For cancer, a biopharmaceutical company and UC San Diego test another kind of immune cell

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When the U.S. Food and Drug Administration approved the first cell-based gene therapies for cancer in 2017, advanced malignancies once seen as terminal suddenly looked treatable, perhaps even curable.

These therapies use immune cells called T cells, genetically engineered with what are called chimeric antigen receptors, or CARs. Successes with these CAR T cells against certain blood cancers have thrilled patients and the medical community.

But these therapies have disadvantages. They must be custom-engineered from each patient's own cells, a costly and logistically complex process that often takes weeks. Many desperately ill patients don't have that time. The cells can sometimes provoke dangerous immune reactions. And they don't work well against some cancers, including many solid tumors.

Seeking to overcome these hurdles, San Diego's Fate Therapeutics, a clinical-stage biopharmaceutical company, and UC San Diego are collaborating to develop another kind of cell therapy. They're using a different kind of immune cell, called a natural killer cell, or NK cell.

Natural killer cells possess their own abilities to sniff out diseased or infected cells. Because cancers work in so many diverse ways, some appear to be more effectively treated by these cells.

And along with UCSD, Fate is preparing more advanced versions of these cells that promise additional advantages, such as being easier to make and, ultimately, equipped with advanced technology to overcome resistant tumors.

The promise of these less-famous relatives of T cells have spawned their own field of therapy. It's big enough for conferences dedicated to these cells, including one in San Diego last spring. Other companies developing natural killer cell therapies include Celgene and Celularity, both from New Jersey; and Ziopharm Oncology, of Boston.

Under the collaboration with UC San Diego, Fate Therapeutics is genetically engineering natural killer cells to create what are called CAR NK cells. The university's end of the collaboration is led by Dr. Dan Kaufman, a professor in the division of regenerative medicine and director of cell therapy at UCSD School of Medicine. He began working with Fate a few years ago, while at the University of Minnesota.

Kaufman and Fate say natural killer cell therapy complements T cell therapy but doesn't replace it. Fate is also developing CAR T cell therapies in collaboration with Memorial Sloan Kettering Cancer Center.

Natural killer cells have a number of potential advantages over T cells, said Kaufman. They don't have to come from the patient, they are potentially safer and may be effective against cancers not as easily targeted by T cells.

"One specific type of leukemia seems to be quite sensitive to (natural killer) cells," Kaufman said. "Part of the goal is how can we make that a more standardized therapy, and how can we potentially target other more refractory tumors, including solid tumors?"

Fate is now in the early stages of testing natural killer cell therapy in

patients with various solid tumors, including resistant or recurrent ovarian cancer, along with a form of resistant leukemia.

So far, this non-engineered product, called NK100, is demonstrating safety and early signs of potential effectiveness in a small number of patients.

The cells are typically taken from a healthy relative, Kaufman said. They must be immune-matched to the patient, but the match doesn't have to be as close as in a bone marrow transplant. However, each dose must still be prepared individually.

BRINGING IN STEM CELLS

Fate is also working on an entirely new approach for cancer immunotherapy, said Scott Wolchko, the company's president and chief executive officer.

This new approach starts with a type of stem cell called an induced pluripotent stem cell, or iPSC. These cells are created in a lab from adult cells, engineered and used as a renewable source for making cells, including natural killer cells or T cells.

If this approach succeeds in clinical testing, cell therapies no longer have to be custom-made for every patient, Wolchko said. "You can manufacture lots of doses in advance, in a single manufacturing run. You can cryopreserve those doses, and ship (natural killer) cells or T cells as needed for patient treatment."

Fate, a publicly traded company, was founded in 2007 on the work of top stem cell scientists. These include Sheng Ding, then at Scripps Research and now at UC San Francisco; and Rudolf Jaenisch at Massachusetts Institute of Technology in Cambridge, Mass. Both are

experts in induced pluripotent stem cells, and have devised more efficient methods of making them.

Fate refers to its first stem cell-derived treatment, consisting of natural killer cells, as FT500. Fate intends to begin testing in early 2019 of the therapy in combination with a well-established class of cancer immunotherapy drugs called checkpoint inhibitors.

Fate expects to get a regulatory green light for clinical testing of FT500 by the end of the year, Wolchko said. If all goes well, treatment should begin early next year.

The next step is to add genetic engineering to the stem cells, producing CAR NK cells. Fate intends to ask regulatory permission to start clinical testing in mid-2019. Actual testing of this therapy, called FT519, is expected to begin later in 2019.

SAME TEAM, DIFFERENT DIVISIONS

Natural killer and T cells belong to two different arms of the immune system, adaptive and innate. For maximum effectiveness in fighting cancer, Fate wants to invoke both.

T cells are part of the adaptive immune system, which provides targeted responses to specific infections. But the adaptive response takes time to kick in. To meet the immediate threat, other immune cells step in to provide ready-made responses suited to most infections. Natural killer cells belong to this wing, the innate immune system.

Natural killer cells have a toolkit of probes that identify likely dangers, Kaufman said. They respond by secreting chemicals, which directly kill targeted cells, as well as other signals that call in the adaptive immune system.

FT500 is to be tested with checkpoint inhibitors because the combination should intensify the anticancer response, Wolchko said.

Checkpoint inhibitors remove a brake on T cells, allowing them to recognize and attack tumor cells. But the T cells need to get to the tumor for this response to work.

Natural killer cells and checkpoint inhibitors can get this process rolling, Wolchko said. The combination unleashes both arms of the immune system, with the various cells working in tandem to target and destroy tumor cells, Wolchko said.

"Once the (natural killer) cells engage the tumor, the checkpoint inhibitors can enable the body's own T cells to recognize and destroy the tumor."

ADDING STEM CELL TECHNOLOGY

To produce off-the-shelf natural killer cell therapy from stem cells, Fate and Kaufman teamed up, contributing their own expertise, said Bob Valamehr, Fate's chief development officer.

Stem cell technology is needed because direct genetic engineering of natural killer cells doesn't work well. But when stem cells are engineered, they can then be expanded into many more stem cells. These stem cells can then be scrutinized to select the highest quality lineage to turn into natural killer cells.

This path from undifferentiated stem cell to differentiated adult cell is known in the field as cell fate. And the company's expertise in directing cells down a desired path is how Fate Therapeutics got its name

Kaufman said the combination of stem cell technology, genetic

engineering and off-the-shelf use yields a very versatile platform—natural killer cells that can be given as needed, and engineered to fight cancer.

Moreover, other features such as safety mechanisms can be added to make even more multi-faceted cancer-killing cells, Kaufman said.

Those extra features are coming soon, Wolchko said: First things first.

For information on Fate Therapeutics' clinical trials, visit fatetherapeutics.com/pipeline