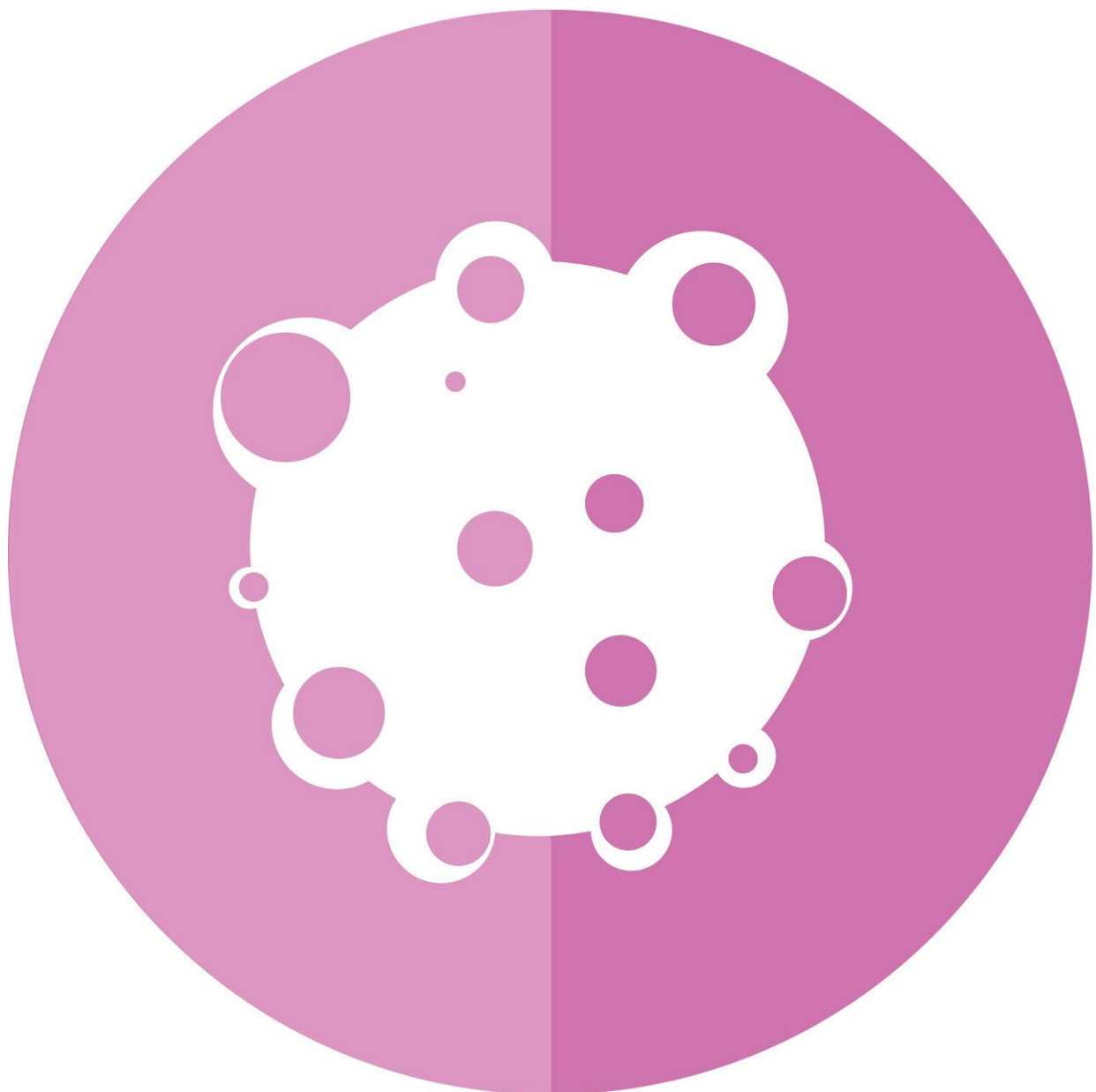


New glioblastoma treatment reaches human brain tumor and helps immune cells recognize cancer cells

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In a major advance for the treatment of the deadly brain cancer glioblastoma, Northwestern Medicine scientists have used ultrasound technology to penetrate the blood-brain barrier and provide a small dose of a chemotherapy and immunotherapy drug cocktail. The study found that this treatment boosted the immune system's recognition of the cancer cells and could lead to a new treatment approach.

