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Protein decoy stymies lung cancer growth in mice, study finds

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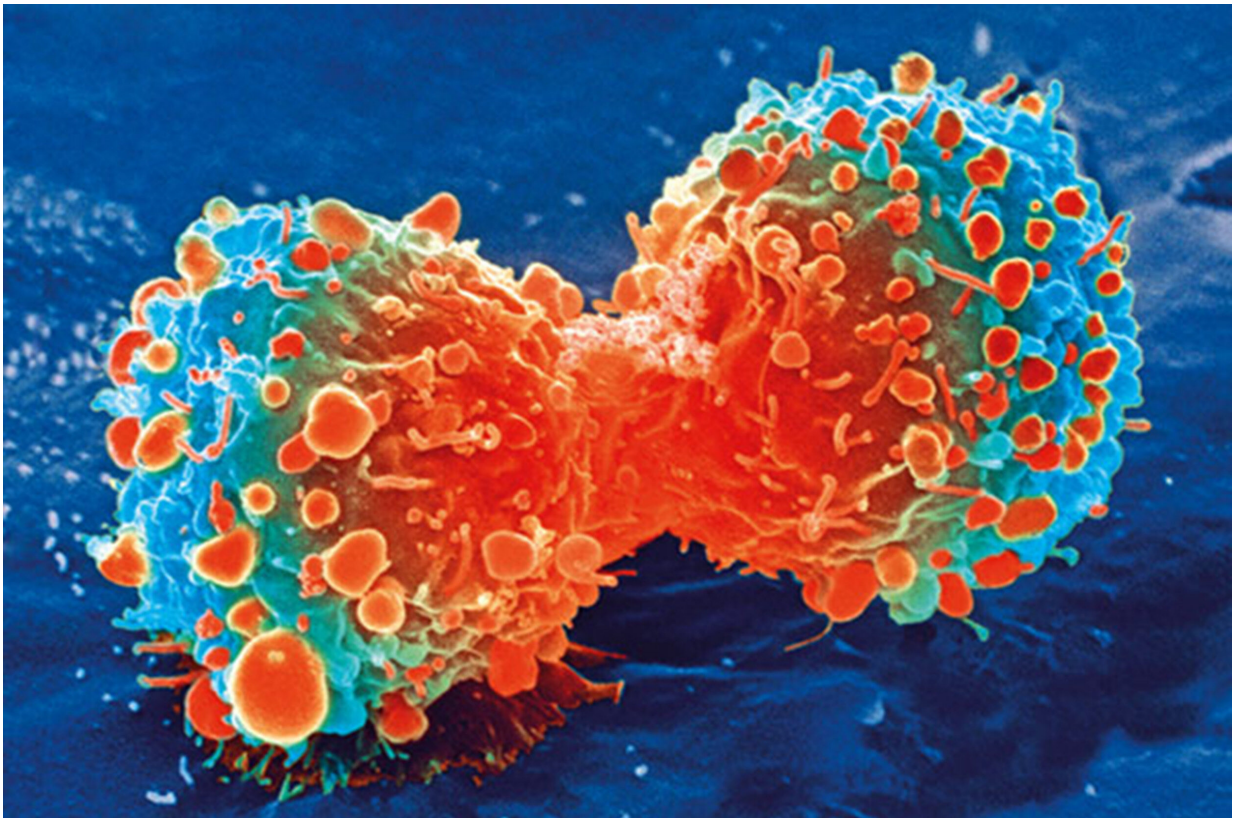

Cancer cell during cell division. Credit: National Institutes of Health

Scientists at Stanford and UC-San Francisco have developed an experimental drug that targets a currently untreatable type of lung cancer responsible for generating roughly 500,000 newly diagnosed cases

worldwide each year.

A paper to be published online Nov. 7 in *Nature Medicine* reports that the researchers slowed the spread of this cancer in mice by neutralizing a single protein that would otherwise set off a chain reaction, causing runaway growth

The paper is the result of a long-term collaboration between Stanford bioengineer Jennifer Cochran, Ph.D., and UCSF cancer researcher Alejandro Sweet-Cordero, MD.

The researchers discovered how a particular type of protein known as a ligand hooks up with three receptor proteins to create conditions favorable for this cancer's spread. The researchers then engineered a decoy version of one of these receptors and delivered it to the tumor site, where it interfered with the growth mechanism behind the cancer.

