MedicalXpress

An off-the-shelf, dual-targeted CAR T-cell product shows promising results in preclinical studies

April 16 2018

FT819, an off-the-shelf, T-cell receptor (TCR)-less CD19 CAR T-cell product that could potentially be made more accessible to cancer patients than conventional CAR T-cell therapies showed positive results in preclinical specificity, functionality, and efficacy studies, according to data presented at the AACR Annual Meeting 2018, April 14-18.

"Chimeric antigen receptor (CAR) T-cell therapy has shown remarkable results in certain cancer patients. However, the therapy is highly personalized, time-consuming to produce, and consists of only enough cells for a single dose treatment with variable quality," said Bob Valamehr, Ph.D., vice president of Cancer Immunotherapy at Fate Therapeutics Inc. "Additionally, today's CAR T-cell therapies only target a single tumor antigen, which can also limit efficacy."

"We aimed to overcome these challenges by demonstrating proof-of-concept for an off-the-shelf, dual-targeted CAR T-cell approach. We started with cells from a healthy donor rather than the patient, created a master cell line, and used the master cell line to produce large quantities of 'universal' CAR19 T cells that are not patient-restricted," Valamehr explained. "These first-of-kind CAR19 T cells, called FT819, can be packaged, stored, and made readily available for treatment of a large number of patients."

The master cell line used to manufacture FT819 is an induced

pluripotent stem cell (iPSC) line. The use of a master iPSC line for the production of CAR T cells provides distinct advantages over autologous (using cells from a patient's own body) and allogeneic (using cells from a donor) approaches, Valamehr explained. "A master iPSC line has unlimited capacity to self-renew, and can be banked and renewably used." Valamehr and colleagues used a proprietary platform that they previously developed to create the master iPSC line.

Conventional CAR T-cell therapies use autologous T cells. New approaches under investigation are using donor T cells; however, donor T cells can attack the patient's tissues and organs, resulting in a potentially severe and fatal immune system reaction known as graft-versus-host disease (GvHD). In order to avoid GvHD, it is critical to deactivate or remove the TCR, Valamehr explained.

Investigators attempting to engineer billions of donor T cells in bulk have experienced challenges with eliminating the TCR, Valamehr said. "FT819 is TCR-less. We ensure complete elimination of the TCR by directing the CAR to a T-cell receptor α constant (TRAC) locus in a single pluripotent cell," he noted.

Michel Sadelain, MD, Ph.D., a collaborator on the FT819 project at Memorial Sloan Kettering Cancer Center, had demonstrated previously that CAR expression under the control of a TRAC locus results in uniform CAR expression, enhances T-cell potency, and vastly outperforms conventionally generated CAR T cells in a mouse model of acute lymphoblastic leukemia.

In addition to a CAR targeting CD19-positive tumor cells, FT819 also has a second targeting receptor designed to broaden the therapy's efficacy. This CD16 Fc receptor can bind to tumor cells coated with antibodies. This enables FT819 to be administered in combination with other proven cancer treatments, like monoclonal antibodies targeting

CD20-positive tumor cells, to potentially overcome tumor antigen escape.

In studies in vitro, FT819 displayed an efficient cytotoxic T-cell response when challenged with CD19-positive tumor cells by producing cytokines (IFN-gamma, TNF-alpha, and IL2) and mediators of cell death (CD107a/b, perforin, and granzyme B). FT819 was also found to be target-specific by attacking only CD19-positive tumor cells and sparing CD19-negative tumor cells. Through the expression of CD16 Fc receptor, FT819 was shown to elicit antibody-dependent cell-mediated cytotoxicity when combined with a therapeutic antibody targeting CD20.

"Through the development of FT819, we believe there is significant opportunity to lower the cost of CAR T-cell manufacture; enhance the quality of the product; and create a readily available supply of a more efficacious product to reach more patients in need," Valamehr said.

FT819 cells were developed using human cells, but the studies used model systems that are not predictive of clinical safety and efficacy, Valamehr cautioned. "We will be required to conduct human clinical trials to fully assess the safety and efficacy of our off-the-shelf iPSC-derived CAR T-cell products."

FT819 is being developed by Fate Therapeutics Inc., of which Valamehr is a full-time employee.

Provided by American Association for Cancer Research