'Dual-target' cell therapy appears to shrink brain tumors, research finds

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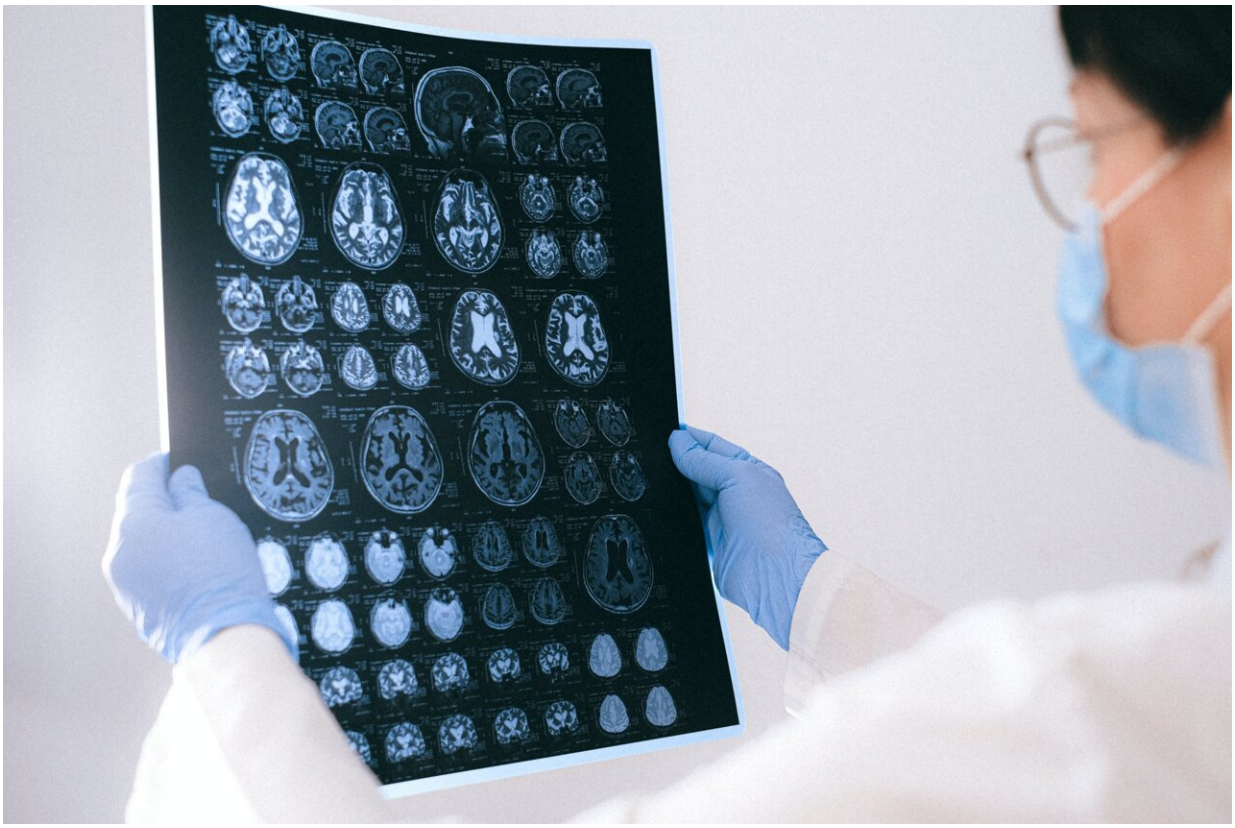

Credit: Anna Shvets from Pexels

Targeting two brain tumor-associated proteins—rather than one—with CAR T cell therapy shows promise as a strategy for reducing solid tumor growth in patients with recurrent glioblastoma (GBM), an aggressive form of brain cancer, according to early results from the first six patients treated in an ongoing Phase I clinical trial led by researchers from the Perelman School of Medicine at the University of Pennsylvania and Penn Medicine's Abramson Cancer Center.

