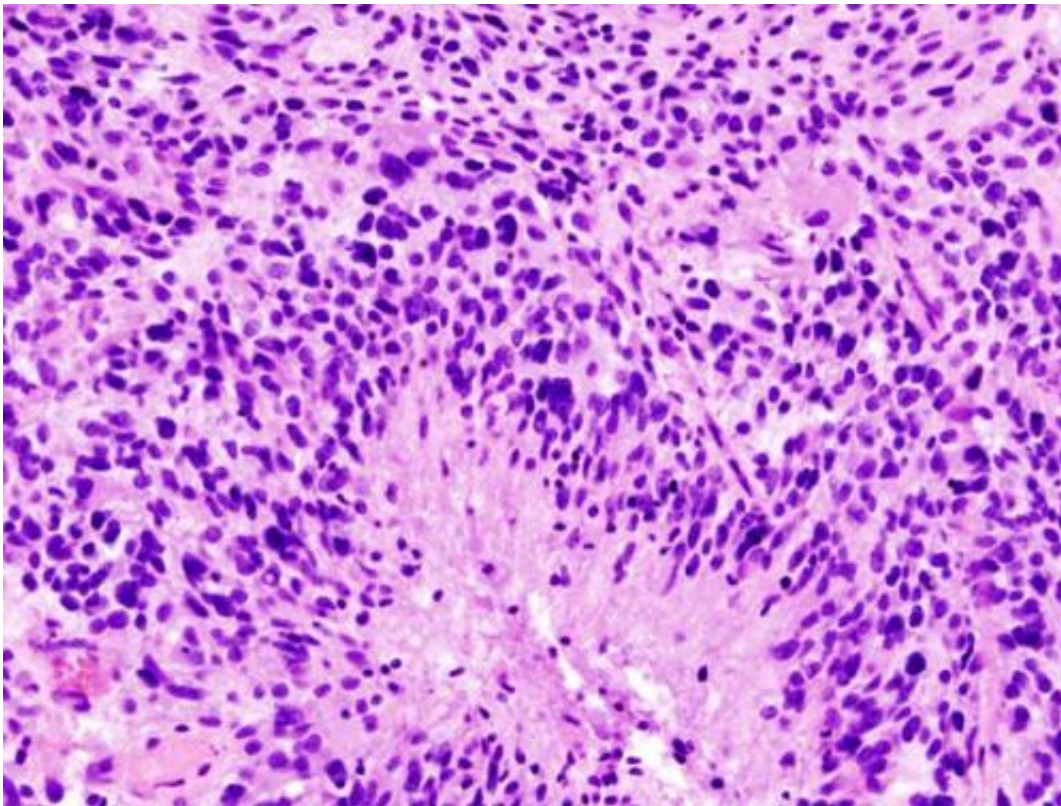


# Personalized cell therapies show more promise in solid tumors

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Glioblastoma (histology slide). Credit: Wikipedia/CC BY-SA 3.0

Investigational "hunter" immune cells engineered to seek out and attack a deadly brain cancer known as glioblastoma (GBM) infiltrated patients' tumors and triggered thousands of more T cells once inside, researchers from Penn Medicine reported in a late breaking abstract at the AACR Annual Meeting 2017 (Abstract LB-053). The findings are among the

results from three studies being presented on chimeric antigen receptor (CAR) therapy with T cells and a newer approach known as CARMA, which successfully pitted engineered macrophages against breast and ovarian tumors.

The GBM results, presented by Donald M. O'Rourke, MD, an associate professor of Neurosurgery at the Perelman School of Medicine at the University of Pennsylvania, fall under a phase I trial testing immune [cells](#) made from patients' own T cells engineered in a specialized laboratory to target a tumor-specific protein known as EGFRvIII, which is found in about 30 percent of GBM tumors.

Last year, O'Rourke and his colleagues reported that these CAR T cells successfully migrated to and infiltrated GBM tumors in nine patients, which has been an ongoing challenge in the treatment of many [solid tumors](#) with CAR because of an unfavorable tumor microenvironment.

