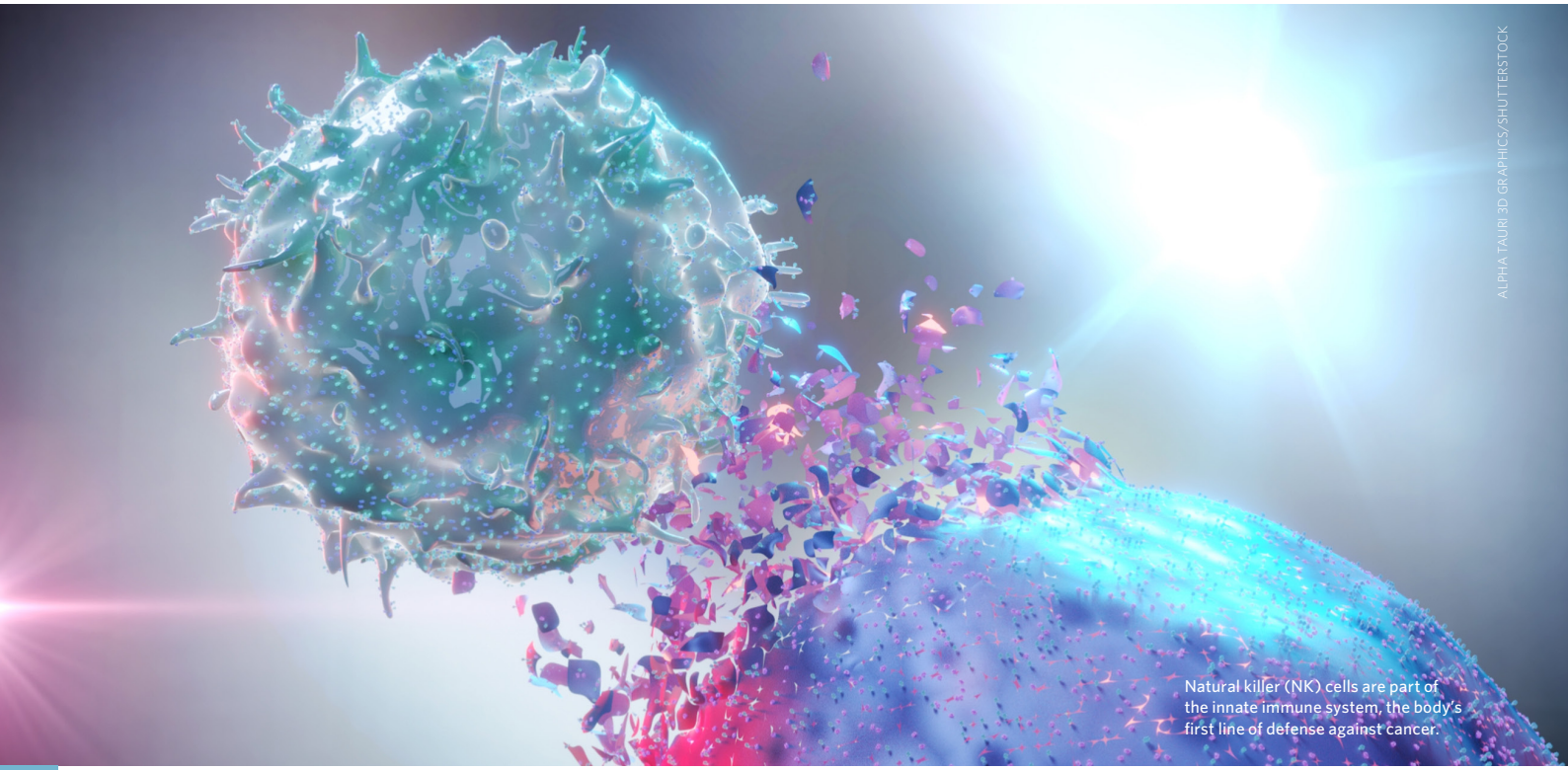


Natural killer (NK) cells are part of the innate immune system, the body's first line of defense against cancer.

