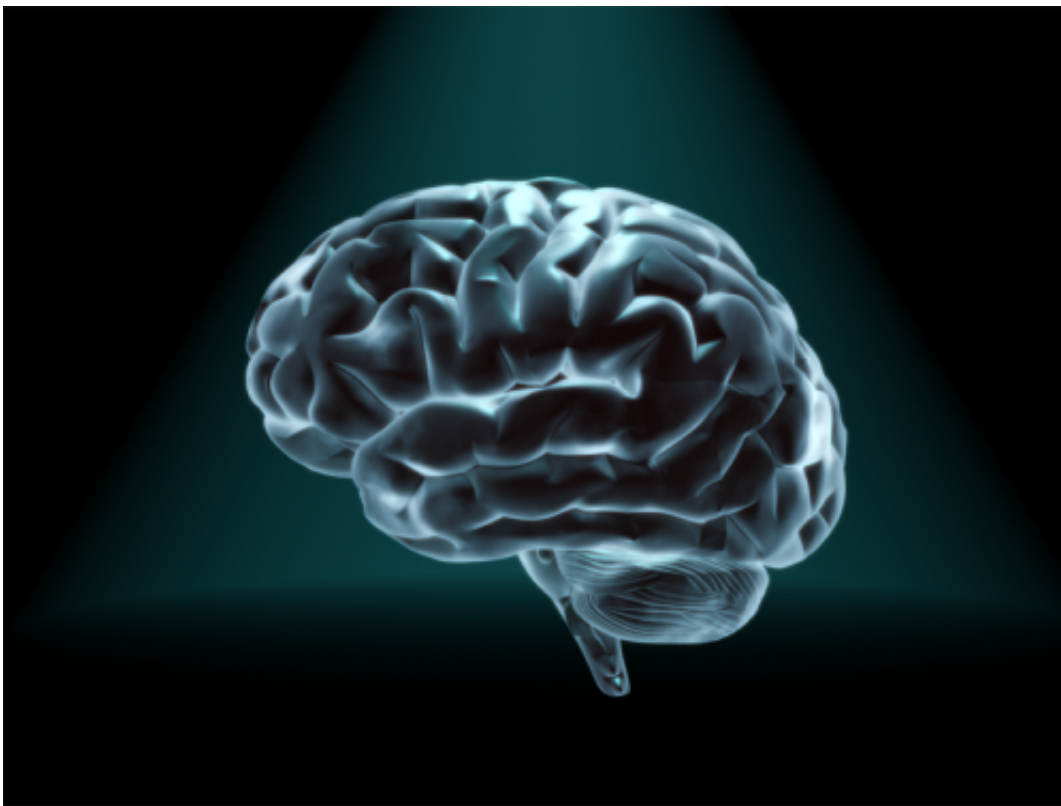


Brain cancer breakthroughs using the immune system offer hope against glioblastoma

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Credit: Human Brain Project

A flurry of new studies suggest scientists are finally figuring out how to harness the immune system to attack a ruthless form of brain cancer. While preliminary, the results offer hope that progress is possible against

glioblastoma, the terrible form of cancer that so swiftly took the lives of Arizona Senator John McCain and President Joe Biden's son Beau.

But the studies, while astonishing, are small. What's needed next is an urgent effort to prove the effect can allow people to live longer and better—and to explore how it can be extended into other types of cancer.

Ever since the first stories emerged more than a decade ago of [blood cancer patients](#) miraculously brought back from the brink by therapies known as CAR-Ts, doctors have dreamed of using the same approach in tumors. The therapies are bespoke: A patient's blood cells are reengineered to spot certain proteins on the surface of cancer cells. But designing therapies that can infiltrate and kill tumors without damaging healthy cells has proven an immense challenge.

Independent work from teams at Massachusetts General Hospital, the University of Pennsylvania and City of Hope Cancer Center in Duarte, California (and published in the *New England Journal of Medicine* and *Nature Medicine*), showed various CAR-Ts can shrink glioblastomas, in some case with dramatic speed. In the Mass General study, for example, one patient's tumor was nearly 20% smaller after just 48 hours—and in just over two months it had decreased in size by some 60%.

That's an astounding result for this aggressive and universally fatal form of cancer. In advanced disease, treatments typically at best keep the tumor from growing, but don't cause it to shrink.

"Collectively it shows we've basically opened the door to a whole new kind of treatment for glioblastoma," says Marcela Maus, who is the director of Mass General's Cellular Immunotherapy Program and led the work featured in [NEJM](#).

Researchers have spent decades trying to come up with better

treatments, but the options have remained depressingly slim: surgery, radiation and chemotherapy. Once the disease recurs, options are even more limited—patients are often told to look for a clinical trial. That's left patients with a heartbreaking prognosis: People typically only live a year to 18 months after the disease is detected.

That's what makes any signs of activity, even in small and preliminary studies, so exciting. Seeing tumors start to melt away within a day of treatment, and in some cases regress completely, has been so exhilarating that Donald O'Rourke, the Penn neurosurgeon who led that institution's trial and has spent 25 years working on this pernicious form of cancer, has had trouble sleeping at night.

There's still a long way to go to a commercialized therapy. For starters, O'Rourke's team and others still need to prove that [tumor](#) shrinkage is lasting and actually allows people to live longer. "We don't want to see an MRI change rapidly, give each other back slaps and two weeks later, the cancer recurs," O'Rourke says.

Still, there's reason to be hopeful. Although some patients' tumors grew again, a handful of patients across the various studies appear to have a prolonged response to treatment. One of the three patients in Mass General's study continued to do well six months after treatment, and three out of the six patients treated by the Penn team have had extended responses.

The various teams think they can improve those results. For example, the Penn team believes providing this therapy earlier in the disease could be key. Their bespoke treatment was given to people whose tumors had recurred several times and had aggressively grown in several areas of the brain, a point at which O'Rourke says, "You're asking too much of the therapy." Offering the treatment immediately after the first recurrence could be the trick to maximizing efficacy.

The Mass General team thinks they might get a more lasting response if they prep the [immune system](#) for the personalized therapy. The next patients enrolled in their trial will receive a small dose of chemotherapy before the cell therapy is administered, an approach that they believe will help the immune cells stick around longer, Maus says.

These new studies also underscore a few important lessons about how to get engineered immune cells to work beyond the blood. For one, they all suggest that the [therapy](#) needs to be delivered locally (for example, injected into the spinal fluid rather than given intravenously). And they also validate some of the ways that scientists have been thinking about targeting tumors. Already, these teams are considering whether similarly designed therapies could be used in other types of cancers, like lung cancers that have spread to the brain or even pancreatic cancer.

If any of these projects are to succeed, they eventually will need industry's help. The trials need to expand beyond single sites at hospitals, for example, and a commercial partner can offer the kind of large-scale, timely production needed for a treatment to have reach. While Penn has licensed its technology to Gilead Sciences Inc., Mass General currently lacks such a partnership.

These studies underscore a fundamental truth in science: Often, it simply takes time and tinkering to get new technologies to work in very tough diseases. But once they start to work, it should be all hands on deck—that means academics and industry coming together—to try to push the next studies as quickly as possible toward better options for cancer patients who so desperately need them.

More information: Bryan D. Choi et al, Intraventricular CARv3-TEAM-E T Cells in Recurrent Glioblastoma, *New England*

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