The findings, published in *Nature Medicine,* suggest that this "dual-target" approach is an encouraging step toward developing effective, long-lasting therapies for solid tumors like GBM.

"This is the first time CAR T cell therapy with two targets, rather than just one, has been administered to patients with glioblastoma," said Stephen Bagley, MD, MSCE, an assistant professor of Hematology-Oncology, and Neurosurgery, and principal investigator in the clinical trial.

"Our results suggest that this is a step in the right direction, and this method, when delivered through a patient's spinal fluid, could be the key to developing therapies that outsmart the complicated defense systems of GBM."

GBM is the most common—and most aggressive—type of cancerous brain tumor in adults. Individuals with GBM usually expect to live 12-18 months following their diagnosis.

Despite decades of research, there is no known cure for GBM, and approved treatments—such as surgery, radiation, and chemotherapy—have limited effect in prolonging an individual's life expectancy. However, even after aggressive treatment, GBM returns in

most patients, which is known as recurrent GBM. The median survival rate for recurrent GBM is less than one year.

CAR T cell therapy uses a patient's own immune system to fight cancer; a patient's T cells—the white blood cells that find and fight illness and infection in the body—are removed, re-programmed to recognize proteins, or antigens, characteristic of a specific type of cancer, and then returned to the body, where they seek out and destroy these cancer cells.

CAR T cell therapy is FDA approved to fight a number of blood cancers, like leukemia, but researchers have struggled to engineer cells to successfully seek out and kill solid tumors, which make up the vast majority of cancer types, including GBM.

"The challenge with GBM and other solid tumors is tumor heterogeneity, meaning not all cells within a GBM tumor are the same or have the same antigen that a CAR T cell is engineered to attack, and every person's GBM is unique to them, so a treatment that works for one patient might not be as effective for another," said Bagley.

"What's more, GBM tumors can evade a patient's immune system, and block immune cells—both engineered CAR T cells, and a patient's own immune cells—that might otherwise fight the tumor. Our challenge is getting our treatment around the tumor's defenses so we can kill it."

In this trial, researchers used a technology developed in the lab of Donald M. O'Rourke, MD, the John Templeton, Jr., MD Professor in Neurosurgery and director of the Glioblastoma Translational Center of Excellence at the Abramson Cancer Center, and scientific advisor to the trial.

This technique delivers CAR T cells targeting two proteins commonly found in brain tumors: epidermal growth factor receptor (EGFR), which

is estimated to be present in 60% of all GBMs, and interleukin-13 receptor alpha 2 (IL13Rα2), which is expressed in over 75% of GBMs. While CAR T cell therapy for blood cancers is typically delivered through an IV, researchers administered these dual-target CAR T cells intrathecally, through an injection into the cerebrospinal fluid, so that the engineered cells could reach the tumors more directly in the brain.

MRI scans 24 to 48 hours after dual-target CAR T cells targeting EGFR and IL13Rα2 that were administered revealed reduced tumor sizes in all six patients, and these reductions have been sustained out to several months later in a subset of patients.

"We are energized by these results, and are eager to continue our trial, which will give us a better understanding of how this dual-target CAR T cell therapy affects a wider range of individuals with recurrent GBM," said O'Rourke. "This cancer is unique in each individual, so a wider range of patients will help us determine the optimal dose, better understand effects like neurotoxicity, and more firmly establish efficacy."

A major concern with CAR T cell therapy, especially when delivered to the brain, is neurotoxicity, which occurs when a toxic substance alters the activity of the nervous system, and can disrupt or kill brain cells, called neurons. The researchers report that in all six patients treated with CAR T cell therapy in this trial, neurotoxicity was substantial but manageable.

More information: Intrathecal bivalent CAR T cells targeting EGFR and IL13Rα2 in recurrentglioblastoma: phase 1 trial interim results, *Nature Medicine* (2024). DOI: 10.1038/s41591-024-02893-z

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