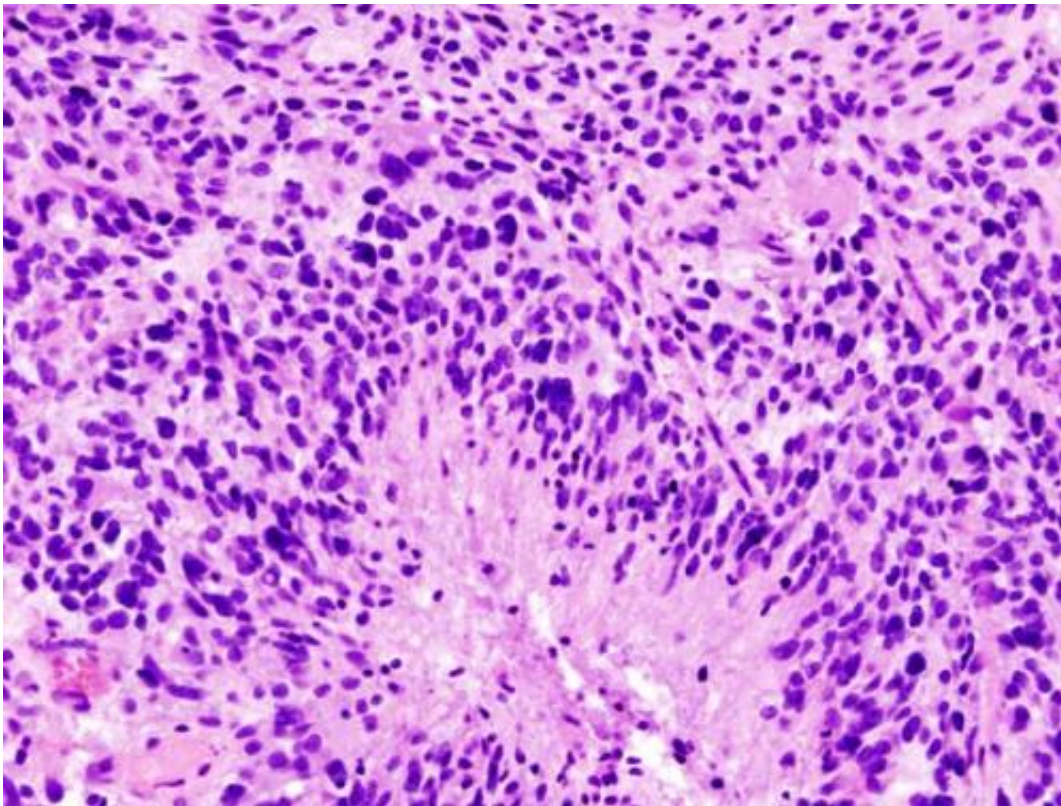


Tetanus shot improves patient survival with brain tumor immunotherapy

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

An innovative approach using a tetanus booster to prime the immune system enhances the effect of a vaccine therapy for lethal brain tumors, dramatically improving patient survival, according to a study led by Duke Cancer Institute researchers.

Appearing online March 11, 2015, in the journal *Nature*, the researchers not only present survival data for a small, randomized and blinded patient trial, they also detail how the tetanus pre-conditioning technique works, providing a roadmap for enhancing dendritic cell immunotherapies that have shown promise treating the most lethal form of brain cancer.

"Patients with glioblastoma usually survive for little more than one year. However, in [patients](#) who received the [immunotherapy](#), half lived nearly five years or longer from their diagnosis, so the findings are promising and significant," said senior author John Sampson, M.D., Ph.D., chief of the Division of Neurosurgery at Duke University Medical Center.

The researchers built the study on earlier findings that glioblastoma tumors harbor a strain of cytomegalovirus (CMV) that is not present in the surrounding brain tissue, creating a natural target for an immune therapy.

