# Smart bomb virus shows promise as brain tumor immunotherapy

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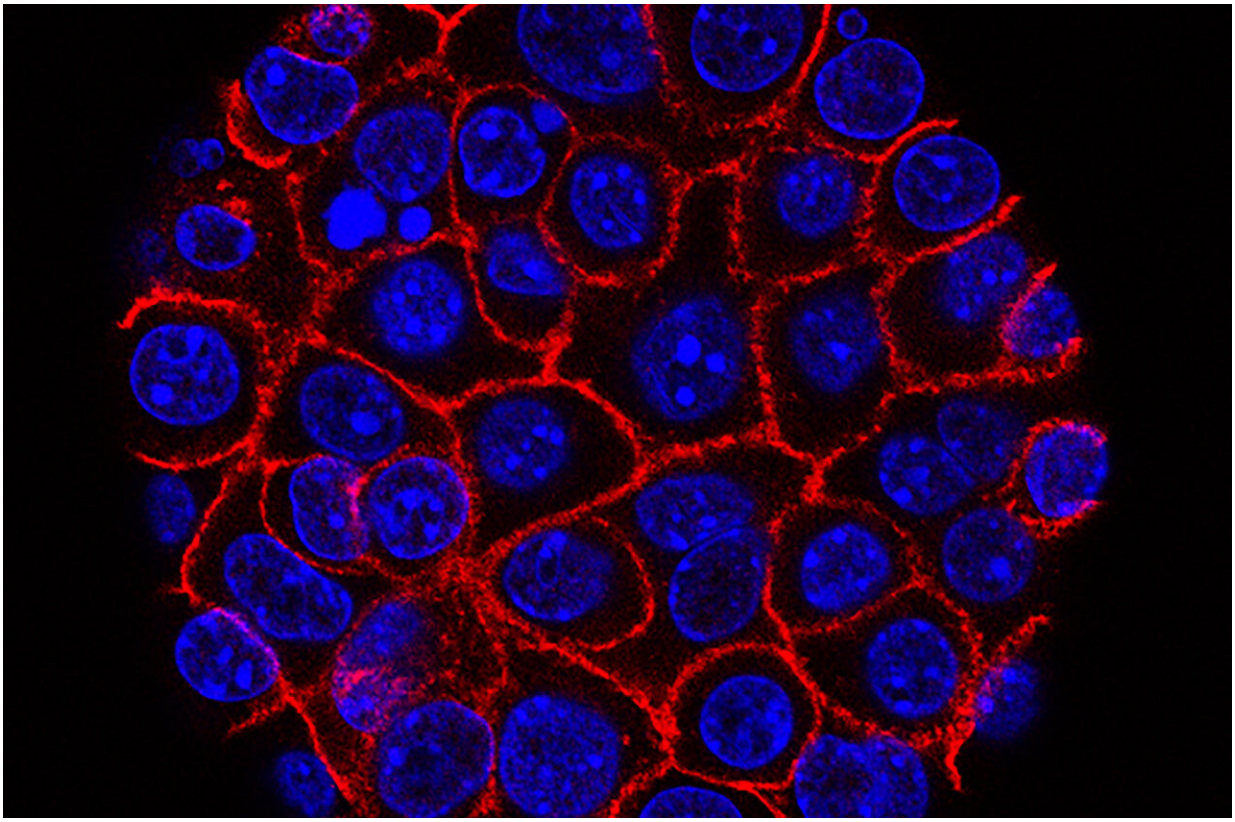

Credit: Min Yu (Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC),USC Norris Comprehensive Cancer Center

A common cold virus engineered to attack the most common and deadly of brain tumors allowed 20 percent of patients with recurrent

glioblastoma to live for three years or longer, researchers from The University of Texas MD Anderson Cancer Center report on a phase I clinical trial in the *Journal of Clinical Oncology*.

The altered adenovirus, called Delta-24-RGD or DNX-2401, was injected one time directly into the tumors of 25 patients whose glioblastoma had recurred after surgery and other treatments, a patient group that typically has a median survival of six months.

