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CAR-T immune therapy attacks ovarian cancer in mice with a single dose

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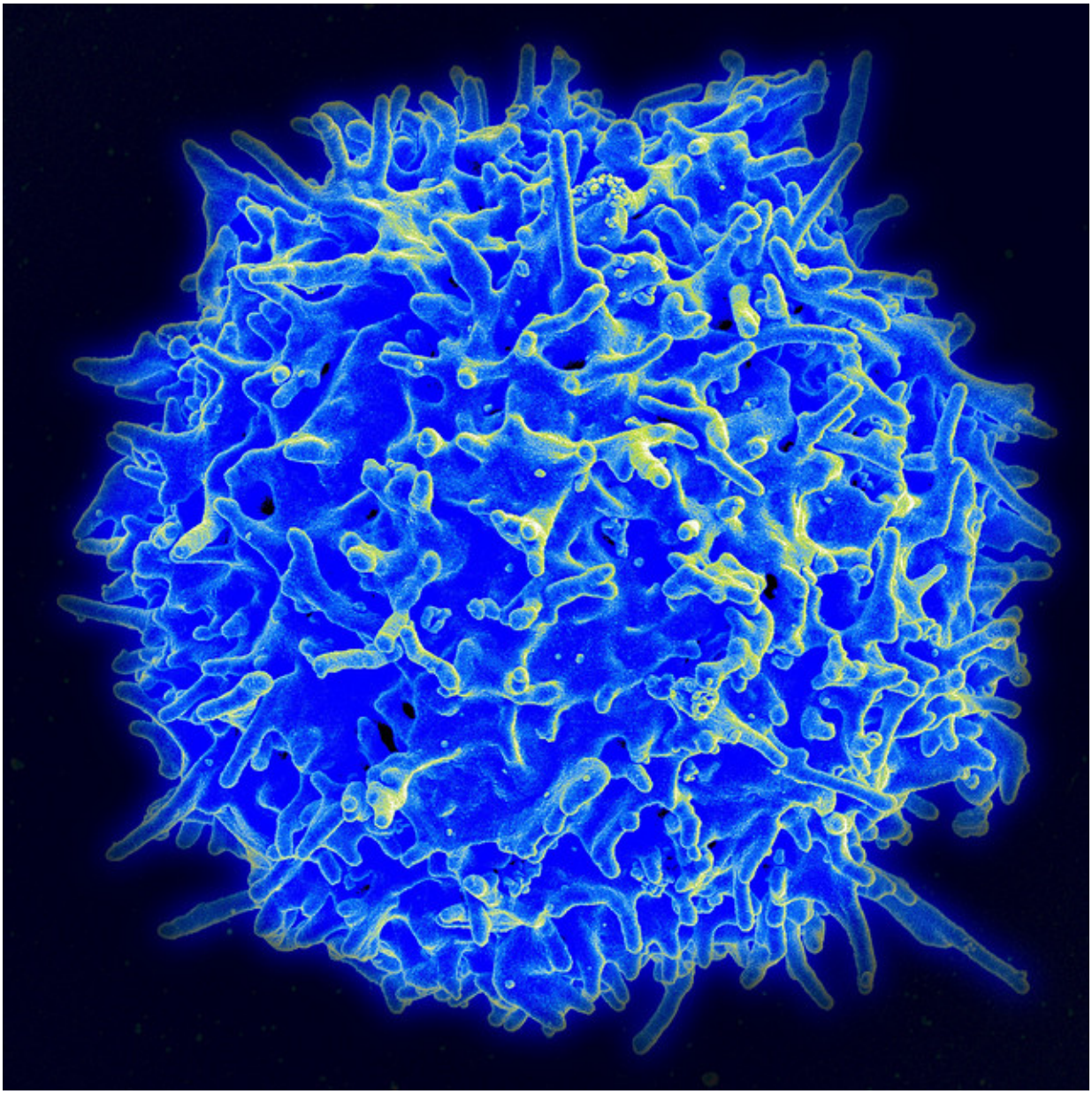

Scanning electron micrograph of a human T lymphocyte (also called a T cell) from the immune system of a healthy donor. Credit: NIAID

CAR-T immune therapies could be effective against solid tumors if the right targets are identified, a new study led by University of Illinois Urbana-Champaign researchers suggests. The researchers have successfully deployed CAR-T in a mouse model of ovarian cancer, a type of aggressive, solid-tumor cancer that has eluded such therapies until now.

