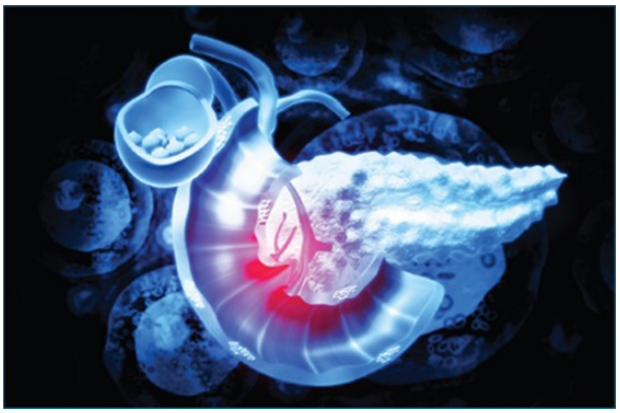
CAR NK CELL THERAPY DIRECTED AGAINST PANCREATIC CANCER

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Using donated umbilical cord blood, researchers from City of Hope National Medical Center in Los Angeles created an off-the-shelf chimeric antigen receptor (CAR) natural killer (NK) cell therapy that prolonged life with minimal side effects in a mouse model of metastatic human pancreatic cancer.

The novel therapy, which targets prostate stem cell antigen (PSCA)—expressed in 60-80 percent of all human pancreatic cancers and associated with poor prognosis—is expected to move into clinical trials at City of Hope within the next 12 months, the researchers said.



“We introduced a manufactured platform that can generate billions of CAR-NK cells from a single cord unit, a freezing process that preserved the potency of the product and substantial in vivo efficacy of the PSCA CAR-NK cells in an animal model of metastatic pancreatic cancer, “ said Kun-Yu Teng, PhD, a postdoctoral researcher in the laboratory of Michael A. Caligiuri with the City of Hope, who presented findings during Week 1 of the virtual annual meeting of the American Association for Cancer Research (AACR), held April 10-15, 2021 (Abstract LB154).

Because pancreatic cancer doesn't display any obvious symptoms in its early stages, it's often not detected until it already has spread to other parts of the body. Treatment options are currently limited, resulting in a low 5-year survival rate of about 9 percent, the third-leading cause of cancer deaths.

For this reason, cancer researchers increasingly are turning to immunotherapies, including the genetic modification of immune cells, mainly T cells and most recently NK cells, to express CARs.

NK cells are among the body's first line of defense against the onset of cancer, capable of recognizing cancer cells early on and destroying them. But cancers can develop ways to hide from the immune system. The genetically engineered cells created by Teng and colleagues are designed to harness the ability of NK cells to target and attack tumor antigens that remain

hidden.

Researchers believe that CAR-NK cells may have certain advantages over CAR T-cell therapy, now approved to treat some hematological malignancies, in addition to hundreds of clinical trials around the world against multiple tumors.

For example, most CAR T cell-based gene therapy products in clinical trials consist of enriched T cells from the patient themselves, whereas NK cell-based approaches can be generated by allogeneic donors—meaning the cells can be taken from a non-related healthy donor, and therefore can be manufactured ahead of time and frozen for storage.

NK cells also have been shown to cause little or no side effects, including graft-versus-host disease, and therefore are suitable for an off-the-shelf therapeutic product that's ready when the patient needs it.

Study Details

In this study, the researchers hypothesized that NK cells encoded with CAR that targets an overexpressed tumor-associated antigen would enhance tumor recognition and destruction by human NK cells. CAR-NK cells were directed against PSCA, common to pancreatic tumors in addition to gastric, bladder, prostate, and some lung cancers.

Here, NK cells are first isolated from donated umbilical cord blood from healthy newborns and genetically modified to express the desired CAR, plus PSCA. The City of Hope researchers also added a soluble IL-15, an immune signaling molecule crucial for optimal antitumor response, in addition to a “suicide gene.”

Multiple doses of CAR-NK cells are then manufactured, with continued cell expansion going from 10s of millions of cells from a single donor cord blood to a hundred billion or more CAR-NK cells within 16 days. The cells are then frozen and preserved for future use. When thawed, they were shown to retain viability and potency.

“Large-scale production should allow our product to be administered to anywhere between 10 and 20 patients once in clinic,” Teng said.

To test the potential effectiveness of CAR-NK cell therapy in the lab against pancreatic cancer, Teng and colleagues added their engineered CAR NK cells targeting PSCA (PSCA+ CAR NK), with soluble IL-15 (sIL-15) and a “suicide gene,” into a culture of pancreatic cancer cells (Capan-1). They compared the results against a control that did not include PSCA (PSCA- CAR NK), but did contain IL-15 and the “suicide gene,” into a culture of PANC-1 pancreatic tumor cells.

“We showed that the co-expression of sIL-15 with PSCA+ CAR NK cells significantly enhances their cytotoxic function against pancreatic tumor cells compared to PSCA- CAR NK cells without expression of sIL-15 determined by a real-time cytolysis assay over 3.5 days,” the researchers wrote in an abstract of their study.

Encouraged by these findings, Teng and colleagues developed a model of metastatic human pancreatic cancer in immunodeficient mice using the PSCA+ Capan-1 cell line. Mice were treated for 45 days.

Compared to cells only expressing IL-15, repeated infusions of human PSCA CAR NK cells from a viably frozen source resulted in a significantly prolonged survival in these mice, including no sign of metastatic disease.

“Only treatment with the PSCA CAR NK cells significantly suppressed tumor growth, protected the pancreas, and delivered from metastatic spread and prolonged survival of the mice, over either arm of the controls studied,” Teng said.

Analysis of the cells isolated from pancreas on Day 48 also showed the near absence of tumor cells and the persistence of NK cells.

“In summary, our in vitro and in vivo studies utilizing viably frozen human PSCA CAR NK cells co-expressing sIL-15 demonstrate significant efficacy in prolonging survival against a human pancreatic tumor cell line without evidence of systemic toxicity, providing a rational to move this novel form of cell therapy into the clinic for PSAC(+) solid tumors,” the researchers wrote in their abstract.

Warren Froelich is a contributing writer.

About CytoImmune Therapeutics, Inc.

Founded in 2017, CytoImmune Therapeutics is a clinical-stage biotechnology company, focused on developing an innovative and differentiated pipeline of NK cell therapies, using proprietary, robust and well characterized NK cell expansion and engineering technologies pioneered by Michael Caligiuri, M.D. and Jianhua Yu, Ph.D. The pipeline includes cytokine induced NK (CI-NK) for lung cancer, FLT3 CAR-NK for acute myeloid leukemia, PSCA CAR-NK cells for solid tumors and GPRC5D BiKE secreting BCMA CAR-NK cells for multiple myeloma. CytoImmune's lead product, CYTO-102 (CI-NK) cell therapy, aims to enter the clinic in combination with atezolizumab (anti-PD-L1 monoclonal antibody) for non-small cell lung cancer in 2022.

Contact:

Name: Emily Trujillo
Phone: 1-646-480-0356
Email: emily@publicize.co

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