The new results showed a dramatic increase (nearly 20-fold) in the number of tumor-infiltrating (TIL) T cells in patients' tumors following that infusion, suggesting that the infused cells can recruit and expand other T cells once in the tumor. To determine this, researchers sequenced the T cell receptor chain of TIL cells from the tumor specimens of five patients before and after their infusion.

Penn is the first institution to open a trial utilizing in this type of CAR T cell therapy for GBM, which is diagnosed in more than 22,000 Americans each year. One of the next steps in the research is to determine whether these tumor-infiltrating cells can initiate a tumor response.

The GBM clinical trial is sponsored by Novartis. In 2012, the University of Pennsylvania and Novartis announced an exclusive global research and licensing agreement to further study and commercialize novel

cellular immunotherapies using CAR technologies.

Another hurdle for CAR T cell therapy in solid tumors is immune inhibitory receptors, such as PD-1 and CTL4A, which can inhibit T cell activation.

In a new preclinical study, presented by Edmund K. Moon, MD, an assistant professor of medicine in the division of Pulmonary, Allergy, and Critical Care at Penn, researchers modified a CAR T cell to quiet one of those molecules, known as SHP1, to help overcome that resistance in certain solid tumors. (Abstract 3749).

Moon and colleagues modified CAR T cells to target the specific protein mesothelin on cancer cells and inserted a genetically engineered SHP1 inhibitor to block PD-1-mediated immune suppression.

The team, which also includes Steven M. Albelda, MD, the William Maul Measey Professor of Medicine at Penn, showed that mice that received the mesoCAR/dnSHP1 T cells had a 60 percent greater decrease in tumor growth compared to mice that only received mesoCARs. TIL infiltration was also significantly higher in tumors harvested from mice that received the mesoCAR/dnSHP1 T cells.

"DnSHP-1 engineering is a powerful and novel way of blocking the suppression of CAR T cells by PD1 and other inhibitory receptors," the authors said.

Results from a preclinical study using a newer CAR therapy approach from the lab of Saar Gill, MD, PhD, an assistant professor of Medicine at Penn, known as CARMA , or chimeric receptor antigen macrophages, were also presented (Abstract 4575).

Macrophages are a type of white blood cell that engulfs and digests cell

debris and bacteria. Under some circumstances, macrophages can also promote cancer, which is perhaps one of the reasons this cell type has not yet been intensively studied for adoptive cellular therapy.

"When you look at solid tumors, you can see that they are very much infiltrated with macrophages," Gill said. "We reasoned that a cell already predisposed to trafficking to tumors might be a good one to genetically engineer to be a cancer killer, instead of what it normally does, which is act as an accomplice to help the tumor grow. We also wanted to make them more powerful and specific."

The team engineered CAR macrophages to target specific proteins on cancer cells (including mesothelin and HER2, which is found in some breast and ovarian cancers) using the viral vector Ad5f35, an adenovirus.

The abstract was presented by Michael Klichinsky, PharmD, a PhD candidate in the department of Systems Pharmacology and Translational Therapeutics at Penn.

Anti-HER2 CARMA demonstrated targeted phagocytosis and killed significantly more HER2 expressing ovarian and breast [cancer cells](#) compared to cell lines treated with the drug trastuzumab, the researchers showed in laboratory experiments. In an ovarian cancer mouse model, CARMA significantly decreased tumor burden (by 100 fold) and demonstrated a 30-day survival benefit compared to untreated mice, the researchers found.

"CARMA exhibited targeted anti-tumor function in both in vitro and in vivo preclinical models," the authors said. "A platform that makes macrophages recognize and kill [tumor cells](#) while simultaneously making them resistant to [tumor](#)-mediated subversion would represent a major advance in the field to treat solid tumors."

Provided by Perelman School of Medicine at the University of Pennsylvania

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