New technology can potentially overcome CAR T-cell immunotherapy limitations

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An engineered organic bispecific adaptor molecule that functions as a bridge between a chimeric antigen receptor (CAR) T cell and a cancer cell can potentially overcome some of the limitations posed by CAR T-cell immunotherapy technologies, according to data presented here at the AACR Annual Meeting 2016, April 16-20.

"Our technology provides a universal platform that incorporates a cell-based immunotherapeutic 'living drug' and an organically synthesized inert small-molecule adaptor," said senior author of the study Philip S. Low, PhD, professor of chemistry and director of the Center for Drug Discovery at Purdue University in West Lafayette, Indiana. "This technology has the potential to extend CAR T-cell immunotherapy beyond its current reach."

Yong Gu Lee, a graduate student in Low's laboratory and lead author of this study, explained that the T cells "constitute the main weapon the immune system employs to kill cancer cells." He added, "A number of labs have recently developed genetically engineered T cells that can recognize and kill cancer cells more efficiently. However, the current CAR T-cell technologies have many limitations."

First, he said, existing technology only allows for developing CAR T cells to target one particular protein present in tumor cells, which means that new CAR T cells have to be genetically engineered for each different cancer cell that expresses a different target protein. Second, engineered T cells are highly cytotoxic, and with current technology it is

not possible to stop them from functioning once tumor cells are eliminated. Third, the target proteins present on cancer cells are also often present on normal cells, which means that the CAR T cells can cause off-target toxicity leading to serious side effects.

To overcome these limitations, Lee and colleagues engineered an adaptor using small organic molecules, and attached a yellow dye, fluorescein isothiocyanate (FITC), on one end, and a ligand on the other end that can bind to a specific protein present on a tumor. The ligand can be designed to target many different tumor proteins, such as the folate receptor, which is present on about a third of human cancers; and prostate-specific membrane antigen, which is present in prostate cancer tumors.

Next, they engineered second-generation CAR T cells based on existing technology and incorporated an anti-FITC antibody fragment into the intracellular domain of CD137 and CD3 zeta chain so it can bind to the FITC end of the adaptor molecule.

When a patient receives CAR T cells and adaptor molecules, the adaptor molecule will bind to the CAR T cell at the FITC end and to the tumor cell at the ligand-binding end.

Because the tumor cell is recognized by the adaptor and not by the CAR T cell itself, the same CAR T cell can be targeted to multiple distinct tumor cells expressing non-overlapping (orthogonal) tumor-specific antigens, simply by administering a cocktail of the correct antigen-matched adaptor molecules. The adaptors survive for no more than 20 minutes in the blood circulation, which means it is possible to control the rate and extent of tumor cell killing and cytokine release in order to avoid serious adverse effects (e.g., tumor lysis syndrome and/or cytokine storm), Lee explained.

"Our new CAR T-cell design allows for more sensitive control of the

rate of tumor lysis and cytokine release, enabling the physician to permanently terminate the cell-killing process as soon as the cancer has been eliminated from the body and avoid sustained off-target toxicity to healthy cells," he said.

Further, by adjusting the binding affinity of the tumor-binding end of the adaptor molecule, it is possible to make the CAR T cell bind only to cells that express high levels of a protein, as in the case of tumor cells, and not to cells that express low levels of the protein, as with normal cells, he explained.

The technology has currently only been tested in animals and not in humans.

"We tested our technology in animal models and learned that our CAR T cells are only able to eradicate tumor cells when the correct antigen-matched adaptor molecules are administered," Lee said. "Moreover, we have demonstrated that we can eliminate two different tumor cell types in the same animal by administering a mixture of the desired adaptor molecules."

Low and team are in the process of patenting their technology.

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