PRECISION ONCOLOGY NEWS

Cytovia's CAR NK Alliance With NYSCF, UCSF Aims to Overcome Negative Side Effects of CAR T Drugs

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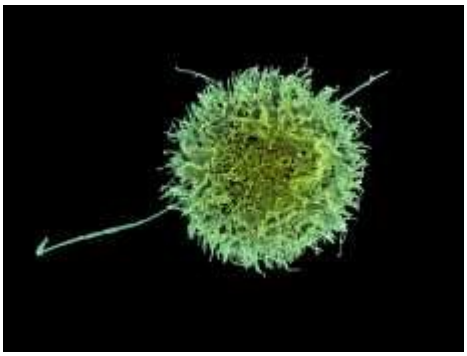

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NEW YORK – Last month, Cytovia Therapeutics unveiled two partnerships in succession: one with the New York Stem Cell Foundation, and one with Justin Eyquem's laboratory at the University of California, San Francisco. These partnerships, which contain a three-year research agreement between the three institutions, will support Cytovia's foray into developing natural killer (NK) cell-based therapies for cancer.

Formed in 2019, Cytovia's focus is natural killer cell-based therapeutics and multifunctional NK engagers. Cytovia CEO Daniel Teper noted that the company's focus on NK cells has its advantages since they are as effective as T cells in responding to tumors, but are safer and easier to manufacture off-the-shelf. Additionally by using "precision gene-editing" to modify chimeric antigen receptors (CAR) on NK cells, the company hopes to advance treatments with maximum anti-tumor effects and minimum off-tumor toxicities.

"The T cell space is saturated, particularly from the cell therapy standpoint, and T cells have weaknesses that can be better overcome with natural killer cells than trying to further improve the current technologies. NK cells are naturally allogeneic. So far, there hasn't been reports of any significant cytokine release syndrome — which has been an indication of the CAR T therapy — neurotoxicity hasn't been reported, [and] no graft versus host disease," said Teper.

But CAR NK therapy requires a lot of adjustments to get the right balance of efficacy and safety. This is where the partnerships come in. The aim of the project is to source stable NK cells and engineer them to target the tumor persistently without producing off-target effects.

In its new assembly of NK cell therapy pipeline, Eyquem at UCSF will genetically edit the NK cells to express desired targets, and the New York Stem Cell Foundation will provide the source of induced pluripotent stem cells and grow them using a differentiation protocol into NK cells all the way through manufacturing.

Induced pluripotent stem cells, or iPSCs, are adult cells that are reconfigured into a stem cell, which can then be differentiated into any kind of cell. Eyquem claims that it's much easier to control the editing of NK

cells derived from iPSCs as opposed to placenta-derived multipotent stem cells or hematopoietic stem cells.

"To ensure that stem cells are a valuable resource for human drug discovery and development, we've built the proprietary NYSCF Global Stem Cell Array, which is a series of robots and a completely automated way to derive induced pluripotent stem cells from either blood or skin, differentiate them to the relevant cell type, and gene-edit them," said Elizabeth Schwarzbach, chief business officer of NYSCF. "This capability that's been built over time is going to be foundational to this type of collaboration where we're looking to provide quality iPSCs as a starting material for this therapeutic."

According to Schwarzbach, NYSCF has worked on projects with other biopharma and academic collaborators. Their key relevant work in the past spans T cells, type 1 diabetes, and other autoimmune conditions. But this is NYSCF's the first project with NK cells.

Using the robots, NYSCF optimizes protocols for differentiation. As a cell goes from an induced pluripotent stem cell to the cell type of choice, in this case an NK cell, there are several steps along that pathway that are critical to differentiation. Researchers will use machine learning to understand which factors — whether it's a small molecule inducer or transcription factors or media — are driving the differentiation, and experiment on various combinations of different factors.

NYSCF has a bio bank of thousands of samples that has been created over time on the Global Stem Cell Array. They include research-grade patient and control iPSCs. "For initially optimizing the protocol, we can use samples that are within our biobank, derived from either blood or skin. We also do have a consent and IRB in place to recruit new patients and derive new patient iPSC lines or control iPSC lines," said Schwarzbach. The cells that will ultimately be given to patients will be from a clinical grade iPSC line that NYSCF creates according to good manufacturing practices.

Schwarzbach added that there are quality control metrics and chain of custody release criteria along the entire derivation process. At the end of the derivation process, to ensure that no mutations have been introduced and all the genetic material is the same, they match it up against a second source of reference sample for the line, like a spit sample.