HARNESSING THE BODY'S NATURAL KILLERS TO TARGET CANCER

Natural killer cells, the body's first line of defence against emerging cancers, could be engineered into powerful, OFF-THE-SHELF CANCER THERAPIES.

Billions of highly trained killers are flowing through your fingers right now. They patrol your internal organs, guard the tissues under your skin against invaders, and wipe out virus-infected cells. They remain vigilant against cancer — recognising and destroying the early signs of tumours before they can gain a foothold.

These tiny terminators, called natural killer (NK) cells, are one of the body's strongest defences against illness and disease — and yet the hundreds of billions of NK cells in our own bodies sometimes aren't enough. Now researchers want to engineer NK cells as reinforcements, and store ranks of those reinforcement NK cells to be called up and deployed as needed (see 'Engineering a tumor killer'). They want to make these engineered NK cells available to cancer patients and others as living drugs, without having to personalize them for each patient, as is the case with other cell therapies.

"We want to make cells that work like drugs," says Dan Kaufman, a professor of regenerative medicine at the UC San Diego School of Medicine and co-founder and chief scientific officer of Shoreline Biosciences. "When you take a blood pressure medicine or a cholesterol medicine, everybody gets the same thing. You know the doses and it's standardized. Using these engineered NK cells, we can do that. We can make hundreds, or potentially thousands, of doses of these NK cells all the same and use them as off-the-shelf therapies."

Immunotherapy strategies

The idea builds on the success of so-called CAR-T cells, which are used as immunotherapies against several types of cancer.

"WE WANT TO MAKE CELLS THAT WORK LIKE DRUGS."

These cell-based therapies are based on a different immune component, called T cells. By collecting a patient's T cells, engineering them to make them more potent, and then infusing them into the body, scientists can supercharge the cancer-fighting ability of the patient's immune system. Five CAR-T cell therapies have been approved by the US Food and Drug Administration against several blood cancers.

NK cell immunotherapy has not yet reached that stage. "The natural killer cell approach in terms of cancer immunotherapy is newer, and rapidly gaining recognition," says Hans-Gustaf Ljunggren, who works on cell therapies at the Karolinska Institute in Stockholm, Sweden. "There are numerous clinical trials going on with various natural killer cell-based products."

Although there are clinical trials of NK cells in progress for

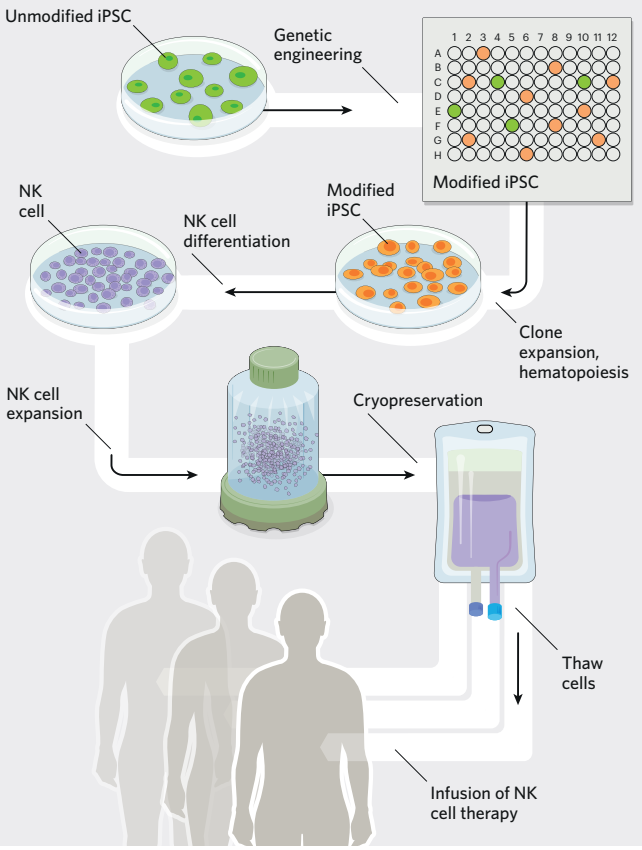
multiple different blood cancers, nothing has been approved yet.[1] "But it's not unlikely that we will see such products within the coming five years," Ljunggren says.