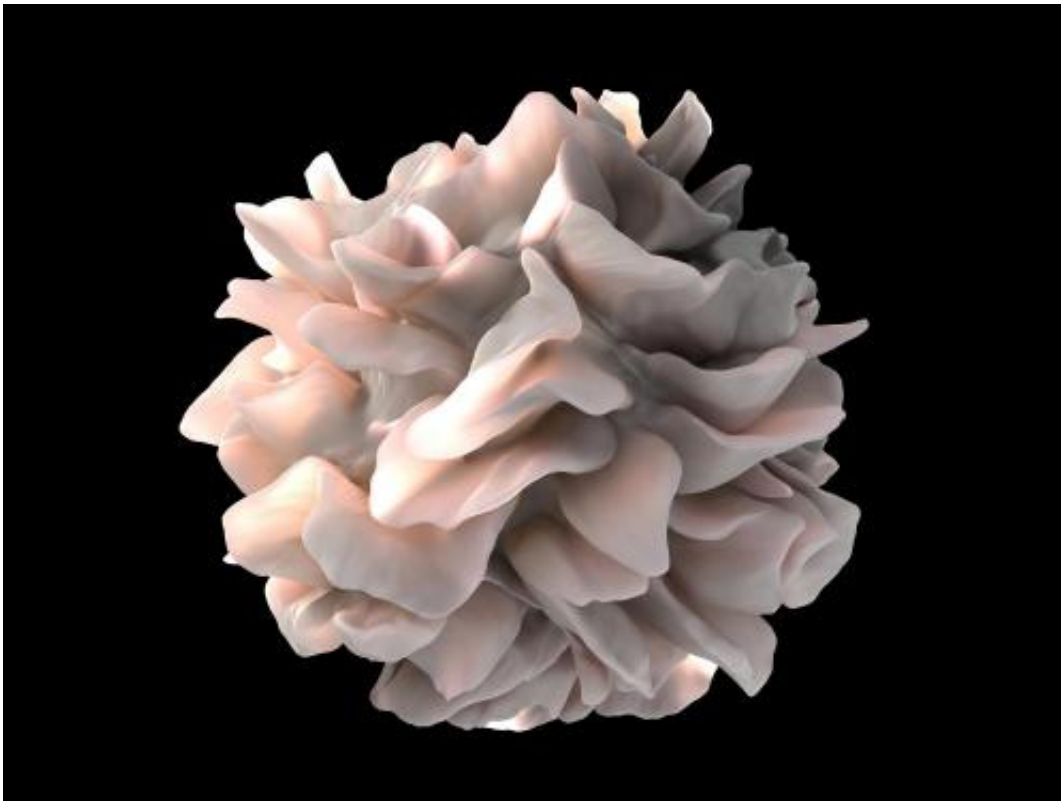
One such targeted approach uses [dendritic cells](#), which train the immune system to respond to specific pathogens. The Duke research team developed a process to extract white blood cells, coax the growth of dendritic cells and load them with the viral antigens.

Armed with these marching orders, the dendritic cells are injected back into the cancer patients, where they head to the lymph nodes and signal the immune fighters to search and attack the CMV-laden tumor.

This immunotherapy worked well, but researchers sought additional gains. So they looked for a way to prime the immune system to be on high alert prior to the infusion of dendritic cells. They chose to use a shot of tetanus/diphtheria toxoid—which is widely available and safe as a clinically approved vaccine - to incite the troops of lymphocytes in the lymph nodes.

In a small human study, they enrolled 12 brain tumor patients, with half randomly assigned to receive a tetanus booster and the other half a placebo injection. The next day, patients in both groups were then given the dendritic cell immunotherapy. Researchers did not know which therapies the patients received.

Patients randomized to get a tetanus shot showed a significant increase in survival from the time of pre-conditioning compared to patients receiving just the dendritic cell therapy, with half living from 51 to 101 months, compared to 11.6 months for the comparison group. One patient from the tetanus group continues to have no tumor growth and is still alive at eight years after the treatment.



An artist's representation of the surface of a human dendritic cell. Credit: Image courtesy of the National Cancer Institute.

"These findings have potential relevance for improving dendritic cell vaccines not only for patients with glioblastoma, but also in the immunologic targeting of other cancers," said co-lead and co-corresponding author, Duane A. Mitchell, M.D., Ph.D., currently director of the University of Florida brain tumor immunotherapy program. "We are obviously pursuing larger-scale confirmatory studies, but are very encouraged by these data and the future applicability."

The researchers used mouse studies to track how the immunotherapy worked. They identified a new role for an immune signaling protein called CCL3, which had previously been known for mediating other immune activities, but had not been associated with creating increased migration of dendritic cells to the lymph nodes. The protein was found to work systemically, not just at the injection site.

"The fact that both mice given tetanus and our patients had elevated CCL3 prompted us to investigate the role of this protein in the mechanism, which in turn revealed that both CCL3 and the recall responses from tetanus boosting needed to work together to increase the migration of our vaccines," said co-lead author Kristen A. Batich, a Duke M.D./Ph.D. candidate.

"While dendritic cell vaccines have shown some promise in the treatment of patients with advanced cancers, including glioblastoma, the dynamics of this process have not been well understood," Sampson said. "Our work identifies an immunologic interaction whereby recall responses to one antigen - tetanus - can influence the migratory capacity of dendritic cells loaded with different antigens - CMV."

The researchers plan a new study to determine whether successful dendritic cell migration could be used as a prognostic indicator of patient survival.

"Our study indicates that dendritic cell migration to the [lymph nodes](#) can be improved significantly by pre-conditioning the vaccine site with a tetanus boost, and this appears to improve antitumor responses and prolonged survival," Batich said.

More information: "Tetanus toxoid and CCL3 improve dendritic cell vaccines in mice and glioblastoma patients," *Nature*, [DOI: 10.1038/nature14320](#)

Provided by Duke University Medical Center

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