"Of those five long-term survivors, three had durable complete responses, which is impressive for a phase I clinical trial in glioblastoma," said lead author Frederick Lang, M.D., professor of Neurosurgery. "Many phase I trials might have one patient who does well, so our result is unusual, but we're always cautious in assessing results with this very difficult disease."

Toxicities were minimal, with two patients experiencing low-grade side effects related to treatment. Dose escalation proceeded to the highest concentration of the virus that could be manufactured, with no dose-limiting side effects. Eighteen patients (72 percent) had some tumor reduction. Median overall survival was 9.5 months.

Imaging of treated patients and analysis of surgically removed tumors from 12 other patients treated with the targeted virus before surgery in a separate part of the trial confirmed both the original tumor-killing mechanism and a resulting immune reaction that the researchers think is behind the long-term responses.

## Viral attack triggers immune response

"We designed DNX-2401 to specifically infect cancer cells, replicate inside those cells to kill them, and spread from cell to cell in a destructive wave throughout the tumor," said senior author and drug co-

inventor Juan Fueyo, M.D., professor of Neuro-Oncology. "The clinical trial shows that happens, as predicted by our preclinical research, and it also shows that in some patients, viral infection was followed by an immune reaction to the glioblastoma that led to the strong responses."

In the three complete responses, imaging showed evidence of inflammation and immune activity a month after treatment, followed by a steady decline in tumor size until at least 95 percent of it vanished.

"In the case of these long-term complete responders, the virus breaks the tumor's shield against immune response by killing cells, creating multiple antigen targets for the immune system," said co-inventor Candelaria Gomez-Manzano, M.D., associate professor of Neuro-Oncology. "These tumors are then completely destroyed."

Glioblastomas normally do not attract the attention of the immune system, with virtually no penetration of tumors by T cells, white blood cells that attack invaders and abnormal cells.

The study showed the immune system wiped out the virus within a month, but tumor reduction in complete responders continued for a year or longer. Analysis of the surgically removed tumors from the second part of the trial showed widespread cell death in the tumors and infiltration of T cells.

With no detectable tumor, minimal initial side effects and no ongoing treatment with other methods that come with stronger side effects, such as radiation and chemotherapy, patients' quality of life is good, the researchers note.

However, about three or four years later, all three patients had recurrences which ultimately proved fatal. In two cases, the tumor that came back was a gliosarcoma, substantially different from the original

glioblastoma. All three lived for at least 4.8 years after treatment, with two having progression-free survival of 42.5 months and 36.4 months.

"We have work to do in the lab to understand how we might permanently defeat these tumors and extend the impact of treatment to more of the 80 percent who did not have a strong response," Fueyo said. The team is conducting research to add new factors to the virus that will stimulate immune response.

Clinical trials combining the smart bomb virus with other therapies to enhance response are open under the leadership of DNAtrix, a Houston-based company formed by Fueyo, Gomez-Candelaria and others to further develop the drug for regulatory approval. Fueyo, Gomez-Candelaria and MD Anderson have equity ownership in DNAtrix as well as intellectual property licensed to DNAtrix. Lang also is a patent holder on DNX-2401.

These relationships are managed in accordance with MD Anderson's conflict-of-interest policies. The plan for DNAtrix may be viewed here. MD Anderson researchers do not lead other clinical trials sponsored by DNAtrix.

One open DNAtrix clinical trial combines DNX-2401 with the immune checkpoint inhibitor pembrolizumab, known commercially as Keytruda, to see if that pairing protects and heightens immune response.

Fueyo, Gomez-Candelaria and Lang originally developed the oncolytic virus called Delta-24 RGD for selective penetration of glioblastoma.

The virus, since renamed DNX-2401 by DNATrix, exploits the fact that the retinoblastoma protein, which normally guards against viral infection, is missing or defective in brain tumors, allowing the virus to more easily invade glioblastoma but not normal cells. To further protect

normal cells, they disabled a protein called E1A that adenoviruses normally use to overcome the retinoblastoma defense.

Provided by University of Texas M. D. Anderson Cancer Center