"This is the second time we've shown how to engineer an effective decoy protein and used it to inhibit tumor growth in animals," said Cochran, the Shriram Chair of the Department of Bioengineering at Stanford, whose group initially developed this strategy in earlier experiments aimed at ovarian and breast cancers.

It was that earlier work which caught the attention of Sweet-Cordero, then a cancer researcher at the Stanford School of Medicine. In 2012, he published a paper showing how a protein called CLCF1 initiated a chain of events that accelerated growth in one of the three main variants of nonsmall cell lung cancer.

"CLCF1 binds to and activates three proteins found on the surface of tumor cells, and together they work to promote the growth of lung cancer," said Sweet-Cordero, who sought out Cochran in 2013 to propose that they work together to thwart this process.

The interdisciplinary collaboration they established continued after Sweet-Cordero joined the UCSF faculty at the end of 2016. His research team performed additional work that helped provide a detailed understanding of the mechanism behind CLCF1's effect on tumor growth. In addition, extensive work on cancer models established that blocking the CLCF1 ligand could be an effective strategy for treating lung cancer.

For its part, Cochran and her team of bioengineers found that designing a receptor decoy for lung cancer was far more complex than its earlier work with ovarian and breast cancer. In those cases, only two proteins, a ligand and a receptor, had to interact to spread the cancer, and the bioengineers sought to shut down that process by designing a mutated version of the receptor.

'Squirting gasoline around the edge of a fire'

But as Sweet-Cordero's research showed, tumor growth was accelerated by the interaction of the CLCF1 ligand with three receptor proteins. The cancer begins in the lung's epithelial cells, which line the surface of the lungs. These cells are nested within supportive cells called fibroblasts. The cancerous epithelial cells induce the fibroblasts to release CLCF1, which recruits the three receptors in a specific order: first, CLCF1 hooks up with CNTFR, and then this duo attracts two other receptor proteins, gp130 and LIFR. Together, these four proteins provide additional fuel to the tumor. "Imagine squirting gasoline around the edge of a fire," Sweet-Cordero said.

Cochran's bioengineers sought to dampen the flames by creating a receptor decoy based on CNTFR, the second protein in the chain, but they had to do so carefully. If the decoy CNTFR paired with CLCF1, and these two proteins then recruited the other two receptors, the proposed remedy could unintentionally fuel cancer growth.

"We had to design a decoy that did two things at once," Cochran said. "It had to preferentially bind tightly to CLCF1, edging out any naturally occurring CNTFR, and once locked in place, it had to repel gp130 and LIFR."

Jun Kim, a Ph.D. student in Cochran's lab, led the painstaking work of designing this dual-purpose decoy. Think of proteins as moving puzzle pieces that fit together to form the body's molecular machinery. Using a variety of bioengineering techniques, Kim made eight, subtle tweaks to CNTFR's shape to increase the decoy's propensity to bind to CLCF1 while warding off gp130 and LIFR.

Neutralizing tumor growth

Cesar Marquez, an MD-Ph.D. student at Stanford who is completing his dissertation in the Sweet-Cordero lab, carried out a series of experiments to test this engineered receptor decoy in mice with lung cancer. The experiments established that the decoy significantly neutralized the growth instigated by CLCF1 and slowed the cancer's spread.

It could require several years of further drug development and animal studies before the researchers can begin testing this treatment in humans. Once at that stage, the researchers are confident they'll be able to identify patients with this particular form of lung cancer because it is associated with mutations in a gene called KRAS. The presence or absence of the KRAS biomarker may identify patients who are most likely to benefit from the receptor decoy drug.

Cochran said her work with Sweet-Cordero is part of a long-term effort to increase the number of tools for fighting cancer.

It's too early to tell whether the decoy treatment will prove effective in patients. But Cochran is optimistic that the drug will be safe for use in

humans, given there was no evidence of toxic side effects in mice. She has her fingers crossed in this regard, as a decoy drug based on her earlier work with ovarian cancer has already shown promising results in early clinical trials.

"As these studies show, when we combine detailed knowledge of a particular disease mechanism with bioengineering prowess, we can achieve some pretty powerful results," she said.

Provided by Stanford University Medical Center