To help translate his own research on NK cells into commercial therapies, Kaufman co-founded Shoreline Biosciences. The company raised $43 million in financing earlier this year and entered into two partnerships with two immunotherapy companies, Kite Pharma and BeiGene, to develop novel cell therapies. The company recently concluded another round of financing that raised an additional $140 million.

One of the goals of NK cell therapies is to make them significantly cheaper than CAR-T cell treatments, Kaufman says. "It's very expensive to take out the T-cells, engineer them and give them back to each individual patient. It costs roughly half a million dollars to make the cells for one patient." The process also takes several weeks.

ENGINEERING A TUMOR KILLER

By genetically engineering their precursors, researchers are boosting the cancer-fighting prowess of immune sentinels called NK cells.



Innate fighters

NK cell therapies can be made more quickly and at lower cost because NK cells function in a different way. T cells are part of the adaptive immune system, the body's second line of defence against both viral infections and cancer. They are primed to recognise specific foreign proteins on the surface of a patient's own cells. Because T cells from one person recognize healthy cells from other people as foreign, only a patient's own T cells can be used as a therapy — hence the need to remove and engineer them at such cost.

NK cells work in the frontline innate immune response, in which they patrol the body and attack any cells that are not recognised as part of the host tissue. This more indiscriminate approach means that NK cells therapies can be sourced elsewhere and more easily given as a standard treatment to many different patients.

"You can essentially establish banks of hopefully potent NK cells that could then be distributed globally to be used for treatment of cancers," Ljunggren explains.

Because they do not need to be taken from a specific patient, Kaufman began developing NK cells for potential therapies from induced pluripotent stem (iPS) cells — skin or blood cells that have been reprogrammed back into an immature state that lets them develop into any other type of cell.

"Dan is one of the pioneers in the generation of the IPS derived NK cells," Ljunggren says. "And now IPS NK cells have become a very interesting and relatively new aspect of cell therapies."

Genetic manipulation

Besides being more universal, deriving the NK therapies from pluripotent stem cells brings another advantage. Manipulating the genome of the stem cells before they are converted to NK cells offers a reliable way to introduce genetic changes that could improve potential therapies.

When faced with attacking NK cells, cancer cell don't sit idly by. "We know there are ways that the tumour cells can sort of evolve to avoid the immune system," Kaufman says.

Kaufman's group has countered by engineering NK cells into better cancer fighters. "We can engineer these NK cells to provide additional mechanisms or more activated cells that seem to be able to overcome those barriers."

They have done this by knocking out a gene called CISH, which is involved in regulating cell-signalling molecules called cytokines. NK cells without the CISH gene are more sensitive to the cytokine IL-15, which leads to greater cell proliferation. As a result, the cells live longer inside the body and show enhanced anti-tumour activity.[2]

Trials ahead

Several challenges remain. Like CAR-T cells, NK cell therapies seem less effective against solid tumours. And because they are not based on host cells, the engineered NK cells can trigger an immune response, which tries to reject them. Researchers deal with that at present with doses of chemotherapy to suppress the host immune system. But Kaufman says they are also working on a new type of "stealth" NK cell that can evade host immunity.

"Can you also engineer these cells to avoid that immune response? That's a challenge for later," he says.

Shoreline has completed preclinical testing on a potential NK cell therapy for acute myeloid leukaemia. The company is now working on ways to manufacture the cells to the required clinical grade, and to test them for safety. That work is on track, Kaufman says, and trials will begin soon. ■

REFERENCES

1. Liu, S. *et al. J. Hematol Oncol* **14**, 7 (2021)
2. Zhu, H. *et al. Cell Stem Cell* **27**, 224–237 (2020)