Treatment shows promise in treating deadly brain cancer
27 May 2020

Researchers of McMaster University and the University of Toronto have developed a promising immunotherapy treatment for a deadly form of adult brain cancer called glioblastoma.

The treatment is a type in which a patient's T cells, which are a kind of immune cell in the blood, are changed in the laboratory so that they will bind to cancer cells and kill them. In this case, the treatment called chimeric antigen receptor T cell (CAR-T) therapy involves genetically engineering a patient's T cells to give the cells the ability to target and bind to a specific protein called CD133 in glioblastoma cells directly and eliminate them.

When used in mice with human glioblastoma, CD133-targetting CAR-T therapy was considered a success due to reduced tumour burden and improved survival.

The data from this study has led to the formation of a new Hamilton-based start-up brain cancer immunotherapy company called Empirica Therapeutics. The company aims to run clinical trials in recurrent glioblastoma patients for the lead program CD133-specific CAR-Ts and other therapies by 2022.

The study details are published in Cell Stem Cell.

Glioblastoma cancers have a dire prognosis, said the study's first author Parvez Vora, a former member of the laboratory team of professor Sheila Singh at McMaster and director of preclinical development at Empirica Therapeutics.

"Upon initial diagnosis, glioblastoma patients undergo aggressive treatment, including surgery to remove the tumour, radiation therapy and chemotherapy. However, cancer relapses in less than seven months, resulting in less than 15 months overall median survival," he said.

"Almost all the glioblastoma tumours come back as a more aggressive recurrent tumour, which has no standard-of-care treatment."

The research was led by the Singh lab at McMaster in collaboration with the Jason Moffat lab at the University of Toronto's Donnelly Centre for Cellular and Biomolecular Research.

The Singh lab has been studying the role of CD133 protein in brain tumours for more than a decade. The lab identified that the protein is a marker of cancer stem cells that have the properties necessary to grow glioblastoma tumours that are difficult to treat.

In this study, researchers investigated if specific targeting of CD133+ glioblastoma with cutting-edge immunotherapy drugs could eradicate the most aggressive subpopulation of cells in the tumour. They also looked at the safety of CD133-targeting therapies on normal, non-cancerous human stem cells including hematopoietic stem cells which create blood cells and progenitor cells which can form one or more kinds of cells.

Researchers subsequently designed three types of
treatments and tested them both in the lab and in mice. The first treatment is the novel human synthetic IgG antibody, which can simply bind to CD133 protein on glioblastoma cells and halt the growth of the tumour. The second is a dual antigen T cell engager antibody, which uses the patient's own immune T cells to eliminate the CD133+ glioblastoma. The third is the CAR-T therapy.

"We found that the CAR-T therapy had enhanced activity compared to the other two therapeutics in preclinical models of human glioblastoma," said Vora.

"The accompanying safety studies in humanized mouse models address the potential impact on hematopoiesis, a vital process in the human body that leads to the formation of different blood cells. CD133-specific CAR-T therapy did not induce any acute systemic toxicity in humanized mouse models that harbored the human hematopoietic system."

Rashida Williams, a graduate student in Moffat's lab at the Donnelly Centre, generated the CD133 antibody, parts of which were used to construct different immuno-modalities including the CAR-T cell.

"Recent advances in immunotherapy have offered hope to patients with previously untreatable cancers," said Jason Moffat, professor of molecular genetics at U of T and the Canada Research Chair in Functional Genomics of Cancer. He is the chief scientific officer at Empirica Therapeutics.

"We hope that our approach of specifically targeting glioblastoma cells with CAR-T therapy will give the patients a better quality of life and increase their chances of survival."

Kristin Hope, associate professor of biochemistry and biomedical sciences at McMaster, is credited for her work generating the humanized models for toxicity testing.

Researchers are exploring combinatorial strategies next along with CD133-specific CAR-Ts to block glioblastoma tumour recurrence completely. Researchers suggest this type of therapy may prove to be effective in patients with other treatment-resistant cancers with CD133 tumour initiating cell populations.

"Our study has provided many novel conceptual insights into the value of targeting an aggressive CD133+ cancer stem cell population in glioblastoma," said corresponding author Sheila Singh, professor in the Department of Surgery at McMaster and the Canada Research Chair in Human Cancer Stem Cell Biology. She is chief executive officer of Empirica Therapeutics.

"We hope that our work will now advance the development of really new and promising treatment options for these patients."


Provided by McMaster University