The research is published in the *Journal for ImmunoTherapy of Cancer*.

"Even with an advanced stage tumor model, even with a single dose, we saw strong anti-tumor effects," said Diana Rose Ranoa, first author of the study. Ranoa is a postdoctoral researcher at the Carl R. Woese Institute for Genomic Biology at Illinois. "There are still a lot of questions to be answered, but this study shows that CAR-T can kill this type of cancer once it recognizes the right target."

T cells are the white blood cells in the immune system that recognize and attack specific foreign invaders to the body. CAR-T therapies use special molecular receptors, called chimeric antigen receptors, that bind to cancer biomarkers. These CARs help a patient's own T cells target the cancer in their body as though it were an outside invader.

While such therapies are effective against blood cancers such as leukemia and lymphoma, cancers that produce solid tumors have remained difficult to treat with CAR-T immune therapies, said study leader David Kranz, a professor emeritus of biochemistry at Illinois. He also is affiliated with the Carl R. Woese Institute for Genomic Biology and with the Cancer Center at Illinois.

"There aren't the same type of targets for these receptors on solid tumors that there are in blood cancers, and it's very difficult to find a target that isn't found in healthy tissues as well," Kranz said. "The other factor is that solid tumor cells have their own way of suppressing the immune response to evade recognition by T cells and other immune cells. A lot of work is being done to try to overcome those two barriers—finding good targets and finding the right kind of CARs that could recognize those targets."

In the new study, the researchers focused on a carbohydrate found on the surface of solid tumor cells, but not healthy cells. They developed CAR molecules with varying affinity for the molecule and tested them first in ovarian cancer cell cultures, and then in live mice with ovarian cancer tumors.

They found that the receptors with the highest affinity for the carbohydrate were highly effective at helping T cells find and destroy the cancer, shrinking or eliminating tumors after just one intravenous or injected dose—and continuing to work for months or even more than a year after the initial dose, extending the lives of the mice.

"We were surprised that the CAR-T treatment was able to do such a good job at regressing the cancer, not just because it did it for a long period of time, but because we administered the treatment at a late stage of cancer," Kranz said. "In almost all the studies that have been done in the mouse models, you treat very early after you put the tumor in. We were treating well after that, starting at stages like where it is usually diagnosed in human patients."

The researchers hope this and other distinctive factors of the study design may give their treatment greater potential for clinical translation to humans. While the standard for cancer trials in mice is to place human cancer cells in mice whose immune system has been compromised so

that the foreign cancer will grow, the Illinois study used mice with functioning immune systems, but targeted a marker present in both mouse and human ovarian cancers.

"Setting up our model in immunocompetent mice allowed us to show how the CAR-T cells behave in the presence of an intact host immune system and to demonstrate that these CARs do not have toxic effects against healthy tissues. The treatment is very specific to the tumor," Ranoa said. "And now we have this CAR that we've demonstrated can kill mouse ovarian cancer—and it has been engineered to recognize the same target in human cancers. So human studies are the logical next step for this line of research."

The researchers plan to test their CAR-T regimen against human cancer cells cultures, as well as continue searching for other possible targets for solid-tumor cancers and the CARs that could find them.

"In this mouse model there was such a potency that it hopefully can be translated to human patients," Kranz said. "To get something so specific against the tumor that doesn't have major side effects for the patient, that's the holy grail."

More information: Diana Rose E Ranoa et al, Single CAR-T cell treatment controls disseminated ovarian cancer in a syngeneic mouse model, *Journal for ImmunoTherapy of Cancer* (2023). DOI: 10.1136/jitc-2022-006509

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