The process also aims to select out CAR NK cells that would produce off-target effects. When genes are knocked out or knocked in across several rounds of editing, more combinations of off-target effects or complications may arise. After several rounds of genome editing, researchers can select the iPSC clone that will have only the on-target effect without the off-target. "I think these collaborations with Cytovia and New York Stem Cell provide this unique opportunity to do several rounds of genome editing with the tools that we're developing, and be sure that we are selecting the optimal clone, and from that clone, create a large bank of the iPSC and then NK Cells for the patients," Eyquem said.

Eyquem's lab is interested in engineering T Cells and NK Cells in order to redirect their functions to tumors. They do that through two different methods. The first way is to engineer immune cells' fate and functions with new receptor design, such as chimeric antigen receptors. The second way is using gene editing to disrupt endogenous genes or insert new ones. Instead of using viral vectors to insert the transgene of chimeric antigen receptors into T or NK cells, Eyquem's lab uses CRISPR/Cas9 to target the transgene integration. Targeted integration results in a more homogeneous and predictable expression level, which help standardize the manufacturing, according to Eyquem. Following that, Eyquem's team will use genome editing to try to identify genes whose disruption or overexpression would improve the function of the T cells or NK Cells.

Eyquem has shown in the past that in the context of T cells, transcriptional control of the CAR transgene can have a substantial impact on the CAR T cell function. He believes that this will also be true for NK cells. As he performs targeted integration of the CAR transgene, he'll also observe the impacts on CAR

expression level and NK cells in terms of effector function, proliferation, and overall antitumor activity, and home in on an endogenous locus that will offer optimal stability and function for the NK cells.

"So far, most of the CAR that have been used were first developed in T cells; the second aim is really to try to fine tune the CAR to be more tailored to NK function," said Eyquem. That could be done by tweaking the co-stimulatory domain in order to deliver a signal that will be more specific to the NK cells. Eyquem views this collaboration as a catalyst for the technology to reach clinical application.

According to Teper, the initial proof of concept will be in multiple myeloma. Teper adds that they will also be looking at chronic lymphocytic leukemia with the antigen CD160, which is expressed in 96 percent of malignant B cells but not on non-malignant B cells. "We have interest in solid tumors, and particularly in ovarian cancer," he said. He hopes to bring the targeted therapies to the clinic within two years.

If they start with a myeloma model, researchers could target multiple myeloma targets that have been identified, such as BCMA or CD38, or maybe both. "The idea is to do a knock-in of the CAR into a specific locus targeting BCMA or CD38," Eyquem said. "We also have the option of disrupting the expression of the gene we are targeting."

The group hopes to prove that their therapy, using the precision gene-editing approach, works better than current CAR T CD38 and CAR T BCMA therapies on the market. Teper said that the CAR NK therapy should also be more accessible than CAR T options due to the availability in outpatient settings and projected lower costs because they will be off-the-shelf.

In addition, Cytovia has another approach in its pipeline that lies outside the scope of the UCSF and NYSCF partnership: an NK engager with multi-specific antibodies.

The NK engager is a molecule comprised of three arms: two that target NK cells and one that targets the tumor antigen. The arm with the tumor antigen would bring the molecule to the tumor, then NK cell would follow and destroy the tumor cell. Teper said that Cytovia is looking at similar targets for both the tri-specific and CAR NK approaches.

Cytovia is not the only company making headway into natural killer cell therapy. Companies like NantKwest, Acepodia, and Fate Therapeutics are all tapping into this market.

Teper noted that Fate Therapeutics is ahead of Cytovia from the pipeline development standpoint based on the Phase I results of iPSC-derived CAR NK cell treatment that researchers presented at the annual American Society of Hematology meeting held in December 2019.

He also highlighted the efforts from MD Anderson to clinically validate the safety and the preliminary efficacy of NK cells. In November 2019, MD Anderson entered into a licensing and research agreement with Takeda to commercialize its CD19-targeted CAR NK-cell therapy and a B-cell maturation antigen (BCMA)-targeted CAR NK-cell therapy. The CD19-targeted CAR NK-cell therapy is being evaluated in an ongoing Phase I/IIa trial, and the companies plan to initiate a pivotal study in 2021.

"That's the most advanced [program] to date in the US, or even globally," said Teper. "The NK space right now has a handful of companies involved and they're all in preclinical or very early clinical development. There's enough of a proof-of-concept and validation of the approach in the cell therapy." As this research project matures in the coming years, Teper's goal is for Cytovia to become one of the leaders in NK therapies, whether it's using CAR NK or multi-specific antibodies.

Filed Under Cancer Drug Discovery & Development research alliance multiple myeloma UCSF