system, which stands for "rewiring of aberrant signaling to effector release," was highly specific for cancer cells dependent on ErbB receptor activity. For their first test they chose to use a protein involved in triggering cell death as the RASER cargo.

## **Killing only overactive cells**

The team compared the RASER system to two therapies currently used for metastatic breast cancer—a chemotherapy regimen and a drug that blocks ErbB activity—on several types of cultured cells: breast and lung cancer cells in which the ErbB pathway was overly active; breast cancer cells in which ErbB activity was normal; and noncancerous breast and lung cell lines.

The researchers found that the traditional chemotherapy regimen of carboplatin and paclitaxel killed all the cells indiscriminately. The effect of the ErbB pathway inhibitor on the viability of the cells varied and did not reliably correlate with ErbB pathway activity levels. Only RASER specifically killed those cells in which the ErbB pathway was overly active while sparing those in which ErbB activity was normal.

While much work remains to be done to learn whether RASER is effective in human tumors, the researchers are excited about the possibilities of re-engineering the system to recognize other receptors mutated in cancers and swapping the cargos to achieve different outcomes. Challenges include learning how best to deliver synthetic proteins into tumors and understanding how the immune system might react to RASER. But Lin is optimistic.

"We have so much more information now about cancer genomics,

signaling and how [cancer cells](#) interact with the immune system," Lin said. "It's finally becoming practical to combine this knowledge with synthetic biology approaches to tackle some of these pressing human health problems. RASER is both customizable and generalizable, and it allows us for the first time to selectively target [cancer cells](#) while sparing normal signaling pathways."

**More information:** "A compact synthetic pathway rewires cancer signaling to therapeutic effector release, " *Science* (2019).  
[science.sciencemag.org/cgi/doi ... 1126/science.aat6982](https://science.sciencemag.org/cgi/doi/10.1126/science.aat6982)

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