Immunotherapy Strategy for Ovarian Cancer Aims to Rewire a 'Kill Switch'

T cells bearing a new engineered protein boost immunotherapy's effectiveness in laboratory models.

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Solid tumors like breast and lung cancer, by their nature, construct all kinds of barriers to an effective immunotherapy.

Kristin Anderson, PhD, a researcher at Fred Hutchinson Cancer Research Center who works on a type of immunotherapy known as T-cell therapy, and her colleagues have been steadily working on identifying and overcoming those barriers. Some of these tumors' roadblocks include cancer cells sneakily masking themselves from recognition by engineered immune cells or sending out signals that cause the therapeutic T cells to commit suicide before they can do their job.

As compared to blood cancers, "there are many additional features in solid tumors that give immunotherapy a higher bar to cross," Anderson said. That's one of the major reasons progress in T-cell therapy is further along for blood cancers than for many solid tumors.

Anderson and her Fred Hutch colleague Shannon Oda, PhD, both of them postdoctoral research fellows working in the immunotherapy lab of Phil Greenberg, MD, are developing new ways to outsmart these cellular cheaters.

Their latest, developed by Oda and tested in ovarian cancer mouse and cell studies in the lab by Anderson: A new type of hybrid protein that, when added to T-cell therapy, tells the engineered immune cells to ramp up their activity in response to what is normally a death signal.

Anderson presented the team's latest progress in a poster at the American Association for Cancer Research's annual meeting in Chicago. Her presentation focuses on their work in mouse models of ovarian cancer as well as human ovarian cancer cells in the lab. Oda has also shown efficacy of new fusion proteins in mouse models of acute myeloid leukemia, or AML, and pancreatic cancer. Their work is part of a host of research aimed at making the next generation of immunotherapies more effective and applicable to more patients.

Building a new route around cancer's roadblocks

In mouse models of all three types of cancer, the hybrid protein is showing promise as a booster for cancer immunotherapies. Mice given T cells engineered to carry the hybrid protein in addition to another protein that targets them specifically to cancer cells survive their cancers significantly longer than mice given the form of T-cell therapy without the hybrid protein.

Ovarian cancer is tricky. It tends to be diagnosed late, due to its lack of symptoms, making it the fifth leading cause of cancer death among women in the U.S. even though by incidence, it is the 10th most common cancer. That's about 14,000 deaths per year, according to the American Cancer Society.

The preclinical model of ovarian cancer, which Anderson will present at the meeting, recapitulates many of the roadblocks that human ovarian cancer mounts. That's why the team's initial results are so exciting for Anderson — they've been able to show, in the mice at least, that they can engineer T cells that can wipe out ovarian tumors even in this very tricky setting.

"We were able to take a model that simulates these suppressive features and engineer a way around one of them," Anderson said.

She was jetting off to the conference even as the ovarian cancer mouse experiments continued, but so far the results are encouraging: Mice who don't receive the targeted T-cell therapy live an average of 77 days; those treated with T cells engineered with the fusion protein and which target ovarian tumors are surviving almost twice as long, so far. They're also living about 33 percent longer than mice treated with T cells bearing only the cancer-targeting protein.

Taking a clinical problem to the laboratory bench

In the mouse model of AML, the first cancer Oda tackled using the fusion protein approach, 90 percent of mice treated with cells carrying the fusion protein survived their disease to 100 days, the endpoint of the experiment. Only 40 percent of those treated with a T-cell therapy without the fusion protein survived that long. The research team published their AML findings in the journal Blood late last year.

The impetus for that study came from the clinic, Oda said. Greenberg leads patient trials using a form of T-cell therapy where the cells are engineered to carry a naturally existing protein, known as a T-cell receptor, that recognizes and homes to cancer cells. That approach is showing promise in some patients with blood cancers, but the researchers knew from their studies that the cells could still be further optimized to make the treatment even better.

"We knew that T cells getting shut down was definitely an issue in the clinic," Oda said.

Leukemia tumors also have tricks to stop T cells from working — T cells' activity is dampened by a molecule on the surface of cancer cells. The protein Oda created to get around that barricade takes the external piece of the existing T-cell protein, the part that reads the "shut off" signal sent by the cancer cells, and fuses it to a piece from another protein that tells the cell to ramp up its activity.

“We’re replacing a brake with an accelerator,” Oda said.

The fusion protein she crafted for the solid tumor studies works a bit differently. The external piece of that protein, when it receives the signal from tumors, normally tells the T cells to commit cellular suicide. The cancer even scatters these deadly messages at the edge of blood vessels, so some of the T cells die before they ever get to the tumor. The fusion protein rewires the cells to interpret the kill switch to instead stimulate their cancer-killing abilities.

The hybrid proteins aren’t yet ready to be added to clinical trials testing these immunotherapies in humans. The T cells engineered specifically for ovarian and pancreatic cancer, those without the fusion protein, also aren’t being used in clinical trials yet — although they are close, Anderson said. She and Oda also hope the fusion proteins could be added to other, existing T-cell therapies to make them even more powerful.

The researchers are also studying other ways the fusion proteins affect the engineered immune cells. The additional engineering seems to be a net positive, Oda said. This single addition may help the therapy get around multiple tumor roadblocks.

“We’re seeing differences in metabolism, in how the cells proliferate and expand in the body, how they’re able to kill the tumor,” she said. “There are multiple T-cell functions we’re positively impacting.”

The studies were funded by the National Institutes of Health, Juno Therapeutics and the Leukemia & Lymphoma Society. Note: Scientists at Fred Hutch played a role in developing these discoveries, and Fred Hutch and certain of its scientists may benefit financially from this work in the future.

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