The scientists made several breakthroughs reported in a new study published in *Nature Communications*.

Scientists showed for the first time that a skull-implantable ultrasound device can enhance the penetration of the chemotherapy drug doxorubicin and immune checkpoint blockade antibodies—a novel immunotherapy treatment combination—into the human brain. The device produces microbubbles that temporarily open the [blood-brain barrier](#), allowing the immunotherapy to enter the brain.

The scientists also showed for the first time that a small dose of doxorubicin (smaller than the dose used for traditional chemotherapy regimens) delivered with the immune checkpoint antibodies can boost the recognition of malignant glioblastoma cells by the [immune system](#) and reinvigorate the lymphocytes ([immune cells](#)) that are in charge of attacking the [cancer cells](#).

An immune checkpoint blockade antibody blocks the deactivation of the immune system by the cancer cells. The immune system has built-in brakes—called immune checkpoints—so that it doesn't overdo it and

injure the body when attacking cancer and infections. Glioblastoma evolves to activate the brakes, and therefore, the immune system (i.e., lymphocytes) won't attack it.

In addition to the [tumor cells](#), glioblastoma contains other cell populations called macrophages and microglia. These are the most abundant components of the tumor microenvironment and the cells that glioblastoma modulates to inhibit lymphocytes. The study showed that the chemo and antibody cocktail altered these cells, enabling the lymphocytes to recognize and kill the cancer cells.

"This is the first report in humans where an ultrasound device has been used to deliver drugs and antibodies to glioblastoma to change the immune system, so it can recognize and attack the brain cancer," said co-corresponding author Dr. Adam Sonabend, associate professor of neurological surgery at Northwestern University Feinberg School of Medicine and a Northwestern Medicine neurosurgeon. "This could be a major advance for the treatment of glioblastoma, which has been a frustratingly difficult cancer to treat, in part due to poor penetration of circulating drugs and antibodies into the brain."

The study was conducted on four patients who had advanced progression of their tumors. They had already been treated with conventional chemotherapy for their tumors as well as an [experimental treatment](#) in a clinical trial, but both times, the tumors returned.

"This is a great example of translational bench-to-bedside-back-to-bench research, which sets an exceptional scenario to learn about the ability of the immune system to kill brain tumors in real-time upon treatment," said co-corresponding author Catalina Lee-Chang, assistant professor of neurological surgery at Northwestern University Feinberg School of Medicine. "Given the lack of effective immune response against these deadly tumors, these findings encourage us to envision a potential new

treatment approach."

Clinical trial launched with new treatment

These new findings are the basis for a novel clinical trial that was just launched at Northwestern using ultrasound to deliver immunotherapy for glioblastoma. The trial will initially enroll 10 participants to determine the safety of the treatment, followed by 15 additional to measure whether the treatment can prolong survival.

Previous large clinical trials have failed to show that this type of immunotherapy can prolong survival in glioblastoma patients. Sonabend, however, believes that by enhancing the delivery of these antibodies and drugs into the brain and relying on biomarkers that indicate which tumors are most susceptible to immunotherapy, this treatment might be shown to be effective for some [glioblastoma](#) patients.

"Here we show in a small cohort of patients that when you use this technology, you can enhance the delivery of the chemotherapy and the antibodies, and change the tumor's microenvironment, so the immune system can recognize the tumor," Sonabend said.

More information: Víctor A. Arrieta et al, Ultrasound-mediated delivery of doxorubicin to the brain results in immune modulation and improved responses to PD-1 blockade in gliomas, *Nature Communications* (2024). DOI: 10.1038/s41467-024-48326-w , www.nature.com/articles/s41467-024-48326-w

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